Published in final edited form as:

Crit Rev Biochem Mol Biol. 2019 December ; 54(6): 484–516. doi:10.1080/10409238.2020.1717430.

Selenium and Selenoproteins in Prostanoid Metabolism and Immunity

Fenghua Qian, **Sougat Misra**, **K. Sandeep Prabhu***

Center for Molecular Immunology and Infectious Disease and Center for Molecular Toxicology and Carcinogenesis, Department of Veterinary and Biomedical Sciences and The Penn State Cancer Institute, The Pennsylvania State University, University Park, PA. 16802, USA

Abstract

Selenium (Se) is an essential trace element that functions in the form of the 21st amino acid, selenocysteine (Sec) in a defined set of proteins. Se deficiency is associated with pathological conditions in humans and animals, where incorporation of Sec into selenoproteins is reduced along with their expression and catalytic activity. Supplementation of Se-deficient population with Se has shown health benefits suggesting the importance of Se in physiology. An interesting paradigm to explain, in part, the health benefits of Se stems from the observations that selenoprotein-dependent modulation of inflammation and efficient resolution of inflammation relies on mechanisms involving a group of bioactive lipid mediators, prostanoids, which orchestrate a concerted action towards maintenance and restoration of homeostatic immune responses. Such an effect involves the interaction of various immune cells with these lipid mediators where cellular redox gatekeeper functions of selenoproteins further aid in not only dampening inflammation, but also initiating an effective and active resolution process. Here we have summarized the current literature on the multifaceted roles of Se/selenoproteins in the regulation of these bioactive lipid mediators and their immunomodulatory effects.

Keywords

Cyclooxygenase; prostaglandin; thromboxane; immune cell; infection

I. Introduction

Selenium (Se) is an essential trace element discovered by Jöns Jacob Berzelius in 1817, named after the Greek goddess of the moon, Selḗnē. In the periodic table of the elements, Se is in the chalcogen group, which consists of oxygen (O), sulfur (S), Se, tellurium (Te), and polonium (Po). Thus, Se possesses some of the properties of S and Te. One of the most distinguishing features of Se is its biological functions that occur via incorporation into selenoproteins through a specialized evolutionary machinery involving multiple components. Co-translational insertion of selenocysteine (Sec) into proteins endows them the enzymatic efficiency when compared to their cysteine (Cys) counterparts (Gladyshev and Hatfield 1999; Hondal et al. 2001; Arner 2010). Even though some organisms such as yeast, fungi, or

*Correspondence: ksprabhu@psu.edu; Tel: +1-814-863-8976.

higher plants cannot synthesize selenoproteins, humans and other eukaryotes utilize Sec for incorporation into a diverse array of cellular redox gatekeepers and other enzymes that play a key role in physiological and pathological conditions. In particular, different components of immune system have been reported to be modulated by the levels and forms of dietary Se and corresponding augmentation of selenoproteins biosynthesis in the body (Brown et al. 2000; Shrimali et al. 2008). This is particularly intriguing given the relationship between Se status and prostanoid metabolism and how the modulation of the latter impacts the immune system.

Here, we discuss the impact of Se and selenoproteins in health and disease with an emphasis on the immune system and its modulation via the regulation of prostanoid metabolism. Relevant studies that have dealt with infections (bacterial, viral, and parasitic), cancer immunity, immunodeficiency (acquired immunodeficiency syndrome, AIDS), and allergic asthma are discussed. Although prostanoids are of considerable importance in cardiovascular, pulmonary, and gastrointestinal systems, this review focuses on Se and/or selenoproteins and prostanoid metabolism in relation to immunity.

II. Se and Selenoproteins

Diet is the primary source of Se in animals and humans. Inorganic Se (mainly selenate and selenite) from soil is converted to organic forms including selenomethionine (SeMet) and methylselenocysteine, and Sec in plants. In mammals, different forms of dietary Se are taken up and metabolized into various intermediary metabolites including selenide (HSe^-), which functions as a Se donor for Sec biosynthesis. Se in the form of Sec was first discovered in the redox-active enzyme, glutathione peroxidase 1 (GPX1) in which Sec is located in the active site (Rotruck et al. 1973). Later, it was recognized that the 21st amino acid was incorporated into GPXs via decoding the stop codon UGA (Chambers et al. 1986; Zinoni et al. 1986). This is an evolutionarily conserved synthetic mechanism shared by all selenoproteins (Salinas G. 2006), which entails a dedicated set of factors as described below. Dietary Se in the form of selenate or selenite is metabolized to HSe^- followed by conversion to selenophosphate by selenophosphate sythetase-2 (SPS2) (Low et al. 1995; Guimaraes et al. 1996). Selenophosphate is further utilized to convert the phosphoseryl-tRNA$^{[Ser]Sec}$ to form Sec-tRNA$^{[Ser]Sec}$ (Diamond et al. 1981; Leinfelder et al. 1988). Sec-tRNA$^{[Ser]Sec}$ controls the expression of selenoproteins by incorporating Sec into a growing polypeptide chain via decoding the stop codon UGA in response to the Sec insertion sequence (SECIS) cis element in the 3'-untranslated region (3'-UTR) (Berry et al. 1991). Other factors including SECIS binding protein 2 (SBP2) (Copeland et al. 2000) and Sec-specific elongation factors (EFSecs) (Tujebajeva et al. 2000) serve as key components of the translational machinery for Sec incorporation with many key mechanistic questions that still remain unanswered (Howard and Copeland 2019). A schematic of Sec formation and incorporation into selenoproteins is presented in Fig. 1.

Use of bioinformatic methods led to the identification of 25 and 24 selenoproteins in humans and rodents, respectively (Kryukov et al. 2003). Thus, the similarity of the selenoproteome between humans and rodents has enabled the use of rodent models to elucidate the physiological function of the selenoproteome as a whole and individual selenoproteins.

However, the expression of selenoproteins in these and other higher mammals is tightly controlled in a tissue and cell-specific manner by hierarchical regulation dictated by developmental stages at both organismal and cellular levels, availability of Se, and sexual dimorphisms (Schomburg and Schweizer 2009). A commonly used model to ablate the selenoproteome utilizes the targeted deletion of Sec-tRNA$^{[Ser]Sec}$ gene (*Trsp*) (McBride et al. 1987; Bosl et al. 1995). *Trsp* knockout mice lack the capacity to synthesize selenoproteins, and thus, present an important tool to distinguish the physiological/pharmacological functions between selenoproteins and supplemented Se compounds that cannot be utilized for selenoprotein biosynthesis in the knockout mice. However, caution should be taken when extrapolating the results from murine models of selenoprotein deletion to humans. More recently, differences in the tolerance to selenoprotein loss between mouse and human were compiled by comparing human loss-of-function variants from a genome aggregation database (gnomAD) with selenoprotein knockout mouse models from large-scale projects IMPC (Santesmasses et al. 2019), suggesting the importance to differentiate the physiological effects of selenoproteins between mouse and human. Table 1 summarizes the currently known selenoproteins and their distributions within the cells of the immune system. A more detailed discussion of the functions of selenoproteins in immunity with emphasis on their involvement in inflammatory pathologies is presented in the following sections.

A family of lipid mediators that regulate various facets of inflammation, as well as its resolution, include cyclooxygenase (COX)-mediated synthesis of prostanoids. Esterified long-chain fatty acids as precursors of prostanoids are prone to oxidation, specifically during inflammation-associated activation of immune cells, including macrophages and neutrophils. This activation process involves physiologically regulated generation of reactive oxygen and nitrogen species. These reactive molecules can oxidize biomolecules, including unsaturated fatty acids, and can directly influence inflammatory pathways when cellular redox-regulatory pathways involving selenoproteins are dysregulated. Among selenoproteins, GPX4 plays a critical role in the reduction of lipid hydroperoxides that regulate the catalytic activity of COXs apart from playing a critical role in ferroptotic cell death (Ursini et al. 1982; Kulmacz and Lands 1983; Dixon et al. 2012; Sengupta et al. 2013). On the other hand, several key redox-sensitive transcription factors, including nuclear factor (NF)-κB, play pivotal roles in the progression and resolution of inflammation by modulating prostaglandin (PG) metabolism at different levels. Herein, we critically evaluate the direct association and plausible connections between redox-regulatory mechanisms involving Se/selenoproteins and inflammation and immunity in the context of PG metabolism.

III. Se/Selenoproteins in Prostanoid Metabolism

A. COX-mediated synthesis of prostaglandin H_2 (PGH_2)

Prostanoids are a class of lipid metabolites generated from the 20-carbon polyunsaturated fatty acids (PUFA), arachidonic acid (ARA 20:4, $\Delta^{5,8,11,14}$) or eicosapentaenoic acid (EPA 20:5, $\Delta^{5,8,11,14,17}$), upon dioxygenation by COXs, which exist in two isoforms COX-1 [prostaglandin endoperoxide synthase 1 (Ptgs1)] and COX-2 (Ptgs2) (Vane et al. 1998). These lipid mediators consist of PGs (PGD_2, PGE_2, and $PGF_{2\alpha}$), prostacyclin (PGI_2), and

thromboxanes (TXs, TXA_2 and TXB_2) from ARA or their 3-series counterparts (PGD_3, PGE_3, $PGF_{3\alpha}$, PGI_3, TXA_3, and TXB_3) from EPA.

Generally, ARA is released from plasma membrane phospholipids upon hydrolysis by phospholipase A2 (PLA_2) (Dennis et al. 2011; Leslie 2015). ARA is abundant in mammalian tissues and serves as a precursor for various bioactive eicosanoids and their metabolites (Fig. 2). Specifically, ARA is oxidized by either COX-1 or COX-2 to produce prostaglandin G_2 (PGG_2) hydroperoxide that is further reduced to its corresponding alcohol, PGH_2, by the peroxidase activity of COX enzymes or by GPX1 (Hong et al. 1989). COX-1 and COX-2 exist as homodimers in the microsomes and nuclear membranes (Rollins and Smith 1980). COX-1 is a constitutively expressed enzyme maintaining tissue homeostasis by providing the physiological levels of PGs in most tissues. However, cytokines such as interleukin (IL)-4 increase the expression of COX-1 via post-transcriptional and translational mechanisms that appears to be important in innate immune responses challenging the long-standing paradigm that COX-1 is devoid of any regulation (Shay et al. 2017). Apart from a few exceptions of its constitutive expression, COX-2 is mainly elevated in inflammation, including pathological conditions such as infections and cancers. COX-2 is expressed upon stimulation by a variety of triggers including cytokines (tumor necrosis factor (TNF)-α, IL-1β) (Feng et al. 1995), hormones (adiponectin) (Ouchi and Walsh 2007), toxins (lipopolysaccharide (LPS)) (Brock and Peters-Golden 2007), oxidative stress (hydrogen peroxide (H_2O_2)) (Feng et al. 1995), and physical stress (shear stress, forced-exercise) (Doroudi et al. 2000; Bilski et al. 2019).

1. Role of COXs in immunity—COX-1 and COX-2 vary in distribution and expression patterns. They modulate the production of different PGs via functional coupling with downstream synthases leading to both inflammation as well as resolution of inflammation. Given the enhanced expression of COX-2 in various inflammatory disorders, selective or conventional inhibitors in the form of non-steroidal anti-inflammatory drugs (NSAIDs) have been highly pursued since 1897 following the synthesis of aspirin (Green 2001). Furthermore, due to the role of COX-2 as well as its metabolites in the regulation of immunity, drug-candidates selectively inhibiting COX-2 have been used to treat immune system malfunction-associated morbidities. For example, celecoxib, a selective COX-2 inhibitor, is used to treat melanoma and breast cancer synergistically with programmed death 1 (PD-1) monoclonal antibody (mAb) in rodent models, which suppressed intra-tumoral expression of COX-2 (Li Y et al. 2016). A combination treatment of celecoxib with sunitinib (a multitargeted receptor tyrosine kinase inhibitor) in renal cell carcinoma increased $CD4^+$ interferon (IFN)-γ^+ and $CD8^+$IFN-γ^+ T cells, while reducing the $CD4^+FoxP3^+$ regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs) (Wang X et al. 2013; Zhao et al. 2017). Similarly, in a murine model of *Mycobacterium tuberculosis* infection, celecoxib impaired T helper type 1 (Th1) response and exacerbated the infection (Mortensen et al. 2019), further confirming the dichotomous role of COX-2 in immune response. While celecoxib has shown promise in oncology, the cardiovascular side effects of this (and similar) drug often preclude its long-term use necessitating alternative methods to “fine tune” expression of this enzyme (Dogne et al. 2006; White et al. 2007). These studies

suggest a unique role for COX-2 in immunity and provide an alternative candidate for the treatment of cancers based on the immunomodulatory mechanism that involves COX-2.

2. Regulation of COXs by Se/selenoprotein(s)—Se supplementation has been shown to downregulate the transcript levels of COX-2 in both bone marrow-derived macrophages (BMDMs) and RAW264.7 macrophage-like cell line that were stimulated with bacterial endotoxin LPS (Kalantari et al. 2008; Gandhi et al. 2011). For example, RAW264.7 macrophages cultured in the presence of sodium selenite (Na_2SeO_3) (0.1–1.5 μM) showed a decreased expression of COX-2 on both mRNA and protein levels comparing to the cells in Se deficient group (6 pmol/ml) upon stimulation with LPS. *In vivo* studies with low Se diet (0.033 mg/kg, Na_2SeO_3) increased the mRNA expression of COX-2 in the kidneys of broiler chicks, while a Se adequate diet (0.2 mg/kg, Na_2SeO_3) dampened the expression of COX-2 (Zhang JL et al. 2016). Other studies also identified the inhibitory effect of Se on the expression of COX-2 in colon cancer cells (Hwang et al. 2006), vascular endothelial cells (Li YB et al. 2011), and chicken neutrophils (Chen J et al. 2017). Taken together, *in vitro* and *in vivo* studies suggest a clear benefit of increased Se on COX-2 expression in experimental models.

These studies bring up an important question whether selenoproteins mediate the effect of Se on the inhibition of COX activity and/or expression. Early work found that GPX1 suppressed the activity of COX from sheep seminal vesicles (Smith WL and Lands 1972); and human plasma glutathione peroxidase activity (presumably GPX2) served as an important regulator of plasma hydroperoxide levels (Maddipati and Marnett 1987), which regulates the “peroxy tone” to modulate the catalytic activity of PG synthases in addition to COX enzymes (Kulmacz 1986; Kulmacz R.J. 1997). Furthermore, increased expression and activity of GPX1 were inversely associated with decreased expression and activity of COX-2 in Se supplemented macrophages (Zamamiri-Davis, Lu et al. 2002).

Phospholipid hydroperoxidase, GPX4, deserves a special attention in relation to COX-2 activity. Overexpression of Gpx4 in rat basophilic leukemia (RBL-2H3) resulted in decreased levels of PGD_2 which was associated with inhibition of production of PGH_2 from ARA by Cox-2 (Sakamoto et al. 2000). GPX4-overexpressing cells exhibited lower levels of lipid hydroperoxides, the availability of which plays a key role in the activation of Cox-2. Use of a chemical GPX4 allosteric activator (compound 102) reduced lipid hydroperoxides and intracellular ROS levels, inhibited ferroptosis, and most importanly, decreased NF-κB activation (Li C et al. 2018). Use of the GPX4 allosteric activator with zileuton, a 5-lipoxygenase (LOX) inhibitor, increased ARA metabolism through 12-LOX and 15-LOX leading to the enhanced production of proresolving metabolites in neutrophils (Li C et al. 2018). Keratinocyte-specific Gpx4 knockout mouse pups showed an impaired hair follicle morphogenesis, which was accompanied with an increased COX-2 expression, thereby suggesting an inverse relationship between Gpx4 and Cox-2 expression. This abnormal phenotype was partially reversed by feeding the nursing dams with a COX-2 specific inhibitor, celecoxib (Sengupta et al. 2013). Furthermore, in a dextran sodium sulfate (DSS)-induced colitis murine model, mice with monocyte/macrophage-specific knockout of selenoproteins ($Trsp^{fl/fl}LysM^{Cre}$) showed a significantly increased expression of COX-2 and exacerbated inflammation in colons compared with their wild type (WT) littermates in the

presence of Se supplementation (0.4 ppm, Na_2SeO_3) (Kaushal et al. 2014). Taken together, the incorporation of Se into selenoproteins was found to be essential in the control of COX-2.

The regulation of COX-2 expression by Se or selenoproteins occurs at multiple levels. For example, the regulation of expression of COX-2 depends on the activation and subsequent nuclear translocation of NF-κB. Cysteine 62 in the DNA-binding motif of p50 subunit of NF-κB is sensitive to oxidation and is necessary to be in the reduced state to mediate DNA binding (Hayashi et al. 1993). Activation of toll-like-receptor 4 (TLR4) by LPS in macrophages, further recruits other proteins, myeloid differentiation factor 88 (MyD88), IL-1 receptor-activated kinases, IRAK4 and IRAK1, followed by TNF receptor-associated factor 6 (TRAF6) [reviewed in (Lu et al. 2008)]. Ubiquitylated TRAF6 binds to two adaptors, transforming growth factor (TGF)β-activated kinase 1 (TAK1) and its binding partners, TAB1–3, which phosphorylate IκB kinases (IKK) in addition to other kinases such as p38 and c-Jun N-terminal kinase (JNK) (Ajibade et al. 2013). Several reports indicate TAK1 functions as a potential upstream redox sensor to maintain a steady state level of the master regulator of antioxidant responses, Nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) (Hashimoto et al. 2016). Selenoproteins, Gpx2 and Txnrd1, are targets of Nrf2 in duodenum (Muller M et al. 2010). Phosphorylated IKKs phosphorylate IκB subunits leading to their proteasomal degradation following dissociation, making the NF-κB dimers translocate to nucleus to activate transcription of a plethora of genes, including COX-2, reviewed in (Tanabe and Tohnai 2002; Gilmore 2006) (Fig. 3).

Se supplementation downregulated the expression of COX-2 by targeting NF-κB through various mechanisms. Se supplementation (0.05 – 1.5 μM, Na_2SeO_3) induced the enhanced production and activity of GPX1 in Se-deficient RAW264.7 macrophages and deceased the expression of COX-2 (≥0.2 μM, Na_2SeO_3) (Vunta et al. 2008). GPX1 was able to protect against oxidative stress-induced by LPS in the Se-deficient macrophages, possibly resulting in the inhibition of mitogen-activated protein kinases (MAPKs), JNK, and extracellular-signal-regulated kinase (Erk) (Kretz-Remy et al. 1996; Vunta et al. 2008). As a result, the dissociation of IκB from NF-κB complex was inhibited leading to its attenuated nuclear translocation and decreased expression of COX-2. Besides, selenite was reported to directly inhibit DNA binding activity of NF-κB by the oxidizing cysteine residue suggesting short-term effects of high dose selenite by acting on NF-κB *per se* (Kim and Stadtman 1997). Overexpression of GPX2 in human breast T47D cell line inhibited H_2O_2-induced oxidative stress and IκB transactivation as well as NF-κB activation (Kretz-Remy et al. 1996) (Fig. 3). A recent study using mice and human colorectal adenocarcinoma (HT-29) cells with stable knockdown of Gpx1 and Gpx2 showed that the inhibitory effect of Gpx2 on NF-κB signaling and its target gene expression was more pronounced than that of Gpx1, while eicosanoid products of COX- and LOX-mediated metabolism increased more strongly in cells that lacked Gpx1 than in those without Gpx2 expression (Koeberle et al. 2020). Other studies have suggested thioredoxin reductase-1 (Txnrd1) to control the transactivation potential of NF-κB in Hela cells via mechanisms that involves phosphorylation of Ser536 within the transactivation domain of p65 in addition to activation of enzymes involved in the pathway of NF-κB activation as mentioned above (Heilman et al. 2011). An alternative mechanism involves the increased production of cyclopentenone PGs (CyPGs) by Se

supplementation that inhibits the kinase activity of IKK1/2 via a direct covalent Michael addition of reactive Cys residue in the kinase domain (Rossi et al. 2000). CyPG, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), inhibited the binding activity of AP-1 [to 3', 5'-cyclic adenosine monophosphate (cAMP) response element (CRE) binding site] and NF-κB, resulting in the attenuated expression of COX-2 through peroxisome proliferator-activated receptor gamma (PPARγ) signaling in CaSki human cervical cancer cells (Han S et al. 2003) (Fig. 3). In addition, epigenetic mechanisms were also shown to regulate COX-2 expression by Se. Treatment of WT BMDMs with Se (500 nM Na_2SeO_3) decreased acetylation of H4K12 at the promoter of COX-2. However, a complete lack of selenoproteins, as in *Trsp* knockout BMDMs, failed to modulate histone acetylation at the site of COX-2 promoter (Narayan et al. 2015). These studies clearly indicated that incorporation of Se into selenoproteins was essential for the regulation of COX-2 expression by Se at multiple levels in activated macrophages.

Studies by Gandhi, Kaushal *et al* (Gandhi et al. 2011) and Hema *et al* (2007) together indicated that Se status affected the function of COX-2, but not COX-1, leading to the production of downstream metabolites via the eicosanoid class switching paradigm. As shown in Fig. 4, Se status also regulated the expression of specific PG synthases, such as hematopoietic PGD synthase (H-PGDS), microsomal PGE synthase-1 (mPGES-1), PGI synthase (PGIS), and TX synthase (TXS), which are downstream enzymes that catalyze the conversion of PGH_2, a highly labile product of COX, into specific effector PGs (Fig. 2). The role of some of these products in immunity and their regulation by Se will be described in the following sections.

B. Role of PGD_2 and CyPGs in immunity

As described in the preceding section, PGH_2 is metabolized by enzymes, PGDS to form PGD_2, which is the major PG in the central neuron system (CNS) (Yermakova and O'banion 2000) and is also of great importance as a mediator in allergy and asthma suggesting its role in extra-neuronal systems, including respiratory system and immune system (O'Sullivan 1999; Matsuoka et al. 2000; Mitsumori 2004). H-PGDS (Kanaoka and Urade 2003) and lipocalin-type PGDS (L-PGDS) (Tanaka T et al. 1997) are two enzymes that catalyze the conversion of PGH_2 to PGD_2 in a glutathione (GSH)-dependent or GSH-independent manner, respectively.

H-PGDS, a sigma-class glutathione S-transferase (GST), is mainly expressed in the hematopoietic and inflammatory cells including mast cells, dendritic cells (DCs), Th2 cells, and other antigen-presenting cells (APCs), such as monocytes and macrophages. This unique expression pattern implies that H-PGDS may contribute to a type-2 immune response through the production of PGD_2 and its downstream CyPGs. But the role of H-PGDS in Th2 immunity may suggest divergent effects depending on the nature of inflammation, type of participating cells, and cytokines produced in addition to the Se status. For instance, H-PGDS acts in a pro-inflammatory manner in airway hyperresponsiveness (AHR) or asthma by producing localized PGD_2, which is characterized by bronchoconstriction and secretion of allergic cytokines, as well as immune cell infiltration (O'Sullivan 1999). PGD_2 can bind to a G-protein coupled receptor (GPCR), Gpr44 [also termed as chemoattractant receptor-

homologous molecule expressed on Th2 cells (Crth2) or PGD_2 receptor 2 (DP2)] on type 2 innate lymphoid cells (ILC2) to upregulate the production of type 2 cytokines, such as IL-4, IL-5, and IL-13 by activating ILC2. Moreover, Gpr44 activation by PGD_2 also enhances the production of two ILC2 activators, IL-25 and IL-33, to mediate ILC2-dependent immune responses (Xue et al. 2014). Mast cells, as another major contributor of type 2 immune response, also produce PGD_2 to activate Gpr44 on ILC2. Furthermore, activated ILC2 can in turn stimulate mast cell activation by secreting IL-3, IL-4, and IL-13 (Xue et al. 2014). However, CyPGs were shown to act preferentially on Gpr44. Interestingly, Se treatment (> 200 nM) led to increased activation of Gpr44 through these non-enzymatic metabolites of PGD_2 (as described below) that decreased COX-2 expression via increased Ca^{2+} mobilization and expression of miR155, which attenuates the activation of NF-κB via downregulating the autocrine loop involving TNF-α in macrophages (Diwakar et al. 2019). Given that oxidative stress is involved in asthma, the interplay of two GPCRs (Gpr44 and another PGD_2 receptor, DP1) and their ligand-specific and temporal regulation may dictate the outcome of whether Se supplementation would be beneficial or not.

In the context of inflammatory bowel disease (IBD), studies showed the pro-resolution effect of H-PGDS where activation of Gpr44 may be involved, while DP1 exerts the opposite function (Sturm et al. 2014). Thus, it appears that differential expression of PGD_2 receptors may play an important role in dictating the outcome. As mentioned earlier, the regulatory role of Gpr44 in IBD and LPS-induced inflammation by a subgroup of PGD_2 metabolites generated via multiple non-enzymatic reactions from PGD_2 (Straus and Glass 2001) cannot be ignored. These metabolites have an alkylidene cyclopentenone structure, and therefore are commonly referred to as CyPGs, which comprise Δ^{13}-PGJ_2, Δ^{12}-PGJ_2, and 15d-PGJ_2 (Fig. 2). Although these small molecules are short-lived bioactive lipids, they are implicated in various physiological and pathological activities (Willoughby et al. 2000). Interestingly, Gpr44 expression was found in the mucosa of patients with IBD and ulcerative colitis patients in remission that also had higher levels of PGD_2 (Vong et al. 2010). Even though the levels of CyPGs were not measured in this study, given that CyPGs can preferentially activate Gpr44 with a high affinity, in addition to the DP1 receptor, Gpr44-dependent activation by these CyPGs may likely mediate the resolution in colitis.

1. Regulation of CyPGs by Se/selenoprotein(s)—Previous studies in our laboratory have indicated a dose-dependent effect of Se (as selenite, Na_2SeO_3; 50–500 nM) on the production of PGD_2 and CyPGs upon LPS stimulation of murine macrophages, while decreasing other PGs (PGE_2, TXA_2, and $PGF_{2\alpha}$) as a result of differential regulation of PG synthases leading to the “eicosanoid class switching” paradigm (Fig. 4) (Gandhi et al. 2011). Intriguingly, Se-supplementation led to increased activation of PPARγ, while inhibition of enzymatic activity of H-PGDS abrogated this increased PPARγ activation, thereby suggesting an interaction of Se and PPARγ where H-PGDS activity was indispensable (Fig. 4). These studies are in agreement with the role of CyPGs as endogenous ligands of PPARγ (Forman et al. 1995; Kliewer et al. 1995) and the trans-repression of NF-κB by ligand-dependent activation of PPARγ (Pascual et al. 2005).

In support, studies in our laboratory have provided evidence of the endogenous production of high levels (high nM) of CyPGs in macrophages treated with Se (>200 nM Se as

selenite). A feedback loop involving the PPARγ-dependent mechanism to sustain such an increase in endogenous CyPGs came from our studies showing two PPAR-response elements (PPREs) in the proximal promoter of H-PGDS that were critical in the upregulation of H-PGDS by Se (Gandhi et al. 2011). The effect of Se was abrogated in the absence of selenoprotein synthesis suggesting that the “eicosanoid class switching” mechanism involved selenoproteins.

To be able to exert physiological effects, CyPGs produced upon Se supplementation need to be protected from subsequent metabolic inactivation. Notably, the degradation of CyPGs is mediated by a key enzyme, 15-hydroxyprostaglandin dehydrogenase (15-PGDH) that catalyzes the oxidation of the hydroxyl group in many bioactive lipid mediators, with some preference to PGE_2 (Ensor and Tai 1995). Recent studies in our laboratory focused on leukemia have found an interesting link between Se, CyPGs, and leukemia stem cells (LSCs) in a chronic myeloid leukemia (CML) model, where supraphysiological levels (dose levels above the requirement where key markers of Se status, such as SELENOP and GPX1 are not elevated with any further increase in dose) of Se were protective. Interestingly, the decreased expression of 15-PGDH was accompanied by enhanced production of CyPGs upon dietary Se supplementation in these mice (Finch et al. 2017). Thus, Se may affect the production of CyPGs through multiple mechanisms involving the upstream and downstream signals of CyPGs, which in turn modulate immune function through diverse mechanisms as described earlier.

C. PGE_2 and its role in immunity

PGES catalyzes the conversion of PGH_2 to form PGE_2, which exerts its biological functions by binding to one of the GPCRs, PGE_2 receptors1–4 (EP1–4). Activation of some isoforms (EP2 or EP3) leads to the elevation of intracellular cAMP, which may in turn result in immune dampening events (Lycke et al. 1990; Phipps et al. 1990; Roper et al. 1990). Contrary to PGD_2 as well as CyPGs, PGE_2 is regarded as a pro-inflammatory mediator in most conditions; however, PGE_2 is also a vital signal that induces the production of other potent pro-resolution mediators such as lipoxins via the modulation of LOX (Serhan and Savill 2005). PGE_2 also plays a role in the regulation of vascular permeability, body temperature, and aging. In particular, the protective role of PGE_2 in gastric mucosa against acid exposure was identified by the administration of NSAIDs. Gastrointestinal bleeding associated with non-selective NSAID usage was ameliorated with PGE_1 analogue, misoprostol (Hunt et al. 1983).

Interestingly, PGE_2 reportedly suppressed the immune functions by inhibiting mitogenesis and thus inducing apoptosis of T cells (Goodwin et al. 1977). In addition, PGE_2 also downregulated the synthesis of Th1 cytokines (e.g., IL-2 and IFNγ), while stimulating Th2 cytokines (e.g., IL-4 and IL-10) (Fedyk et al. 1997), which may also be a part of the pro-resolution program. With regard to the effect of PGE_2 on B cells, studies have shown that PGE_2 may affect the outcome of B cells due to its impact on B cell development. In other words, PGE_2 can induce the apoptosis or proliferation of immature or mature B cells, respectively (Goodwin et al. 1977). In addition to the proliferating activity on mature B cells, PGE_2 can induce an immunoglobulin (Ig)-class switch favoring the production of IgG1

and IgE, while diminishing the synthesis of IgM and IgG3 (Phipps et al. 1991). The profoundly enhanced production of IgG1 and IgE by PGE_2 in mature B cells may result from the response to LPS synergizing with IL-4 (Morawetz et al. 1996). Intriguingly, the activation of EP2 or EP2 and EP4 mediated Ig-class switching in mature B cells has been reported to require intracellular cAMP (Fedyk and Phipps 1996). While the above data were generated in *in vitro* studies, *in vivo* studies also indicated high levels of PGE_2 to be associated with elevated secretion of IgE (Gao et al. 2016). In an EP2 knockout mouse, IgE production was markedly suppressed in response to ovalbumin (OVA) challenge. Mechanistically, interaction between EP2 and PGE_2 enhanced the activation of Signal Transducer And Activator Of Transcription 6 (STAT6) that is stimulated by IL-4, thus promoting the Ig-class switching favoring the production of IgE (Gao et al. 2016). Accordingly, antagonists of EP2 or EP4 or inhibitors of PGES are thought to be therapeutic candidates for type I hypersensitivity reaction, which is an immediate allergic reaction mediated by IgE. In contrast to this notion, exogenous PGE_2 as well as EP2-selective agonists significantly caused attenuated AHR induced by house dust mite (HDM) or other allergens (Melillo et al. 1994; Sestini et al. 1996; Gauvreau et al. 1999; Herrerias et al. 2009; Serra-Pages et al. 2015). However, other studies showed that inhibition of COXs worsened airway inflammation in mice exposed to OVA (Gavett et al. 1999; Peebles et al. 2002; Hashimoto et al. 2005; Nakata et al. 2005; Peebles et al. 2005; Torres et al. 2009). Much like the literature related to Se in allergy and asthma, a similar inconsistency exists in the role of PGE_2 in allergy and asthma that may be ascribed to experimental models (Maunsell et al. 1968; Van Hove et al. 2007).

1. Regulation by Se/Selenoprotein(s)—Given that the function of COX-2 is regulated by Se levels, it is speculated that Se may also modulate the allergic disorders by changing the metabolism of PGE_2 by regulating the production of PGH_2, the precursor of PGE_2. Given that signaling mechanisms involving STAT activation by IL-4 can be increased by Se supplementation (Nelson et al. 2011), it is very likely that some of the downstream pathways activated by PGE_2-EP receptor could be also impacted by Se; however, further studies are necessary to tease out the underlying intricate mechanisms. In a clinical study of ulcerative colitis, increased plasma or intestinal mucosal PGE_2 was reported to be associated with disease activity (Wiercinska-Drapalo et al. 1999). Previously, studies in our laboratory demonstrated that Se status was inversely correlated with IBD-induced inflammation in a murine model, where mice treated with DSS-induced acute colitis maintained on either Se-deficient (<0.01 ppm; Na_2SeO_3) or Se-adequate (0.08 ppm; Na_2SeO_3) diets showed exacerbated inflammation and poor survival compared to mice on Se-supplemented (0.4 ppm; Na_2SeO_3) or Se-high (1.0 ppm; Na_2SeO_3) diets (Kaushal et al. 2014). Similarly, $Trsp^{fl/fl}LysM^{Cre}$ mice lacking selenoprotein expression in monocyte/macrophage cells showed comparable disease pattern, as seen in Se-deficient WT mice, despite being on a Se-supplemented diet (Kaushal et al. 2014). Furthermore, increased production of PGE_2 were seen in DSS-treated WT mice on Se-deficient or Se-adequate diets for eight weeks compared to those on Se-supplemented diet suggesting Se status clearly had an impact on PGE_2 levels. Koeberle *et al* (Koeberle et al. 2020) demonstrated that unstimulated HT-29 cells lacking Gpx1 and Gpx2 showed higher baseline levels of PGE_2 and PGD_2 compared to the control cells. Interestingly, IL-1β stimulation of Gpx1 knockdown cells increased levels

of PGE_2 more than PGD_2 suggesting distinct and overlapping roles of Gpx1 and Gpx2 in controlling PGE_2 during colonic inflammation.

High levels of PGE_2 induced by Se deficiency was a combined effect of increased mPGES-1 expression in addition to low expression and activity of 15-PGDH, which was differentially regulated by Se supplementation (Kaushal et al. 2014). 15-PGDH, a nicotinamide adenine dinucleotide $(NAD)^+$-dependent enzyme, can oxidize many prostanoid metabolites. Even though 15-PGDH is reported to preferentially mediate the oxidative reaction from PGE_2 to 15-keto PGE_2, 15-PGDH could potentially inactivate CyPGs. Besides, specialized proresolving mediators (SPMs) metabolized from EPA and docosahexaenoic acid (DHA), such as resolvin E1 (RvE1) and protectins, are also substrates for 15-PGDH-catalyzed reaction (Ensor and Tai 1995; Fredman et al. 2012). These results suggest that 15-PGDH may possess a dual role in inflammation and resolution that need to be further elucidated. More recently, studies in our laboratory have found that the colonic expression and activity of 15-PGDH was increased by Se supplementation to inactivate PGE_2 in DSS-induced colitis, which was corroborated by increased levels of 15-keto PGE_2 (Kaushal et al. 2014). A specific inhibitor for 15-PGDH, CAY10397, abrogated the anti-inflammatory effect of Se supplementation on colitis. Similar results were observed in a second model of IBD induced by *Citrobacter rodentium* infection (unpublished results).

Furthermore, elevated expression of GPX2 in Se supplemented mice with colitis may elucidate how selenoproteins regulate the activity of 15-PGDH to further impact the production and activity of PGE_2. In addition, other selenoproteins [selenoprotein P (SEPP1) (Andoh et al. 2005), selenoprotein S (SelenoS) (Seiderer et al. 2007), selenoprotein K (SelenoK) (Marciel and Hoffmann 2019)] are also implicated in inflammation associated with IBD. With respect to the production of PGE_2, selenoproteins may also regulate the synthases, particularly PGES enzymes. For example, GPX2 knockdown in HT-29 colon cancer cells led to increased expression of microsomal PGES-1 (mPGES-1), one of the inducible isoforms of PGES, accompanied by increased production of PGE_2 (Banning et al. 2008). It is well-known that mPGES-1 expression can be induced by pro-inflammatory cytokines, IL-1β (Leclerc et al. 2013) and TNF-α (Bage et al. 2010) that are both downregulated by Se (Zhang F et al. 2002). On the other hand, pediatric patients with Kashin–Beck disease (KBD), a Se deficiency-induced cardiomyopathy, had increased serum levels of IL-6, IL-1β, and TNF-α (Zhou et al. 2014). An increased serum level of TNF-α is interesting in the context as it is known to destabilize GPX4. Under severe Se deficiency as in KBD, an elevated level of TNF-α could have profound effects on GPX4 with possible implications on ferroptotic cell death of cardiomyocytes. In fact, it was shown that whole blood level of *GPX4* was about 10 times lower in the disease group when compared to the control group (Du et al. 2012).

It has been reported that TNF-α and IL-1β have a common downstream target molecule, NF-κB, which is also identified as a regulator for PGE_2 production. Thus, based on the data, we speculate that Se supplementation may orchestrate the production of PGE_2 through GPXs/IL-1β and/or TNF-α/NF-κB/mPGES-1 signaling axis. Moreover, another key transcription factor, PPARγ, may also participate to mediate the anti-inflammatory effects of

Se supplementation by counteracting the activity of NF-κB, while increasing the expression of H-PGDS to dampen the expression of other PG synthases (Gandhi et al. 2011).

Unlike mPGES-1, there is not much evidence available with regard to the role of mPGES-2, which is highly expressed in intestine, heart, and brain, where it is thought to maintain the physiological biosynthesis of PGE_2 (Tanikawa et al. 2002). While mPGES-1 is inducible upon LPS treatment or pathological triggers such as ischemia, hypoxia, and physical stress, mPGES-2 is more likely to play a constitutive role in physiological and pathological conditions (Murakami et al. 2003). Interestingly, mPGES-2 knockout mice had no measurable changes of PGE_2 production in any tissues (Jania et al. 2009). Further observations did not reveal any lymphoid tumors in mice lacking mPGES-2 expression. Taken together, it appears that mPGES-2 may be dispensable in mice and humans (Nakanishi et al. 2010). In addition to the two microsomal forms, a third isoform, cytosolic PGES (cPGES), is reported to be important for the development of pulmonary system. cPGES knockout mice succumbed to pulmonary immaturity in the perinatal period, likely due to the defective stabilization of the glucocorticoid receptor complex (Lovgren et al. 2007). Preliminary studies in our laboratory suggest that dietary Se does not impact the regulation of mPGES-2 and cPGES in activated macrophages (Kaushal et al. 2014).

D. The role of PGI_2 in immunity

Prostacyclin (PGI_2), first isolated from swine and rabbit aortas, is formed from its precursor PGH_2 through the activity of PGIS (CYP8A1) predominantly expressed within the cardiovascular and pulmonary endothelium (Moncada et al. 1976; Mubarak 2010; Chu et al. 2015). Many studies identified PGI_2 to antagonize the activity of TXA_2 in the vasculature by inhibiting platelet aggregation and promoting vasodilation (Rustin et al. 1987; Kinsella 2001; Gleim et al. 2009; Smyth et al. 2009; Tonelli et al. 2015). Interestingly, such a counter regulation is also observed between PGI_2 and PGE_2, specifically during the development of atherogenesis. In this case, augmented production of PGI_2 mediated a cardioprotective effect in mPGES-1 knockout mice where the production of PGE_2 was attenuated. Surprisingly, suppression of thrombogenesis by the interaction of PGI_2 and its receptor, IP, limits atherogenesis (Tang et al. 2016). In addition, in human lung carcinoma, elevated PGE_2 was implicated in tumor progression and inhibition of apoptosis, whereas PGI_2 as well as its analog, iloprost, inhibited initiation of lung cancer (Keith et al. 2002; Keith et al. 2004; Nemenoff et al. 2008).

From an immune context, both PGI_2 and PGE_2 are considered pro-inflammatory mediators in the initial phase of inflammation by enhancing vascular permeability and subsequently facilitating leukocyte infiltration (Hata and Breyer 2004). However, on its own, the immunomodulatory role of PGI_2 includes both anti-inflammatory [e.g., atherosclerosis, pulmonary arterial hypertension (PAH)] and pro-inflammatory [e.g., rheumatoid arthritis (RA), osteoarthritis (OA)] roles depending on the downstream signaling pathways following IP activation (Stitham et al. 2011). An IP receptor-independent mechanism involving $PPAR_{\beta/\delta}$ activation can be induced by PGI_2 analogs and IP agonists that subsequently results in vasodilation by inducing phosphoinositide 3-kinase (PI3K)–Akt–nitric oxide synthase

(NOS) pathway (Jimenez et al. 2010) to favor the proresolving effects of PGI_2 in cardio-pulmonary vascular diseases.

Apart from the vascular endothelium, PGIS is also expressed by macrophages. Previous studies in our laboratory demonstrated a biphasic dose response to increasing Se levels in LPS-treated macrophages, where doses up to 100 nM (as selenite) increased the transcript levels of PGIS. However, further addition to Se (above 100 nM) led to drastic transcriptional downregulation (Gandhi et al. 2011). The role of such a biphasic regulation of PGIS by Se on macrophage physiology and function is currently unknown.

1. Regulation of PGI_2 by Se/selenoprotein(s)—Although the regulation of PGI_2 by Se is relatively less well studied, literature is replete with studies demonstrating the role of PGI_2 in the context of atherosclerosis with reference to endothelial cells. Evidence from bovine mammary endothelial cells (BMECs) has shown that Se deficient (0 μg/L, Na_2SeO_3) culture conditions resulted in significantly decreased production of PGI_2 and PGE_2, whereas increased hydroperoxyeicosatetraenoic acid (15-HPETE) was produced compared to Se-adequate (10 μg/L, Na_2SeO_3) treatment (Cao et al. 2000). In another study related to the vascular homeostasis in rats, experimental Se deficiency (0.022 mg/kg diet versus adequate 0.159 mg/kg diet) led to markedly decreased concentration of plasma 6-keto-$PGF_{1\alpha}$, a stable metabolite of PGI_2 (Qu et al. 2000). Thus, it appears that Se status plays a role in the maintenance of vascular system homeostasis by regulating the production of PGI_2 in the endothelium. Although exact mechanisms of regulation of PGI_2 by Se remain unknown, accumulating evidence has provided the following ideas. In atherosclerosis, observational studies revealed an inverse relationship between selenoproteins (GPX1, Txnrd1, SelenoP, and SelenoS) and the development of atherosclerosis. Specifically, *Gpx1* knockout mice on an *ApoE* knockout background ($Gpx1^{-/-}ApoE^{-/-}$ double knockout) accelerated the progression of atherosclerosis compared to control mice (*ApoE* single-knockout) (Torzewski et al. 2007). In another study, ebselen, a synthetic organoselenium GPX1 mimetic and a substrate for Txnrd1, significantly improved the atherosclerotic lesions in the aorta of diabetic *ApoE* knockout mice (Chew et al. 2009). *In vitro* studies also found that GPX1 activity and PGI_2 production were concurrently enhanced in human endothelial cells cultured in Se-containing medium (Na_2SeO_3, 30 or 90 μg/L) (Ricetti et al. 1994). Furthermore, Se deficient endothelial cells stimulated with TNF-α or H_2O_2 produced a much less PGI_2; while Se adequate endothelial cells treated with exogenous lipid hydroperoxide, 15-HPETE, led to decreased expression of PGIS (Weaver et al. 2001). In summary, based on the available data, it appears that Se supplementation-induced expression of GPX1 attenuates the synthesis of 15-HPETE as well as other ROS to derepress PGIS expression leading to substantial increase in PGI_2 and its related anti-atherosclerotic functions within the vascular system.

E. The role of TXA_2 in immunity

TXA_2 and its stable metabolite, TXB_2, are generated from PGH_2 by the enzyme TXS (Neri Serneri et al. 1983). Apart from platelets, macrophages also express TXS and produce TXA_2 (Wetzka et al. 1997). Although it has a very short half-life of 30 seconds at 37 ˚C, TXA_2 is a potent vascular constrictor and platelet activator, which antagonizes the effect of PGI_2. Upon

induction by stimulation such as ischemia-reperfusion in the lungs, TXA_2 can contribute to pulmonary hypertension and bronchoconstriction (Zamora et al. 1993). In IBD (both Crohn's disease and ulcerative colitis) patients, high levels of TXA_2 accumulated in the intestinal epithelia (Zifroni et al. 1983), which might be a therapeutic target for IBD treatment (Taniguchi et al. 1997; Howes et al. 2007). Regarding its involvement in immune disorders, previous studies also identified the contribution of TXA_2 in asthma (Dogne et al. 2002), atopic dermatitis (Tanaka K et al. 2002), and inflammatory tachycardia (Takayama et al. 2005). In the thymus, $CD4^+CD8^+$ immature thymocytes exhibited elevated expression of TXA_2 receptor (TP) as in platelets (Ushikubi et al. 1993). Activation of TP by an agonist (STA2) induced apoptosis in these cells (Ushikubi et al. 1993). Furthermore, the ability of TXA_2 to impair the interaction between DCs and T cells as well as DC-dependent T cell proliferation was reported (Kabashima et al. 2003). Collectively, TXA_2-TP signaling may affect the adaptive immunity by interfering the maturation and activity of T cells.

1. Regulation of TXA_2 by Se/selenoprotein(s)—Studies in pregnancy-induced hypertension (PIH) have suggested a potential link between TXA_2 and Se (Fitzgerald et al. 1990; Han L and Zhou 1994). Clinical studies found that PIH patients had increased TP expression on platelets (Liel et al. 1993). In a *TXS* knockout mouse study, pregnant mice showed decreased hypertension upon *TXS* deletion (Pai et al. 2016). Interestingly, a decreased incidence of PIH upon Se supplementation was seen in pregnant women (Han L and Zhou 1994). Moreover, other research findings correlated Se supplementation with diminished production of TXA_2 (Meydani 1992; Haberland et al. 2001; Arnaud et al. 2007).

Previous studies in our laboratory provided a mechanism mediated by Se and/or selenoproteins on the modulation of pro-inflammatory or anti-inflammatory prostanoids that we termed as "eicosanoid class switching" (Gandhi et al. 2011; Nelson et al. 2011; Diwakar B.T. 2016) (Fig. 4). In both RAW 264.7 macrophage-like cells and primary BMDMs, supplementation with selenite significantly reduced the markers for pro-inflammatory macrophage phenotype (M1) in the presence of LPS stimulation. In IL-4 treated macrophages, Se supplementation upregulated the expression of markers for anti-inflammatory macrophage phenotype (M2) (Nelson et al. 2011). As a result, "eicosanoid class switching" favored the production of D-series PGs (PGD_2 and CyPGs), while inhibiting the production of E-series (PGE_2) and TXA_2 (Gandhi et al. 2011; Kudva et al. 2015). Se supplementation downregulated the expression of TXS-1 and TXA_2 in macrophages (Gandhi et al. 2011) and endothelial cells (Cao et al. 2000). Use of macrophages in which selenoprotein machinery was disrupted led to the conclusion that Sec incorporation in selenoproteins was key in the downregulation of TXS (Gandhi et al. 2011). Much like mPGES-1, NF-κB also serves as a key transcription factor that drives the expression of TXS (Stachowska et al. 2009; He et al. 2013). In LPS-treated macrophages, downregulation of NF-κB by Se supplementation was associated with an increased activation of PPARγ, leading to the attenuation of TXA_2 production (Prabhu et al. 2002; Zamamiri-Davis et al. 2002; Vunta et al. 2008). It is thought that signaling by Se/selenoprotein/NF-κB/PPARγ axis impacts the TXS-mediated regulation of TXA_2 synthesis by Se.

In summary, Se and selenoproteins regulate the production of various PGs through "eicosanoid class switching" where proresolving PGD_2 and downstream CyPGs are increased, while others like PGE_2, PGI_2, and TXA_2 are inhibited (Fig. 4). Previous clinical studies have emphasized the importance of measurement of baseline Se levels in patients, which is a useful guideline for Se intake (Pazirandeh et al. 1999; Hadjibabaie et al. 2008; Khanna et al. 2010; Stevens et al. 2011). However, none of the clinical studies, including the SELECT (Selenium and Vitamin E Cancer Prevention Trial) for prostate cancer, have considered the NSAIDs as a confounding factor to explain if the health benefits of Se supplementation are associated with prostanoids. Further studies are required to associate modulation of PGs as a function of Se in diet, with better biomarkers of Se status (such as SELENOP), to clearly exclude the confounding role of NSAIDs.

Along with prostanoids, hydroperoxy- and hydroxy- metabolites of ARA derived from LOXs and their involvement in inflammation and resolution of inflammation are equally important. Early studies confirmed that Se/selenoproteins also regulated biosynthesis of leukotrienes by inhibiting different LOXs. 5-LOX from rat basophilic leukemia cells was inhibited by GPX1 (Haurand and Flohe 1988) and GPX4 (Weitzel and Wendel 1993); and Se deficiency-induced overproduction of leukotrienes was normalized by restoration of GPX4 (Hatzelmann et al. 1989). Similarly, 5-LOX in B cells was reported to be inhibited by Se/GPX4 (Werz and Steinhilber 1996). Moreover, other LOXs, such as 12-LOX in human platelets (Hill TD et al. 1989) and 15-LOX from rabbit reticulocytes (Schnurr et al. 1996), were also negatively regulated by GPX3 (Jin et al. 2011) and GPX4, respectively. Using a GPX4 knockout mouse model, the regulation of this selenoprotein on the inhibition of 12,15-LOX was confirmed (Seiler et al. 2008). These findings have expanded our understanding of the role of Se/selenoproteins beyond prostanoid metabolism, to include other eicosanoids, such as leukotrienes; for more information, see (Samuelsson et al. 1987; Back et al. 2011; Back et al. 2014).

IV. Se/selenoproteins in Immunity

A. Immune cells

As the first line of defense, innate immune cells possesses immediate protective mechanisms including antimicrobial enzymes and peptides, as well as the complement system, which can target various pathogens for lysis or phagocytosis by phagocytic cells (Murphy and Weaver 2016). Furthermore, additional mechanisms are activated by pathogen-associated molecular patterns (PAMPs) to subsequently induce an inflammatory response by producing chemical mediators, enzymes, chemokines, and cytokines (Murphy and Weaver 2016). Adequate consumption of Se has been demonstrated to be important in the functions of various innate immune cells including granulocytes, monocytes and macrophages, DCs, and natural killer (NK) cells and their functions (McKenzie et al. 1998).

1. Polymorphonuclear (PMN) leukocytes—Granulocytes, also called PMNs, are comprised of neutrophils, eosinophils, basophils, and mast cells. Although PMN leukocytes are all short-lived in circulating blood, they mediate the innate immunity through the production of antimicrobial factors and the participation in the development of inflammation

and the phagocytosis (Havemann and Gramse 1984). PMN leukocytes therefore build up a powerful barrier to defend against pathogens that involves ROS as part of their arsenal. Interestingly, Se and/or selenoproteins have been indicated to play a role in modulating PMN leukocyte functions.

Neutrophils isolated from Se adequate cattle showed a greater ability to kill the ingested intracellular fungi (e.g., *Candida albicans* (Boyne and Arthur 1979)) and bacteria (*Staphylococcus aureus* and *Escherichia coli* (Grasso et al. 1990; Hogan et al. 1990)). However, the phagocytic capacity of neutrophils was reportedly not dependent on Se status (Grasso et al. 1990; Hogan et al. 1990). During phagocytosis, neutrophils generate large amounts of ROS including superoxide and H_2O_2 through NADPH oxidases (NOXs, mainly NOX2), which together induce oxidative burst and have a strong antimicrobial effect (Babior et al. 2002). Antioxidant selenoproteins reduced the respiratory burst cascade by lowering the activity of NOXs (Venardos et al. 2007). On the other hand, excessive levels of ROS can also be detrimental to the neutrophils (Arruda and Barja-Fidalgo 2009). Therefore, to overcome the detrimental effect of ROS during the early (or initiation) phase of inflammation, self-protective mechanisms within the neutrophils are of paramount importance. Human PMNs treated with TNF-α led to increased expression of GPX4 via CCAAT-enhancer-binding protein ε (C/EBPε) through ROS signaling, suggesting that selenoproteins also mediate the self-protection of neutrophils against oxidative damage during activation (Hattori et al. 2005). These results support the notion that Se/selenoproteins may play a key role in neutrophil physiology.

Eosinophils participate in the defense against parasitic and fungal infections in addition to their role in allergy and asthma. GPX activity in eosinophils from asthmatic patients was enhanced indicating that the antioxidant protection against the large amount of ROS may help eosinophils survive (Misso et al. 1998). Given that eosinophils can also produce PGD_2, it will be interesting to examine the exact role of selenoproteins and the impact on eicosanoid class switching mechanisms (Fig. 4) and their role in eosinophil functions, which are currently unknown.

2. Macrophages—Macrophages are not only phagocytes that play a role as the first-line of defense in innate immunity, but also as APCs to present antigen in combination with major histocompatibility complex (MHC) II proteins to their cognate T cell receptors (TCRs) on $CD4^+$ T cells to mediate adaptive immune responses. In addition, macrophages play a pivotal role in supporting efficient erythroid differentiation (Sadahira and Mori 1999; Chow et al. 2013; Liao, Carlson, et al. 2018).

An *in vitro* study on J774.1murine macrophages indicated that Se supplementation increased phagocytosis of macrophages stimulated with LPS, where SelenoK was required for phagocytosis (Safir et al. 2003). Macrophages from *SelenoK* knockout mice were less effective in FcγR-mediated phagocytosis (Norton et al. 2017). On the other hand, overexpression of SelenoK in BV2 microglial cells, which are CNS resident macrophages, increased the phagocytosis through upregulation of inositol trisphosphate (IP3)-Ca^{2+} signaling (Meng et al. 2019). In addition, selenoproteins were shown to regulate macrophage migration as in the case of mice lacking *Trsp* in macrophages, which exhibited a diminished

migration of macrophages (Carlson et al. 2009; Norton et al. 2017; Meng et al. 2019). Recent studies in our laboratory have indicated macrophages lacking selenoproteins poorly support stress-erythroid differentiation during short-term irradiation of the bone marrow or treatment with hemolytic agents (phenylhydrazine) suggesting a pivotal role for selenoproteins (Liao, Hardison, et al. 2018). Monocyte-derived macrophages form a rosette structure, termed as erythroblastic islands, in physical association with erythroid cells in an effort to provide nutrients, including key signaling molecules such as heme, supporting the notion that macrophages act as nursing cells. Our studies indicated that during Se deficiency in murine models, these rosette structures were poorly organized that, in part, led to poor recovery during stress-erythropoiesis (Liao, Hardison, et al. 2018). Current studies are focused on elucidating the underlying mechanisms and the role of specific selenoproteins in regulating these functions.

Macrophages partake important roles in both the inflammatory and resolution phases of an infection by differentiating into two contrasting phenotypes, the pro-inflammatory M1 macrophage (also termed as classically-activated macrophage) and anti-inflammatory M2 macrophage (or alternatively-activated macrophage) that represent two ends of the spectrum with several intermediate stages that are poorly defined with regard to their pathophysiological roles. M1 macrophages are formed upon the stimulation by IFN-γ secreted from type 1 innate lymphoid cells (ILC1) or NK cells and are involved in type 1 immune response (Barros et al. 2013). On the other hand, M2 macrophages are induced by IL-4, IL-13, or IL-10 produced by mast cells, eosinophils, neutrophils, and other Th2 cells and is linked to a type 2 immune response (Barros et al. 2013). Currently, this dichotomy is challenged by two paradigms: First, *in vitro* studies overlook the complexity and combined effects of various stimuli, which are important *in vivo*, making it difficult to apply the *in vitro* results to *in vivo* situations. Second, the disparities within macrophage activation and disease progression in humans and mice pose a problem when translating the results from murine experiments to humans since the markers used to define M1 and M2 polarization vary between mouse and human (Martinez and Gordon 2014). Instead the commonly used mouse proteins Ym1, Fizz1, and arginase-1 that have no homologs in human, use of conserved markers such as transglutaminase-2 (TGM2), mannose receptor C type 1 (MRC1/CD206), and CD68 antibodies may help in translation. However, this classification is still valuable for providing basic understanding of the mechanisms in the context of inflammation and resolution.

Previously, we discussed that Se mediated the phenotypic switching from M1 to M2 during inflammation associated with sterile or parasitic infection. Se supplementation significantly attenuated the phenotypic markers for M1 in the presence of LPS stimulation, while upregulating M2 markers, which increased further following IL-4 stimulation or during helminth infection (Nelson et al. 2016; Shay et al. 2017). Studies with various pharmacological inhibitors to inhibit CyPGs in Se-supplemented mice or administration of CyPGs to Se-deficient mice suggested that such an effect was a result of “eicosanoid class switching” as described earlier (Fig. 4). The key question that remains to be answered is the identity of specific selenoproteins that aid in macrophage polarization. Based on the literature, it is believed that selenoproteins GPXs (Nelson et al. 2011), SelenoP (Bosschaerts et al. 2008), and methionine sulfoxide reductase B1 (MsrB1) (Lee et al. 2017), may

represent a growing list of candidate selenoproteins that display a potential in regulating the polarization of macrophages.

3. T cells and B cells—Mounting evidence has shown that *in vivo* Se levels may modulate the proliferation and differentiation of T cells. In a study using porcine splenocytes, Se was reported to promote TCR activation-induced T cell proliferation in association with increased mRNA expression of GPX1 and Txnrd1 (Ren et al. 2012). T cells from mice fed high Se diet (1.0 mg/kg) had a much higher proliferation rate than those from Se low (0.08 mg/kg) and medium (0.25 mg/kg) diets (Hoffmann FW et al. 2010). An *in vivo* study using athymic, immune-deficient NU/J nude mice showed that $CD4^+$ T cells were increased in Se-sufficient mice (1.0 mg/kg) compared to mice on Se-deficient (0 mg/kg) or Se-adequate (0.15 mg/kg) diets (Cheng et al. 2012). Furthermore, higher Se levels increased free thiols in activated $CD4^+$ T cells, which likely played an important role in the clonal expansion of these cells by favoring the TCR-induced oxidative burst in cells (Hoffmann FW et al. 2010). Interestingly, some selenoproteins including Gpx1, Txnrd1, and other antioxidant proteins in the same cells showed high enzymatic activity implying a potential protective mechanism to counter the high demand for ROS and the need to mitigate possible damage by ROS (Hoffmann FW et al. 2010).

In addition to the effect on T cell proliferation, Se was also reported to modulate T cell differentiation. Studies by the Hoffmann laboratory showed that high Se diet (1.0 mg/kg) induced a biased differentiation of $CD4^+$ T cells toward Th1 immunity with a high level of IFN-γ (Hoffmann FW et al. 2010). Similarly, mice fed Se-nanoparticles exhibited an enhanced Th1 response after Hepatitis B virus (HBV) vaccination (Mahdavi et al. 2017). *Trsp* deletion in T cells showed atrophy of thymus and exhibited decreased numbers of mature T cells along with hyperproduction of ROS (Shrimali et al. 2007; Shrimali et al. 2008) and attenuated TCR signaling (Shrimali et al. 2007). This suggests that selenoproteins regulate T cell immunity, in part, by scavenging excess ROS.

B cell-mediated humoral immunity is dependent on the formation of various antibodies. Naïve B cells can be activated by antigens in two ways: thymus-independent or thymus-dependent, where the latter derives help from T_{FH} cells, which are already activated by the same antigens (Murphy and Weaver 2016). These antibodies can exert their functions by binding to pathogens and prevent their entry into cells or indirectly activate complement system to effect killing by phagocytes.

Several reports have suggested that Se levels might regulate the function of B cells. Mice fed Se-deficient (0 mg/kg) or Se-high (1.0 mg/kg) diets showed decreased numbers of peripheral B cells (Cheng et al. 2012). Similar trends were seen in SeMet-treated mice where mice on low (0.02 ppm) and above-adequate (2 ppm) diets had reduced B cell numbers in the spleen (Vega et al. 2007). On the contrary, a small human study where dietary Se intake showed increased B lymphocyte numbers in a time-dependent manner. B cells in the Se supplemented group were only increased at day 45, but returned to levels as in Se low group at day 100 (Hawkes et al. 2001). A clinical trial showed that subjects consuming Se at 50 or 100 μg/day for 15 weeks had an improved anti-viral immunity; however, titration of antibodies against poliovirus was unchanged by Se intake (Broome et al. 2004). In contrast,

other research also identified enhanced antibody response against diphtheria vaccine upon Se supplementation (Hawkes et al. 2001). It is unclear whether Se regulates antibody formation depending on the type of infection. More recently, researchers found that splenic B cells from $Sep15^{-/-}$ mice synthesized increased IgM *in vitro* upon LPS stimulation, although *in vivo* and *in vitro* clearance of bacterial infection was not changed (Yim et al. 2018). Still, limited information regarding the role of Se in B cells warrants further studies.

B. Immune responses

1. Bacterial infection—Se deficiency is often associated with bacterial infections. For instance, Se status is implicated in the progression of tuberculosis in patients infected with *Mycobacterium tuberculosis* (Grobler et al. 2016). Particularly, patients with pulmonary tuberculosis showed decreased Se levels compared to normal subjects (Ramakrishnan et al. 2012). Dietary supplementation with Se was reported to reduce the mortality in tuberculosis patients concomitantly infected with human immunodeficiency virus (HIV) (Range et al. 2006). Another study also found that Se supplementation could attenuate oxidative stress in tuberculosis patients receiving chemotherapy, which might be helpful for protecting host cells from excess ROS (Seyedrezazadeh et al. 2008). Other than *Mycobacterium tuberculosis*, Se may also play a role in the defense against other bacterial infections such as *Helicobacter pylori* (Ustundag et al. 2001), *Dichelobacter nodosus* (Hall et al. 2013), and *Listeria monocytogenes* (Wang C et al. 2009).

Interestingly, in a mouse model of Se and vitamin E deficiency, mice infected with *Citrobacter rodentium* showed significantly higher bacterial burden in mice maintained on diets devoid of Se and vitamin E than mice on nutritionally adequate diets. Se- and vitamin E-deficient mice also had upregulated expression of pro-inflammatory cytokines such as Il-6, Il-17, Il-22, Tnf-α, and Ifn-γ in addition to decreased expression of Gpx1 (Smith AD et al. 2011). Although it is possible that the anti-bacterial effect is exerted by a combination of Se and vitamin E, the alteration of Gpx1 suggests the beneficial role of Se, which is currently being investigated in our laboratory and will be reported in the near future.

2. Viral infection—Se levels are closely related to viral infections, as exemplified by Keshan disease, which is caused by the deficiency of dietary Se (Chen et al. 1980). Coxsackie B viruses (CVB), as a preeminent etiology of human acute myocarditis and a common cause of dilated cardiomyopathy are present in cardiomyocytes in patients with Keshan disease (Levander and Beck 1997). Supplementation of dietary Se eliminated the infection of CVB and effectively treated Keshan disease (Cermelli et al. 2002). *Gpx1* knockout mice infected with CVB3 developed a disease resembling Keshan disease, whereas mice expressing normal Gpx1= could not be induced to develop any myocarditis by CVB3 infection (Beck et al. 1998). The protective effect of Gpx1 was speculated to modulate the viral genome via the incorporation of Se into viral GPX and that the viral GPX could lead to the transformation of a pathogenic phenotype to a mutant nonpathogenic phenotype (Zhang W et al. 1999). Another mitochondrial selenoprotein, Txnrd2, was suggested to play an important role in the development of Keshan disease. Cardiac specific ablation of Txnrd2 expression led to a dysfunction in the heart that was reminiscent of the cardiac abnormality in Keshan disease (Hara et al. 2001). As an antioxidant factor expressed in mitochondria,

Txnrd2 is responsible for scavenging excess ROS (Chen C et al. 2017). Thus, disturbance of mitochondrial function due to the lack of Txnrd2 led to exacerbated oxidative stress, which may cause damage to heart (Rohrbach et al. 2006; Stanley et al. 2011). Whether Txnrd2 protects myocardium from CVB infection and if CVB infection affects the expression of Txnrd2 are important questions that should be further studied. In addition to CVB, HIV/AIDS is another disease where a strong inverse association with Se has been established in preclinical and clinical studies.

AIDS is caused by the infection of HIV and characterized by a progressive disease latency accompanied by gradual loss of $CD4^+$ T cells. Previous findings have associated Se deficiency with accelerated disease progression (Bologna et al. 1994; Baum and Shor-Posner 1997; Campa et al. 1999). For example, HIV-1-seropositive subjects were reported to present low levels of zinc, Se, vitamin A, and vitamin B_{12}. However, Se was the only predictor significantly associated with mortality. Se-deficient and Se-adequate participants had an overall survival of 31.4 months and 57.4 months, respectively (Baum 2000). As in Keshan disease, manifestations of cardiomyopathy were also reported in HIV/AIDS patients (Kavanaugh-McHugh et al. 1991). Interestingly, Se supplementation improved the general health of these patients, including cardiac function (Kavanaugh-McHugh et al. 1991). These findings suggest that Se supplementation may be a candidate for adjunct therapy in HIV/AIDS.

Clinical trials were carried out to identify the potential effects of Se supplementation on HIV disease progression. An early study showed that patients taking 100 μg/day of Se for one year had better outcomes in terms of decreased hospitalizations (Burbano et al. 2002). In another cohort that analyzed 450 HIV-1^+ patients taking Se yeast 200 μg/day for 9 months, Se was found to reduce the viral burden and improve $CD4^+$ cell counts (Hurwitz et al. 2007). However, in a randomized double-blinded trial of supplementation with different nutrient combinations (multivitamin, Se, multivitamin + Se, placebo), a significant improvement of $CD4^+$ cell counts was only observed in multivitamin + Se group (Baum et al. 2013). Still, these data support a beneficial role of Se supplementation in HIV spectrum disease with a caveat of its coadministration in combination with other anti-viral drugs. *In-vitro* studies by Kalantari *et al* (2008) showed Se supplementation in the form of selenite (100 nM) reduced pro-viral transcription in human macrophages. This effect was dependent, in part, on the redox modulation of HIV-1 Tat (transactivating protein) by Txnrd1. Furthermore, the reduction of disulfides in Tat by Txnrd1 appeared to increase the covalent interaction of electrophiles, such as 15d-PGJ_2, with Cys-SH group in Tat thus limiting the reoxidation of Cys-SH as well as ensuring sustained inhibition of Tat-dependent transcription activity (Kalantari et al. 2008; Kalantari et al. 2009). These encouraging preclinical studies provide a strong rationale to revisit the role of Se in HIV/AIDS with an emphasis on new mechanisms in patient derived cells harboring the virus and if NSAIDs interfere in the biological activity of Se.

1. Parasitic infection—The role of Se and/or selenoproteins in parasitic infections have also been examined. Compelling data have shown that antioxidant-dependent properties of Se may induce the resistance to parasitic infection by *Trypanosoma* (Smith A et al. 2005). In a mouse model of *Trypanosoma cruzi* infection, 3 ppm of dietary Se alleviated intestinal

megasyndromes (de Souza et al. 2010). In addition, Se deficiency was also linked to megasyndromes in clinical patients (Jelicks et al. 2011). *Trypanosoma cruzi* infection causes Chagas disease, a progressive cardiomyopathy. Literature is replete with studies demonstrating low Se levels are associated with the increased severity of Chagas disease (de Souza et al. 2002; Gomez et al. 2002; Rivera et al. 2002). Furthermore, supplementation of Se from 2 ppm to 16 ppm was shown to play a beneficial role in the resolution of Chagas disease in mice (Davis et al. 1998; de Souza et al. 2003; de Souza et al. 2010; Souza et al. 2010). It is well-established that oxidative burst contributes to disease progression in Chagasic patients (Wen et al. 2006; de Oliveira et al. 2007) and such an excess of oxidative stress is associated with decline in mitochondrial functional (Wen et al. 2006). High doses of Se exhibited a preventive effect of mitochondrial dysfunction in Chagas disease (Tirosh and Reifen 2007; Pineyro et al. 2008).

Previously, our laboratory reported the role of Se and selenoproteins in a helminthic parasitic infection caused by *Nippostrongylus brasiliensis* (Nelson et al. 2016). Mice on Se-adequate diet (0.08 ppm) showed a significantly enhanced adult worm clearance compared to those on a Se-deficient diet (<0.01 ppm). This was associated with a phenotypic switching of macrophages from a pro-inflammatory M1 towards an anti-inflammatory M2 phenotype in the jejunum. Furthermore, use of $Trsp^{fl/fl}Cre^{LysM}$ mice that lack selenoproteins in monocytes and macrophages indicated that despite the presence of a higher level of Se in the diet (Se-supplemented: 0.4 ppm), there were more adult worms in $Trsp^{fl/fl}Cre^{LysM}$ mice compared to the infected WT control mice (Nelson et al. 2016). This implies that incorporation of Se into selenoproteins is indispensable for the parasite clearance activities of macrophages. As mentioned above, phenotypic switching of macrophages was accompanied by “eicosanoid class switching” favoring the production of CyPGs (Fig. 4). Use of indomethacin, a COX inhibitor, clearly showed the interaction between Se and eicosanoids during infection. Interestingly, inhibition of COX activity worsened the outcome of infection in these mice. However, treatment of mice with 15d-PGJ_2 protected the mice that lacked endogenous eicosanoids following indomethacin treatment. Thus, Se-dependent CyPG production and the consequent induction of M2 macrophages was critical in the mediation of the anti-parasitic function of Se (Nelson et al. 2016). In addition to innate immune responses, it appears that adaptive immune mechanisms mediated by T effector cells are also involved in the elimination of *Nippostrongylus brasiliensis* mediated by Se. Enhanced production of Th2 signature cytokines (*e.g.*, IL-13) and increased amounts of IL-4 producing T cells indicated that Th2 immune response might also play a role here (Nelson et al. 2016). However, further studies are required to explain how selenoproteins regulate the Th2 immune response during such infections.

2. Cancer immunity—The interaction between cancer cells and the immune system is well recognized. The origin of this interaction stems from the “cancer immunoediting” theory, which divides the process of tumor growth into three phases: elimination, equilibrium, and escape (Mittal et al. 2014). Immune cells recognize and try to destroy initial tumor cells in the elimination phase; however, if such an anti-tumor activity fails, tumor cells and immune system tend to establish an equilibrium where tumor cells gain

more mutations to aid in their survival. In the escape phase, tumor cells escape the immune surveillance and avoid being targeted by the immune system.

$CD8^+$ cytotoxic T cells are thus far considered as a key element of anti-tumor immunity. These cells attack tumor cells presenting peptide:MHC I complex and induce their apoptosis. Studies showed that Se supplementation might enhance the proliferation and differentiation of cytotoxic T cells (Petrie et al. 1989). This effect was likely mediated by the increased levels of IL-2 and IFN-γ in tumor microenvironment (TME) (Farrar et al. 1981; Kern et al. 1981; Knuth et al. 1984; Roy et al. 1993). Besides, the presence of Th1 cells was also correlated with a better prognosis in tumors (Haabeth et al. 2011; Fridman et al. 2012). As mentioned above, Se supplementation causes skewing of $CD4^+$ T cells differentiation towards Th1 effector cells (Hoffmann FW et al. 2010; Mahdavi et al. 2017). Furthermore, under certain circumstances, Se showed positive anti-tumor effects through the induction of a Th1 immune response (Yazdi et al. 2012; Yazdi et al. 2015).

However, tumor cells also succeed in circumventing the killing by cytotoxic T cells by downregulating MHC I molecules (Leone et al. 2013). Such an adaptive change of MHC I can trigger the targeting by NK cells through “missing-self” recognition (Karre 2002). Interestingly, Se was reported to facilitate anti-tumor function of NK cells by enhancing IL-2/IL-2R interaction (Kiremidjian-Schumacher L. et al. 1996; Enqvist et al. 2011). Unfortunately, it is still unclear which selenoprotein(s) in NK cells regulate this function or whether cellular niche that responds to Se activates the NK cells to cause such an effect.

Abundant experimental evidence has identified tumor-associated macrophages (TAMs) as M2-like phenotype that supports tumor progression and metastasis (Sica and Mantovani 2012). Macrophage reprogramming from M2 phenotype to M1 phenotype contributes to enhancing the efficacy of cancer drugs and suppressing tumor growth (Larionova et al. 2019). Interestingly, numerous studies confirmed that Se could shift M2 to M1 in various cancers to effectively retard tumor progression (Kiremidjian-Schumacher L et al. 1991; Mao et al. 2016; Gautam et al. 2017). It is also believed that enhanced differentiation of Th1 cells is responsible to secrete polarizing cytokines for M1 macrophages (Barros et al. 2013). Compared to the macrophage phenotypic switching induced by Se supplementation mentioned above, these studies suggest that Se might affect macrophages in a tumor context differently from those in inflammatory scenarios leading to a broader question regarding the diversity of signals and/or cells within inflammatory networks.

Studies in our laboratory on the role of Se in myeloid leukemias have suggested the interaction of the immune system with cancer stem cells. Acute myeloid leukemia (AML) represents a malignant disorder that is characterized by infiltration of abnormally proliferated hematopoietic stem and progenitor cells in bone marrow, peripheral blood, and occasionally other tissues (Sabattini et al. 2010). As in many other hematologic malignancies, AML has a high relapse rate following current induction therapies, where initial remission rates after induction therapy decline from 90%, 70%, 60%, to 40% in pediatric, young, middle-aged, and older patients, respectively (Prchal and Levi 2010). Such a poor prognosis is due to the ability of proliferation and differentiation of leukemia stem cells (LSCs), where patients tend to relapse leading to minimal residual disease (MRD) (van

Rhenen et al. 2005). Despite the poor prognosis, we have achieved exciting developments in the insight into the cytogenetic and molecular heterogeneity of AML, even though most of the novel therapies have failed to effectively bring about overall and long-term survival benefit.

In 1956, Se was reported to be effective to treat leukemia where leukemic patients (two AML and two CML) had improved leukocytosis and a decreased spleen size after administration of Se cystine (Weisberger and Suhrland 1956). Since then, various studies have demonstrated anti-leukemic effect of different forms of Se using *in vitro* and *in vivo* model systems (Batist et al. 1986; Li J et al. 2003; Philchenkov et al. 2007). Taking cues from our previous research that has indicated the ability of Se at supraphysiological levels to inhibit the viability of CML LSCs (Gandhi et al. 2014) involving the endogenous CyPGs as well as the eicosanoid class switching paradigms (Finch et al. 2017), we have embarked on targeting the self-renewing and drug resistant LSCs that are responsible for the post-remission relapse of AML to achieve the eradication of LSCs as our goal to treat AML using new paradigms. In support of the role of Se therapy in AML, several studies have reported significantly decreased serum levels of Se were observed in patients with AML, CML, acute lymphoblastic leukemia (ALL), and acute nonlymphocytic leukemia (ANLL) (Pazirandeh et al. 1999; Hadjibabaie et al. 2008; Khanna et al. 2010; Stevens et al. 2011). These observations imply an inverse causality between serum levels of Se and the progression of hematopoietic malignancies.

Despite this, further research is required to understand if Se supplementation is beneficial in leukemia patients given the role of selenoprotein, GPX4-induced ferroptosis in the context of leukemias. Ferroptosis is a unique type of iron-dependent programmed cell death driven by the accumulated lipid peroxides (Yang and Stockwell 2016). Blocking the activity of GPX4 or inhibiting GSH can induce ferroptosis (Yang et al. 2014). Besides, Se utilization by GPX4 is critical for the inactivation of GPX4 by ferroptosis inducers (Ingold et al. 2018). Ferroptosis inducers inactivate GPX4 by covalently modifying the active site selenocysteine (Yang et al. 2016). This distinct cell death involving the inhibition of GPX4 has been demonstrated to be a candidate mechanism for leukemia treatment. In ALL, inhibition of GPX4 by RSL3 triggered the production of ROS and led to ferroptosis. GPX4 inhibited LOXs, while inhibitors of LOXs reversed the cell death induced by GPX4 in ALL cells further lending credence to the idea that GPX4-regulation of LOXs prevents ferroptosis as a result to protect ALL cells from cell death (Probst et al. 2017). In AML, Erastin, a ferroptosis inducer, also induced ferroptosis in AML cell line, HL-60 cells and enhanced the sensitivity of these cells to chemotherapy (Yu et al. 2015). However, it will be interesting to see if a similar mechanism is functional in a primary cell system involving AML LSCs.

Compared to the anti-tumor effect of Th1 cells, Th2 cells are generally regarded as tumor-promoting cells (Fridman 2012; Fridman et al. 2012). However, in the context of hematologic cancers, this could challenge the existing paradigm. In high-risk ALL, IL-4, a signature cytokine for Th2 immunity, was able to induce apoptosis of leukemia cells (Manabe et al. 1994). Similar results were corroborated from an *in vitro* study on B cell ALL (Manabe et al. 1994). In children with M5-AML, IL-4 was reported to inhibit the proliferation of leukemia cells (McKenna et al. 1996). To gain the insight of the anti-tumor

role of Th2 immune response in leukemias, further studies are essential. AML leukemia blasts-induced T cell anergy may be a potential explanation where the effect of IL-4 treatment may be less severe than a full-blown Th2-mediated immune response (Narita et al. 2001). The profound effect of Se on IL-4-induced M2 macrophages has been reported in our laboratory which may also reflect Se's role in Th2-M2 immune response (Shay et al. 2017). More studies are required to address the role of Se and Th2 immunity in cancers, particularly hematologic malignancies.

3. **Allergic asthma—**Asthma is a common inflammatory disease affecting the respiratory system where both innate and adaptive immune mechanisms are involved. Its pathobiological mechanisms include AHR, excess mucus secretion, and reversible narrowing and obstruction of airways (Maddox and Schwartz 2002). Compared to nonallergic (idiopathic) asthma, allergic asthma is more often discussed in the context of immunology as the concomitant presence of humoral immune (high serum IgE) and cell-mediated immune (increased Th2 cells and related cytokines) responses (Grove et al. 1975).

Interestingly, oxidative stress has been identified as an important contributor to the pathogenesis of allergic asthma (Riedl and Nel 2008). Several epidemiological analyses provided the association between asthma and Se status. Literature is replete with studies that have shown low Se levels to be negatively associated with lung function and positively correlated with the severity of asthma (Omland et al. 2002; de Luis et al. 2003; Qujeq et al. 2003; Guo et al. 2011). Furthermore, serum Se levels as well as GPX expression were decreased in asthmatic adults (Guo et al. 2011) and children (Kocyigit et al. 2004). However, other studies have indicated no association between Se and asthma (Ford et al. 2004). In several studies, high Se levels and GPX activity were thought to exacerbate the condition of asthma leading to the notion of a "U" shaped relationship that remains to be clearly established (Dunstan et al. 2006; Garcia-Larsen et al. 2007). In addition, a few interventional studies were carried out by supplementing asthmatics with dietary Se; however, due to the differences of formulation, duration, dosage of Se used, it is impossible to derive any conclusions regarding the benefits of Se intake in these settings (Dunstan et al. 2007; Shaheen et al. 2007).

Studies with an allergic asthma model (with OVA challenge in OT-1 and OT-2 mice) suggested that mice fed 0.25 ppm Se diet had the more severe asthma than mice on diet with 2.7 ppm Se (Hoffmann PR et al. 2007). High Se (2.7 ppm) level was reported to mediate the skewing of Th0 cells towards Th1 and Treg differentiation away from Th2 differentiation (Hoffmann PR et al. 2007). Given that Th2 phenotype is a hallmark feature of asthma, this differentiational switching of Th cells is recognized as a major mechanism that provides some rationale to suggest the benefit of high Se in asthma. Furthermore, *Gpx1* knockout mice failed to develop allergic asthma when challenged with OVA (Won et al. 2010); while disruption of *Gpx2* exhibited a protective role in a murine asthma model (Dittrich et al. 2010). It is still unclear why these two GPXs have opposing effects in asthma. Future studies are needed in order to understand the functions of selenoproteins in asthma.

V. Summary

Optimal Se status is critically important for health/physiological homeostasis. It is very clear that perturbation of Se levels may result in severe consequences on human health. But the concept of dietary supplementation needs to be optimized taking into account the baseline levels of Se as defined by better biomarkers that are more informative than plasma or serum Se. Studies from many laboratories, including ours, have suggested a strong-link between Se, selenoproteins, and novel bioactive lipid mediators, in the form of CyPGs, which clearly impacts inflammation and pro-resolution pathways at various levels in a multicellular network consisting of various immune cells. However, time seems propitious to make a translational leap where this mechanism is put to its final test in well controlled studies. This is particularly true since many of the clinical trials with Se supplementation performed to date, including the SELECT for prostate cancer (Lippman et al. 2009; Klein et al. 2011), did not exclude the use of NSAIDs suggesting a possible interference in the ability of bioactive and proresolving lipid mediators to effect resolution of inflammation. Such studies will ultimately give us a better appreciation of the role of this unique trace element in pathology and therapy.

Acknowledgements

This work was supported, in part, by grants from the National Institutes of Health R01 DK077152, Office of Dietary Supplements, R01 CA162665, USDA-NIFA Hatch project number 4605; Accession # 1010021, American Institute for Cancer Research (K.S.P). We thank Shaneice Nettleford and Tai-Jung Lee for their timely help and suggestions.

Abbreviations used:

AHR	airway hyperresponsiveness
AIDS	acquired immunodeficiency syndrome
AKR1B1	Aldo-keto reductase family 1, member B1
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANLL	acute nonlymphocytic leukemia
APC	antigen-presenting cell
ARA	arachidonic acid
BMDM	bone marrow-derived macrophage
BMEC	bovine mammary endothelial cell
cAMP	3’, 5’-cyclic adenosine monophosphate
CAR	chimeric antigen receptor
C/EBP	CCAAT-enhancer-binding protein

CML	chronic myeloid leukemia
CNS	central neuron system
COX	cyclooxygenase
cPGES	cytosolic PGES
CRE	cAMP response element
Crth2	chemoattractant receptor-homologous molecule expressed on Th2 cells
CVB	coxsackie B virus
CyPG	cyclopentenone PG
Cys	cysteine
DC	dendritic cell
DHA	docosahexaenoic acid
DP2	PGD_2 receptor 2
15d-PGJ$_2$	15-deoxy-$\Delta^{12,14}$-prostaglandin J_2
DSS	dextran sodium sulfate
EFSec	Sec-specific elongation factor
EPA	eicosapentaenoic acid
ER	endoplasmic reticulum
ERAD	ER-associated degradation
Erk	extracellular-signal-regulated kinase
GI	gastrointestinal
GPCR	G-protein coupled receptor
GPX	glutathione peroxidase
GSH	glutathione
GST	glutathione S-transferase
HBV	Hepatitis B virus
HDM	house dust mite
HIV	human immunodeficiency virus
H_2O_2	hydrogen peroxide

15-HPETE	hydroperoxyeicosatetraenoic acid
H-PGDS	hematopoietic PGDS
HSe^-	selenide
$H_2SePO_3^-$	selenophosphate
IBD	inflammatory bowel disease
IFN	interferon
Ig	immunoglobulin
IKK	IκB kinase
IL	interleukin
ILC	innate lymphoid cell
IP3	inositol trisphosphate
IRAK	IL-1 receptor-activated kinase
JNK	c-Jun N-terminal kinase
KBD	Kashin–Beck disease
LOX	lipoxygenase
L-PGDS	lipocalin-type PGDS
LPS	lipopolysaccharide
LSC	leukemia stem cell
mAb	monoclonal antibody
MAIT	mucosal associated invariant T cell
MAPK	mitogen-activated protein kinase
MDSC	myeloid derived suppressor cell
MHC	major histocompatibility complex
mPGES	microsomal PGES
MRD	minimal residual disease
MsrB1	methionine sulfoxide reductase B1
MyD88	myeloid differentiation factor 88
NAD	nicotinamide adenine dinucleotide
Na_2SeO_3	sodium selenite

NF	nuclear factor
NK	Natural killer
NOS	nitric oxide synthase
NOX	NADPH oxidase
NF-E2	nuclear factor erythroid 2
Nrf2	NF-E2-related factor 2
NSAIDs	non-steroidal anti-inflammatory drugs
O	oxygen
OA	osteoarthritis
OVA	ovalbumin
PAH	pulmonary arterial hypertension
PAMP	pathogen-associated molecular pattern
PBMC	peripheral blood mononuclear cell
PD-1	programmed death 1
PG	prostaglandin
15-PGDH	15-hydroxyprostaglandin dehydrogenase
PG	prostaglandin
PGDS	PGD synthase
PGES	PGE synthase
PGI_2	prostacyclin
PGIS	PGI synthase
PHGPX	phospholipid hydroperoxide GPX
PIH	pregnancy-induced hypertension
PI3K	phosphoinositide 3-kinase
PLA_2	phospholipase A2
PMN	polymorphonuclear
Po	polonium
PPARγ	peroxisome proliferator-activated receptor gamma
PPRE	PPAR-response element

PSTK	phosphoseryl-tRNA kinase
Ptgs	prostaglandin-endoperoxide synthase
PUFA	polyunsaturated fatty acid
RA	rheumatoid arthritis
ROS	reactive oxygen species
RvE1	resolvin E1
S	sulfur
SBP2	SECIS binding protein 2
Se	selenium
Sec	selenocysteine
SECIS	Sec insertion sequence
SELECT	Selenium and Vitamin E Cancer Prevention
SelenoK	selenoprotein K
SelenoP	selenoprotein P
SelenoS	selenoprotein S
SeMet	selenomethionine
SEPP1	selenoprotein P
SerS	seryl-tRNA synthase
SPM	specialized proresolving mediator
SPS2	selenophosphate sythetase-2
STAT6	Signal Transducer And Activator Of Transcription 6
TAB	TAK1-binding protein
TAK1	TGFβ-activated kinase 1
TCR	T cell receptor
Te	tellurium
T_{FH}	follicular T helper
TGFβ	transforming growth factor β
Th	T helper
TLR4	toll-like-receptor 4

TME	tumor microenvironment
TNF	tumor necrosis factor
TRAF6	TNF receptor-associated factor 6
Treg	regulatory T cell
Trsp	Sec-tRNA$^{[Ser]Sec}$ gene
TX	thromboxane
Txnrd1	thioredoxin reductase-1
TXS	TX synthase
3'-UTR	3'-untranslated region
WT	wild type

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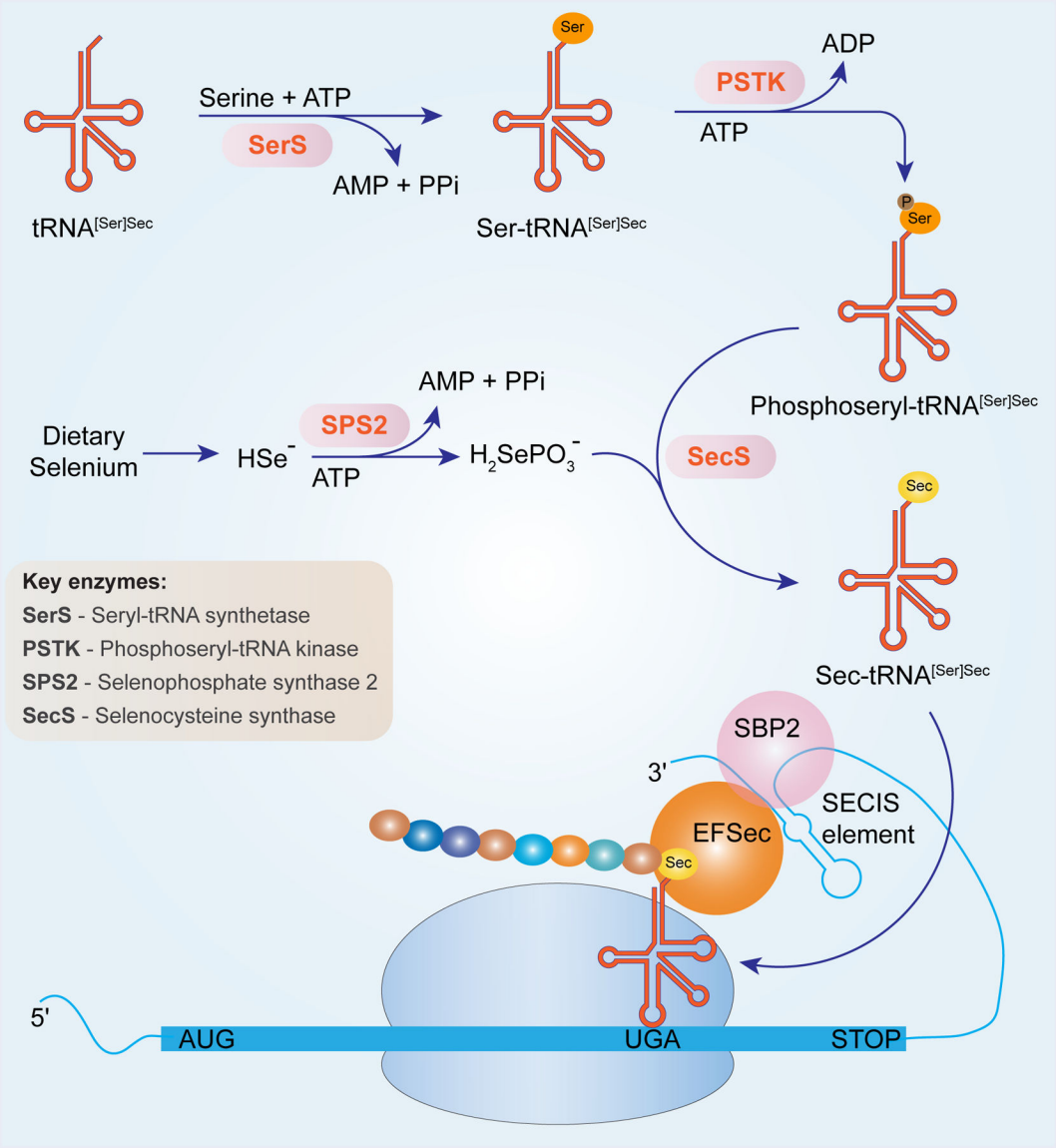

Figure 1. Sec formation and incorporation into selenoproteins.

Dietary Se including selenite and selenate is converted to selenide (HSe^-). The generation of selenophosphate ($H_2SePO_3^-$) is catalyzed by SPS2 from selenide and ATP. Selenophosphate is charged on to $tRNA^{[Ser]Sec}$ by seryl-tRNA synthase (SerS). Phosphorylation of seryl-$tRNA^{[Ser]Sec}$ by phosphoseryl-tRNA kinase (PSTK) forms an intermediate, phosphoseryl-$tRNA^{[Ser]Sec}$, which accepts selenophosphate to phosphoseryl-$tRNA^{[Ser]Sec}$ to generate Sec-$tRNA^{[Ser]Sec}$. When SECIS is present in the 3'-UTR of mRNA, Sec incorporation is efficiently carried out by decoding UGA. Several factors such as SBP2, EFSec are also recruited to aid in the translation process.

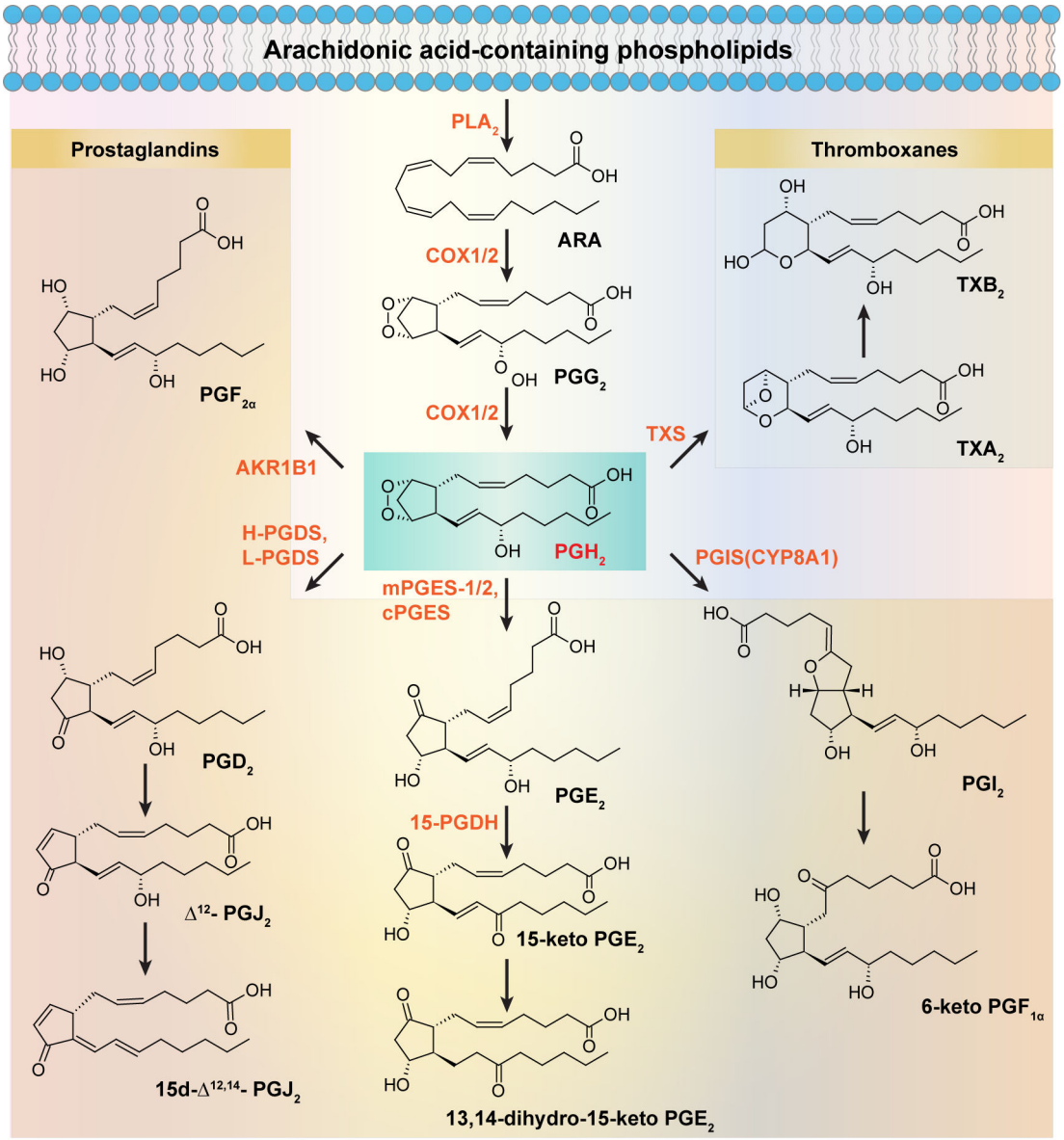

Figure 2. Pathways of prostaglandin metabolism.

Upon stimulation, phospholipids in the plasma membrane are acted upon by PLA_2 to release ARA, which is further converted to PGG_2/PGH_2 by COX1/2. PGH_2 is the common precursor for D-series (PGD_2, Δ^{13}-PGJ_2, Δ^{12}-PGJ_2, 15d-PGJ_2), E-series (PGE_2), prostacyclin (PGI_2), $PGF_{2\alpha}$, and TXs (TXA_2, TXB_2) that is catalyzed by specific synthases.

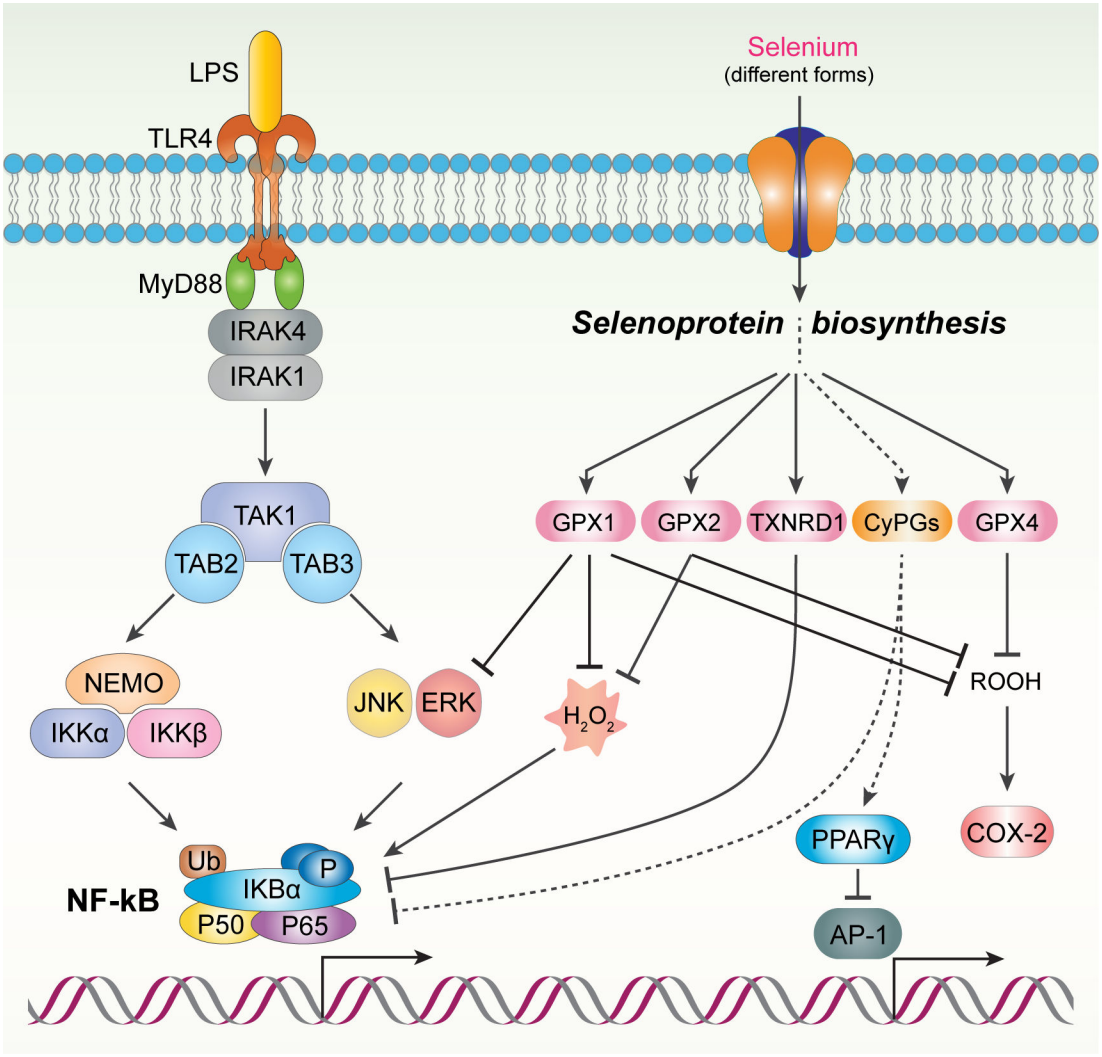

Figure 3. Regulation of COX-2 expression by Se/selenoproteins summarized from different cells.

In LPS-stimulated macrophages, LPS binds TLR4 and recruits MyD88, IRAK4, IRAK1, TRAF6. TRAF6 induces the activation of TAK1–3 which phosphorylates IKK leading to the degradation of IκB. As a result, NF-κB binds to the promoter region of COX-2 and induces the transcription of COX-2. In the presence of Se, GPX1 inhibits two MAPK (JNK and Erk) which can mediate the dissociation of IκB from NF-κB. In human breat T47D cell line, overexpression of GPX2 inhibits oxidative stress and IκB transactivation and NF-κB activation. In Hela cells, Txnrd1 inhibits NF-κB via mechanisms involving the phosphorylation of p65 in NF-κB. In CaSki cells, 15d-PGJ_2 inhibits the binding affinity of AP-1 to CRE in the promoter region of COX-2 through PPARγ which downregulates the expression of COX-2. Additionally, 15d-PGJ_2 can directly bind NF-κB and inactivate it which leads to the downregulation of COX-2.

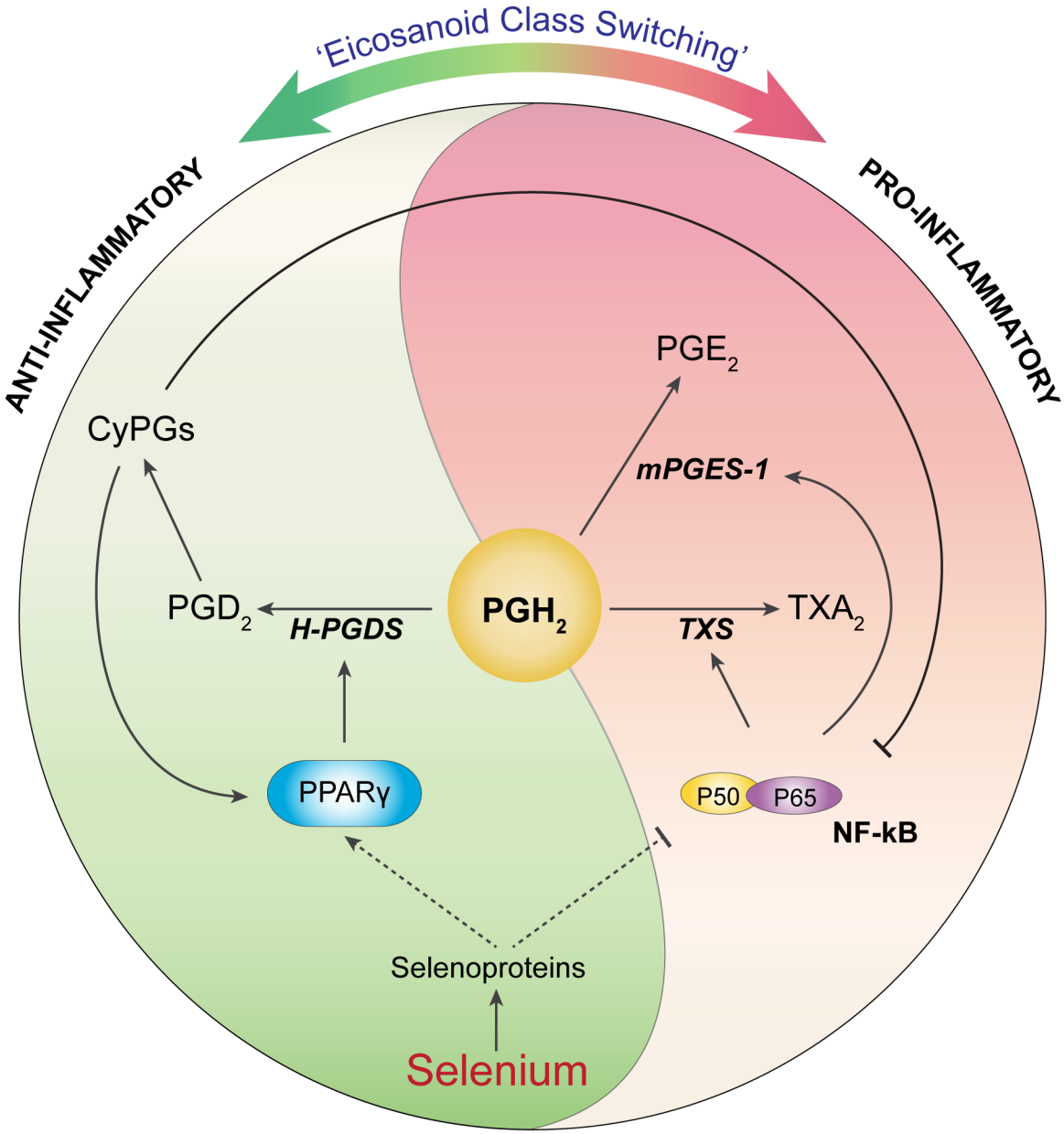

Figure 4. Schematic representation of "eicosanoid class switching" mediated by selenoproteins generated from macrophages.

Supplementation of Se upregulates the expression of selenoproteins, which mediate the shift of the ARA pathway to produce more anti-inflammatory PGD_2 and its downstream CyPG metabolites, while decreasing the levels of pro-inflammatory PGE_2 and TXA_2 via the regulation of PG synthases (mPGES-1, TXS, and H-PGDS) as well as two transcription factors, i.e. NF-κB and PPARγ.

Crit Rev Biochem Mol Biol. Author manuscript; available in PMC 2021 January 30.

Table 1.

Summary of the distribution and functions of human selenoproteins

Selenoprotein	Subcellular location	†RNA expression in immune cells	†Expression in tissues and organs	Function
*GPX1 (cGPX)	cytoplasm; mitochondrial membrane	unclear	ubiquitous expression; high in kidney and liver	antioxidant; cardioprotective and anti-angiogenic (Galasso et al. 2006; Thu et al. 2010)
GPX2 (GI-GPX)	cytoplasm	NK cell > intermediate monocyte > neutrophil > naïve B cell > classical monocyte	gastrointestinal epithelium	antioxidant; dual role in carcinogenesis ((Brigelius-Flohe and Kipp 2012; Krehl et al. 2012; Muller MF et al. 2013; Emmink et al. 2014)
GPX3 (pGPX)	secreted abundantly in plasma	neutrophil > classical monocyte > myeloid DC > intermediate monocyte > total PBMC	plasma, kidney, thyroid gland	antioxidant; tumor suppressor (Barrett et al. 2013)
**GPX4 (PHGPX)	cytoplasm mitochondria and nuclei	total PBMC > eosinophil > classical monocyte > basophil > non-classical monocyte	ubiquitous expression	antioxidant; regulation of ferroptosis and phospholipid hydroperoxide levels (Seiler et al. 2008); involved in spermiogenesis (Ursini et al. 1999)
GPX6	Secreted protein	neutrophil > eosinophil > non-classical monocyte > intermediate monocyte	olfactory epithelium and embryonic tissues; secreted in male reproductive system	antioxidant (Kryukov et al. 2003)
**Txnrd1 (TrxR1)	cytoplasm nucleoplasm	neutrophil > basophil > eosinophil > non-classical monocyte > myeloid DC	ubiquitous expression	antioxidant; embryonic development (Conrad et al. 2004; Jakupoglu et al. 2005)
Txnrd2 (TrxR3)	cytoplasm Mitochondrial membrane	classical monocyte > intermediate monocyte > myeloid DC > non-classical monocyte > eosinophil	ubiquitous expression	antioxidant; embryonic development (Conrad et al. 2004; Jakupoglu et al. 2005)
**Txnrd3 (TGR/ TrxR2)	cytoplasm nucleoplasm	naïve CD4 T cell > naïve CD8 T cell > classical monocyte > NK cell > intermediate monocyte	testis-specific expression	antioxidant; involved in spermiogenesis (Su et al. 2005)
DIO1	plasma membrane	myeloid DC > classical monocyte > naïve CD4 T cell > intermediate monocyte > memory CD4 T-cell	thyroid gland, kidney, liver	regulation of the circulating thyroid hormone levels (St Germain and Galton 1997)
DIO2	ER membrane	neutrophil > basophil > classical monocyte > plasmacytoid DC > eosinophil	thyroid gland, cervix, uterine	regulation of muscular thyroid hormone levels (St Germain and Galton 1997)
DIO3	plasma membrane	not detected	thyroid gland, cervix, uterine, placenta	Inactivating thyroid hormone (St Germain and Galton 1997)
*SelenoH	nucleoplasm and nucleoli	plasmacytoid DC > classical monocyte > total PBMC > myeloid DC > intermediate monocyte	ubiquitous expression	antioxidant (Martin-Romero et al. 2001; Kryukov et al. 2003)
SelenoI	plasma membrane	memory B cell > naïve CD8 T cell > Treg > naïve CD4 T cell > plasmacytoid DC	ubiquitous expression	catalyzing the synthesis of phosphatidylethanolamine (Kryukov et al. 2003)
SelenoK	ER membrane	basophil > eosinophil > neutrophil > total PBMC > γδT cell	mainly expressed in heart and skeletal muscle; also present in other organs such as pancreas, liver, placenta	involved in ERAD and protein palmitoylation (Shchedrina et al. 2011; Fredericks et al. 2014)

Selenoprotein	Subcellular location	†RNA expression in immune cells	†Expression in tissues and organs	Function
SelenoM	ER membrane	naïve CD4 T cell > memory CD4 T cell > Treg > memory B cell > naïve CD8 T cell	expression is the highest in brain; also present in thyroid, heart, lung, kidney, uterus, placenta	the exact function remains unknown; possibly involved in neurodegeneration (Korotkov et al. 2002)
SelenoN	ER membrane	basophil > eosinophil > classical monocyte > intermediate monocyte > naïve CD4 T cell	ubiquitous expression	regulating the muscular regeneration (Moghadaszadeh et al. 2001)
SelenoO	mitochondrial membrane	eosinophil > classical monocyte > myeloid DC >MAIT cell > memory CD8 T cell	ubiquitous expression	the exact function remains unknow; possibly involved in redox regulation (Kryukov et al. 2003)
SelenoP (SEPP1)	secreted protein in plasma	plasmacytoid DC > NK cell > MAIT cell > naïve CD4 T cell > neutrophil	secreted to plasma by liver; but also seen in all tissues (Hill KE et al. 2003; Schomburg et al. 2003)	transporting Se to peripheral tissues
*SelenoR (MsrB1)	cytoplasm nucleoplasm	neutrophil > eosinophil > classical monocyte > basophil > total PBMC	ubiquitous, mainly enriched in liver and kidney	antioxidant; regulation of actin polymerization (Lee et al. 2013)
SelenoS (SEPS1)	ER membrane	plasmacytoid DC > basophil > memory CD8 T cell > γδT cell > MAIT cell	ubiquitous expression	involved in ERAD and inflammation as well as immune response (Turanov et al. 2014)
SelenoT	ER membrane Golgi complex	total PBMC > neutrophil > classical monocyte > MAIT cell > basophil	ubiquitous expression; abundant in brain at embryonic stages; but undetectable in the adult; persistently high expression in adult endocrine organs	possibly involved in redox regulation (Ursini et al. 1999)
SelenoV	unclear	neutrophil > classical monocyte > MAIT cell > naïve CD4 T cell > plasmacytoid DC	testes-specific expression	possibly involved in redox regulation (Kryukov et al. 2003)
*SelenoW	cytoplasm, a small fraction is bound to the cell membrane	eosinophil > Treg > total PBMC > naïve CD4 T cell > memory CD4 T cell	highly expressed in skeletal muscle, heart, and brain	antioxidant; possibly involved in muscle growth and differentiation (Vendeland et al. 1995)
SPS2	nucleoplasm	NK cell > eosinophil > naïve CD4 T cell > MAIT cell > memory CD8 T cell	ubiquitous expression	autoregulation and synthesis of selenoproteins (Low et al. 1995; Guimaraes et al. 1996)
*Sep15 (SelenoF)	ER membrane	naïve B cell > plasmacytoid DC > memory B cell > total PBMC > basophil	Brain, prostate, testis, liver, and kidney	possibly implicated in cancer etiology (Kumaraswamy et al. 2000; Ferguson et al. 2006)

*Stress-responsive selenoproteins;

**Housekeeping selenoproteins;

†Data were extracted from “The Human Protein Atlas” (https://www.proteinatlas.org)

ER: endoplasmic reticulum; ERAD: ER-associated degradation; GI: gastrointestinal; MAIT: mucosal associated invariant T cell; PBMC: peripheral blood mononuclear cell; PHGPX: phospholipid hydroperoxide GPX