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Pas de Deux: Control of Anti-Tumor Immunity by Cancer-Associated Inflammation

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Summary

In many settings, tumor-associated inflammation, supported mainly by innate immune cells, contributes to tumor growth. Initial innate activation triggers secretion of inflammatory, regenerative and anti-inflammatory cytokines, which in turn shape the adaptive immune response to the tumor. Here we review the current understanding of the intricate dialogue between cancer-associated inflammation and anti-tumor immunity. We discuss the changing nature of these interactions during tumor progression and the impact of the tissue environment on the anti-tumor immune response. In this context, we outline important gaps in understanding considering basic research and findings in the clinic. The future of cancer immunotherapy and its utility depend on improved understanding of these interactions and the ability to manipulate them in a predictable and beneficial manner.

Introduction: ENTRÉE

Tumor-associated inflammation was initially described by Virchow in the 19th century. It is now appreciated to be an important driver of malignant progression, and as such has become an extensively studied aspect of cancer biology and a focal point for drug development efforts. (Galdiero et al., 2018; Grivennikov et al., 2010; Ruffell and Coussens, 2015). As has been amply discussed (Grivennikov et al., 2010), cancer-associated inflammation can predate the appearance of visible tumors, being caused by a non-cancerous inflammatory conditions, such as colitis or hepatitis. It can also prepare the scene for malignant and metastatic lesions that are being supported through a variety of inflammatory cytokines,

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DECLARATION OF INTERESTS

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growth factors and angiogenesis-promoting proteins. Inflammation, in rare cases, may also contribute to accumulation of oncogenic mutations (Shaked et al., 2012). Conversely, oncogenic mutations and other signaling alterations inherent to cancer cells can promote tumor-elicited inflammation via production of chemokines and cytokines, alterations in tissue structure and oxygen pressure, and of particular importance in gastrointestinal and lung cancers, loss of barrier integrity that facilitates translocation of microbial products.

The majority of cell types involved in tumor-associated inflammation belong to the innate arm of the immune system, acting, by-and-large, in a tumor-supportive manner that should be contrasted with anti-tumor immunity, the working of the adaptive arm of the immune system. Realizing the incredible capacity of adaptive immune cells, whether they are expressing rearranged B and T cell receptors or secreting antibodies that recognize an infinite array of peptide and polysaccharide antigens, Burnet and Thomas came up with the immunosurveillance hypothesis (Ribatti, 2016). Lacking hard support and contradicted by the finding of little difference in cancer rates between immune-intact and immune-deficient experimental animals, immunosurveillance was replaced with the immunoediting hypothesis according to which early tumors avoid immune rejection by editing their tumor antigens (Ward et al., 2016). Alternatively, early tumors establish an immunosuppressive microenvironment (Zou, 2005). Importantly, tumor-associated inflammation and anti-cancer immunity are not necessarily antagonistic and as discussed below, the relationships between them are intricate, being time and context dependent.

The impact of tumor-associated inflammation on the cancerous cell itself and its role in malignant progression are extensively discussed elsewhere in this issue (**Grivennikov & Greten**). This review is focused on the delicate and ever-changing dialogue between tumor-associated inflammation and anti-cancer immunity. Understanding of this dialogue is essential for identifying strategies for implementation of more effective immunotherapies. As almost everything in biology is governed by the law of action and reaction, it is naïve to expect that the mere dismantling of tumor-promoting inflammation would activate anti-tumor immunity. Accordingly, here we focus on the interactions between tumor-associated inflammation and antitumor immunity, using gastrointestinal and liver cancers as the primary examples. We will use the Pas de Deux (French: step of two) ballet dance concept as an analogy to the intricate and fluid interactions between cancer-related inflammation and immunity. A “grand pas de deux” is typically structured in five parts: entrée (introduction), adagio (description and initiation), two variations (a solo for each dancer), and coda (conclusion and the final work). Our goal is to assemble the current understanding of these interactions into a framework that can lead to further investigation and the development of more effective cancer-directed immunotherapies. As coda, we highlight the many gaps in basic knowledge that need to be filled to move the field forward.

ADAGIO: Initiation and General Description

Our common perception of inflammation is that it is troublesome, annoying, and even damaging, a pathological response that needs to be prevented through the use of anti-inflammatory drugs. However, inflammation deserves much respect and appreciation, as it is one of the most primordial protective responses elicited by injury and infection, being

essential for both tissue regeneration (Karin and Clevers, 2016) and innate immunity (Kotas and Medzhitov, 2015). Likewise, adaptive immunity is commonly viewed as highly beneficial and protective, but anyone who has suffered from allergy, dermatitis, or an auto-immune disease is fully aware of the nasty nature of uncontrolled immunity, coined by Ehrlich as “horror autotoxicus” (Fruton, 1957). A typical inflammatory response evoked by either injury or infection can be divided into three phases: initiation, amplification, and resolution. At each phase, acute inflammation has different effects on either cellular or humoral immunity (Iwasaki and Medzhitov, 2015). Triggered either by damage associated molecular patterns (DAMP) released by dying cells or pathogen associated molecular patterns (PAMP) released or presented by mislocalized commensals or invading pathogens, the initial inflammatory response entails degranulation of neutrophils and platelets and subsequent activation of tissue macrophages. The chemotactic peptides, lipid mediators (leukotrienes and prostaglandins), chemokines, and cytokines that are released during the initial inflammatory response lead to recruitment, differentiation, and activation of circulating monocytes and lymphocytes that congregate at the site of injury or infection or on the nascent tumor, which may be perceived as an irregularity in tissue structure. In addition to conversion of monocytes to macrophages, this response also involves activation of dendritic cells (DC), thereby augmenting their ability to take up antigens and present them to naïve T cells. Activated DC and macrophages also express a variety of co-stimulatory molecules that potentiate T cell activation as well as immunoregulatory cytokines, such as IL-10, IL-12, and IL-23, that dictate the nature of the ensuing immune response (Merad et al., 2013). Thus, during the initiation and amplification phases, inflammation plays an important immunostimulatory function and its complete suppression may compromise anti-tumor immunity. The resolution phase, however, is characterized by production of anti-inflammatory lipid mediators and cytokines such as resolvins, IL-10 and TGFβ, as well as growth factors (e.g. EGF family members), all of which are needed for termination of damaging inflammation, clearance of cell and microbial debris, and initiation of tissue repair and regeneration. To prevent over-stimulation of potentially damaging adaptive immunity, these molecules lead to further modulation of adaptive immunity, enhancing the generation of regulatory T and B cells that suppress ongoing immune activation (Figures 1). Interference with these reparative and anti-inflammatory factors may augment anti-tumor immunity but carries the risk of enhanced injury, bleeding, etc.

This well-orchestrated and choreographed response assumes a considerably different face during chronic inflammation, the kind of inflammation associated with tissue destructive autoimmunity as well as tumor growth and progression. It is not always clear exactly how tumor-associated inflammation is initiated. It has been speculated that the disorderly structure formed by premalignant lesions is perceived by innate immune cells as tissue injury. The perception of tissue injury is further propagated by DAMP release from dying cancer cells and formation of hypoxic tumor cores (Tafani et al., 2016). In other cases, for instance cancers of the gastrointestinal system or the airways, adenoma formation results in loss of barrier integrity, leading to a chronic influx of PAMPs and even live commensals that maintain long-lasting, smoldering inflammation that is characterized by ongoing production of cytokines, such as IL-6, IL-23, IL-10, and IL-17 (Grivennikov et al., 2010, 2012). Chronic tumor-associated inflammation is also accompanied by ongoing production of TGFβ that, in

addition to its ability to activate cancer-associated fibroblasts (CAF) and stimulate tumor angiogenesis, supports differentiation of immunosuppressive cell types, including regulatory T cells (Treg) and IgA-expressing plasmocytes (Massagué, 2008; Sanjabi et al., 2009; Shalapour et al., 2017). Another highly important and multifaceted inflammatory and regulatory cytokine is VEGF. While being the major mediator of vascular permeability during the initiation phase, VEGF stimulates formation of new blood vessels during resolution and healing (Ferrara et al., 2003). Healing, which is often perturbed during chronic autoimmunity, favors immunosuppression over immune activation, thereby boosting tumor growth, progression, and eventual immune evasion.

Here, we will mainly focus on how inflammation directly shapes the development and response of $CD8^+$ T cells, $CD4^+$ T helper (Th) cells and B cells, the main adaptive immune cell types, mostly through production of immunoregulatory cytokines and chemokines, and how these influence adaptive immune cells' response to cancer cells. We will not deeply discuss innate LC (iLC), γδ T cells or NK T cells (Chou and Li, 2018; Fleming et al., 2017; Pahl and Cerwenka, 2017; Zitti and Bryceson, 2018). We will also focus on how inflammation regulates non-hematopoietic cells and thereby indirectly shapes adaptive cancer immunity.

Main Inflammation Inducers: Stress and Damage Signals

Tumor growth results in disturbance of tissue architecture and stress. Some of this stress, as exemplified by the hypoxic response, is due to the much higher glycolytic rate of rapidly dividing cancer cells compared to the surrounding normal cells and the slow growth of newly-formed tumor blood vessels. Tumor hypoxia results in HIF-1α induction, CAF activation and secretion of TGFβ (Ammirante et al., 2014) and a large number of chemokines that trigger the influx of diverse myeloid and lymphoid cell types, including pro-angiogenic monocytes and macrophages (Cruz et al., 2017; Dolan et al., 2006). Thus, in addition to inflammation, tumor hypoxia supports formation of an immunosuppressive microenvironment (Barsoum et al., 2014). Another important consequence of tumor growth within a barrier epithelium, as represented by formation of colonic adenomas, is barrier disruption, which is followed by an influx of microbial products, such as endotoxin and nucleic acids, that activate resident tissue macrophages and DC through engagement of Toll-like receptors (TLRs), including TLR2, 4, and 9 and activation of transcription factor MyD88 (Grivennikov et al., 2012). Many types of cancers also exhibit endoplasmic reticulum (ER) stress, an important contributor to tumorigenesis (Wang and Kaufman, 2014). ER stress induced by saturated fatty acids and cholesterol (Nakagawa et al., 2014; Wang et al., 2006) or different metabolic disorders further enhances inflammation by activating JNK–AP-1 and IKK-NF-κB signaling cascades that stimulate the production of pro-inflammatory cytokines (e.g., TNF, IL-6, IL1β) that support tumorigenesis, while modulating immune cell function, as outlined above (Garg et al., 2012). ER stress within DC can result in immunosuppression (Cubillos-Ruiz et al., 2015). Within cancer cells, most stress responses have also been linked to immunogenic cell death-associated release of DAMPs and upregulation of "eat-me signals" that were proposed to support cross-presentation and priming of cytotoxic $CD8^+$ T cells (CTL) (Kepp et al., 2013, 2015).

Most cancers exhibit oxidative stress and many chemotherapeutic drugs further enhance production of reactive oxygen species (ROS) within cancer cells (Conklin, 2004). Oxidative stress can result in damage to both nuclear and mitochondrial DNA, and non-oxidized DNA fragments that are released to the cytoplasm lead to activation of cGAS-STING signaling, thereby culminating in type I IFN induction (Chen et al., 2016). Type I IFN potentiates T cell activation but can also enhance pro-tumorigenic inflammation (Liu et al., 2018). Oxidized DNA fragments, however, especially oxidized and fragmented mitochondrial DNA, lead to activation of the NLRP3 inflammasome, thereby inducing pro-tumorigenic IL-1β and IL-18 (Zhong et al., 2018). Stressed cells, cancer cells included, express stress antigens, such as CD1d and NKG2D, that engage NK receptors and lead to NK cell activation, which can have direct antitumorigenic effects (Bauer, 1999) but can also support tumor-promoting inflammation (Ogura et al., 2018). Extreme hypoxia and cell stress can result in cell death. Whereas apoptotic cell death is usually tolerogenic, necroptotic cell death can trigger inflammation or immune stimulation (Green et al., 2009). Certain chemotherapeutic drugs, such as anthracyclines, oxaliplatin, and methotrexate, were reported to cause a more poorly defined form of cell death referred to as immunogenic cell death, by virtue of its ability to enhance adaptive immunity to model antigens injected into mice (Galluzzi et al., 2017). While the exact mechanism of immunogenic cell death is nebulous, it is well accepted that DAMPs engage TLRs and thereby lead to DC maturation and enhanced antigen uptake and cross-presentation (Zelenay and Sousa, 2013). Altogether, this enhances T cell priming although it also leads to production of pro-tumorigenic inflammatory cytokines. Immunogenic cell death, however, is not essential for T cell priming, as DC can also sample antigens that are expressed by live cells and cross-present them to naïve T cells, leading to formation and expansion of effector T cells (Cruz et al., 2017). Moreover, by releasing DAMPs (e.g. IL-1α, HMGB1) and inducing molecules like TIM-1, CD154 and CD47 through oxidative stress, therapy-induced cancer cell death and hypoxia can be either immunosuppressive or support development of immunosuppressive cells (Griffith and Ferguson, 2011; Liu et al., 2015; Seifert et al., 2016; Shalapour et al., 2015; Steinman, 2012; Xiao et al., 2015; Ye et al., 2018).

VARIATIONS: Hematopoietic Cells, Particularly Myeloid Cells, in the Inflamed TME

The initiation of a successful anti-tumor immune response requires T cell priming which is mediated by antigen presenting cells (APC), the most common of which are DC that pick up tumor antigens and present them to naïve T cells (Guermonprez et al., 2002; Steinman, 2012). Different inflammatory signaling pathways modulate antigen delivery to APC. ER stress suppresses DC development and supports tumor progression (Cubillos-Ruiz et al., 2015), whereas mitophagy in epithelial cells supports anti-tumor immunity by increasing the cross-dressing of DC with MHCI molecules (Ziegler et al., 2018). Cross-dressing, or trogocytosis, is the mechanism in which entire peptide–MHCI complexes from donor cells are transferred to the DC, which presents them on its surface (Cruz et al., 2017; Dolan et al., 2006). Inflammation and inflammatory signals induce DC maturation and enhance their expression of various co-stimulatory molecules (Blanco et al., 2008) (Figure 2).

Although tumor-associated DCs have been described (Böttcher and Reis e Sousa, 2018; Merad et al., 2013), the most common myeloid cells in the tumor microenvironment (TME) are tumor-associated macrophages (TAM). The phenotype and function of these highly plastic cells are easily altered and adapted in response to various environmental and metabolic cues (Mantovani et al., 2017; Ruffell and Coussens, 2015). Obviously, initial inflammatory activation results in production of cytokines, such as IL-1β, TNF, and IL-6, that promote tumor growth as well as VEGF that supports neo-angiogenesis. However, even during late phases of inflammatory activation, TAMs support tumor progression through production of immunosuppressive cytokines (Figure 2), PD-L1 (Kuang et al., 2009), B7-H4 (Kryczek et al., 2006) and indoleamine 2,3-dioxygenase (IDO), a tryptophan hydrolyzing enzyme that attenuates effector T cell functions (DeNardo and Ruffell, 2019; Ruffell and Coussens, 2015). Immunosuppressive TAMs also produce TGFβ and IL-10 (Figure 2). Similar tumor-supporting functions can be expressed by inflammatory monocytes and granulocytes, which produce VEGF, ARG1, PGE2, and IL-10 (Veglia et al., 2018).

Pro- and Anti- Inflammatory Cytokines as Modulators of T Cell Responses

Tumor resident myeloid cells secrete numerous cytokines that exert either pro-inflammatory or anti-inflammatory effects. The impact that these cytokines have on malignant cells and components of the tumor microenvironment has been reviewed (Galdiero et al., 2018). Here we restrict our discussion to their impact on anti-tumor immunity. A major pro-inflammatory cytokine is IL-6. In addition to its well-studied proliferation, and survival-supporting effects on normal and malignant epithelial cells, mediated through STAT3 and YAP transcription factors (Taniguchi and Karin, 2018), IL-6 is an immunomodulatory cytokine that promotes Th cell differentiation and effector functions (Dienz and Rincon, 2009), and also affects a subset of naïve $CD8^+$ T cells (Yang et al., 2016). IL-6 can support Th2 differentiation by up-regulating IL-4 production, which is not as anti-tumorigenic as Th1 differentiation and was even shown to support tumor growth (De Monte et al., 2011; Diehl et al., 2002). IL-6 can also act immunosuppressively by inhibiting IFN-γ production and Th1 differentiation via SOCS1 induction (Diehl et al., 2000). Inhibition of Th1 differentiation precludes the mounting of a robust anti-tumor CTL response by making $CD8^+$ T cells helpless (Bevan, 2004). IL-6 together with TGFβ contributes to Th17 cell differentiation (Bettelli et al., 2006; Ivanov et al., 2006), thereby supporting early tumorigenesis (Grivennikov et al., 2012; Jin et al., 2019). IL-6 also induces IL-21 production by $CD4^+$ T cells (Diehl et al., 2012; Dienz et al., 2009; Suto et al., 2008) and is required for generation of T follicular helper (Tfh) cells (Nurieva et al., 2008), in which it leads to BCL6 induction through STAT1 activation (Choi et al., 2013). By inducing Tfh differentiation and IL-21 production, IL-6 indirectly promotes class-switch recombination (CSR) which requires activation-induced cytidine deaminase (AID) induction, converting B cells to plasma cells, thereby enhancing antibody secretion (Diehl et al., 2012; Dienz et al., 2009; Suto et al., 2008) (Figure 3). The generation of IgA-producing plasma cells, as discussed below, suppresses tumor-directed CTL responses in prostate and liver cancers (Shalapour et al., 2015, 2017). Altogether, IL-6 shifts anti-tumor immunity to a tumor-supportive immunosuppressive response, an important aspect of its tumor-promoting function that so far has been overlooked (Figure 3).

However, the role of regulatory T cells (Treg) and Th17 cells seem to be tumor type and context dependent. Th17 cells seem to support the initiation of malignant transformation in liver, colon and lung (Grivennikov et al., 2012; Jin et al., 2019; Knochelmann et al., 2018), however they may have an antitumorigenic function in late stages of colon cancer and melanoma (Muranski et al., 2008; Viaud et al., 2013). Tregs, on the other hand, suppress inflammation and development of colorectal adenomas but support development of liver tumors, breast cancer metastasis and advanced carcinomas, when they have the ability to suppress $CD8^+$ T cells (Saito et al., 2016; Tanaka and Sakaguchi, 2017). In fact, part of the anti-tumor activity of CTLA4 blocking antibodies is probably due to conversion of Treg into effector T cells (Paterson et al., 2015; Wei et al., 2018). Treg can also support cancer through secretion of cytokines in breast cancer (Tan et al., 2011).

Other important immunomodulatory cytokines produced by activated macrophages and DC are IL-12 and IL-23, which are heterodimers that share a common p40 subunit (Teng et al., 2015). Whereas IL-12 has anti-tumorigenic activity in skin cancer, IL-23 is pro-tumorigenic in both skin and colon (Grivennikov et al., 2012; Langowski et al., 2006; Teng et al., 2010). However, IL-23 receptors are not expressed by epithelial cells, and pro-tumorigenic IL-23 activity in early colorectal cancer depends on its ability to expand IL-17 producing cells, including Th17 and γδT cells (Grivennikov et al., 2010). Unlike IL-23, IL-17A, the predominant pro-tumorigenic IL-17 family member, acts directly on tumor progenitors that express IL-17 receptor A (Wang et al., 2014) and its signal transducing subunit, Act1 (Wu et al., 2012; Zepp et al., 2017). Moreover, expression of IL-23 receptor (IL-23R) in tumor-associated Treg enables STAT3 activation on IL-23 binding, inducing upregulation of Foxp3 and increasing secretion of immunosuppressive IL-10, thus constituting an IL-23-mediated tumor-supportive inflammation (Kortylewski et al., 2009) (Figure 3A). At the same time, IL-23 inhibits IL-12 dependent anti-tumor immunity.

During the resolution phase and in chronic tumor-associated inflammation, macrophages produce IL-10 and TGFβ, both of which have strong immunosuppressive activity (Sanjabi et al., 2009). IL-10 can inhibit the function of a variety of immune cells, thus playing an important role in dampening T cell mediated inflammation and immunity, while supporting chronic inflammation (Corinti et al., 2001; Moore et al., 2001). In fact, IL-10 is a multifunctional cytokine that has diverse effects on most immune cells, with the ability to inhibit activation and effector function of T cells as well as monocytes and macrophages (Moore et al., 2001). IL-10 also regulates growth and/or differentiation of CTL, Th cells, B cells, NK cells, mast cells, granulocytes, DCs, keratinocytes, and endothelial cells. However, IL-10 can also exert a stimulatory effect on $CD8^+$ T cells, aiding in tumor regression (Emmerich et al., 2012; Mumm et al., 2011). Conversely, it was recently shown that IL-10 can directly modulate $CD8^+$ T cell activation and function through modification of cell surface protein glycosylation, increasing the antigenic threshold required for T cell activation (Smith et al., 2018). Although initially identified as a growth factor and later found to be a tumor suppressor, TGFβ plays a central role in supporting and regulating tumor development and metastasis as well as tumor-directed immune responses (Li and Flavell, 2008; Massagué, 2008). Particularly, TGFβ exerts a pleiotropic effect on adaptive immune cells, regulating both effector and regulatory $CD4^+$ Th cells, $CD8^+$ CTLs, and supporting generation of immunosuppressive IgA^+ plasma cells (Shalapour et al., 2017;

Travis and Sheppard, 2014) (Figure 3B). TGFβ receptors are expressed on both immune and non-immune cells and were shown to regulate immune cell functions (Travis and Sheppard, 2014) as well as have critical effects on innate immune cells and fibroblasts, some of which are discussed below.

A specialized group of cytokines, remotely related to IL-10 and produced by different cell types, especially plasmacytoid DC, are type I and II IFNs. Although the primary function of type I IFNs is innate antiviral immunity, they also exert potent immunostimulatory activity that augments effector T cell functions (Corrales et al., 2015; Woo et al., 2015). Type II IFN or IFNγ is produced by diverse cell types, including activated Th1 and CTLs. Although IFNγ has an important immunostimulatory function mediated by upregulation of MHC-I class I (HLA-A,B,C) molecules and their associated antigen processing and presentation machinery (Zhou, 2009), its continuous production induces PD ligand 1 (PD-L1) and leads to exhaustion of chronically stimulated effector $CD8^+$ T cells (Benci et al., 2016). This regulatory response has evolved as a protective mechanism that prevents collateral damage during anti-viral immunity and is triggered by IFNγ in cooperation with IL-10 (Sanjabi et al., 2009). However, the same response is also mounted by cancer cells as a way to suppress immunosurveillance (Alspach et al., 2018; Sharma et al., 2017). The dual effects of IFNγ on anti-tumor immunity have been discussed (Mandai et al., 2016) and were even compared to the dual effects of IL-10 (Wilke et al., 2011). Therapeutic manipulations capable of dismantling IFNγ-induced immune dysfunction while retaining strong immunostimulatory effects, other than PD-L1 or PD-1 blocking antibodies, remain a major challenge.

Immunosuppressive B Cells and Plasmocytes

First identified in treatment refractory prostate cancer (PCa), ISP are derived from naïve B cells that are recruited into the TME by CAF-generated CXCL13 and CXCL12 (Ammirante et al., 2014; Shalapour et al., 2015). Upon encounter of B-cell receptor (BCR) specific-antigens, that could be bacterial-, food-, or tumor-derived and further exposure to TGFβ and other cytokines including IL-21 from circulatory Tfh cells, lymphotoxin β (LTβ), IL-33, and IL-10, naïve B cells undergo CSR to replace their surface-expressed IgM-BCR with surface-expressed IgA (Cerutti, 2008; Shalapour et al., 2015, 2017). IgA^+ plasmocytes, which are generated in response to chronic inflammation (Figure 3B), have the ability to not only suppress CTL activation in the context of cancer development or during cancer therapy (Shalapour et al., 2015, 2017) but can also regulate and dampen neuroinflammation (Rojas et al., 2019). These anti-inflammatory and immunosuppressive effects are in line with the well-established homeostatic and regulatory role of IgA^+ plasmocytes in mucosal immunity (Gutzeit et al., 2014; Macpherson et al., 2018; Mantis et al., 2011). However, the primary role of IgA is also to maintain bacterial homeostasis, therefore IgA^+ plasmocytes may suppress the growth of tumors that depend on microbial signals.

B cells and humoral immunity have also been described to regulate anti-tumor immunity through other mechanisms, either by expressing cytokines such as IL-10 or IL-35, inducing antibody-mediated cytotoxicity through NK cells, or activating the complement system components C5a or C3a, which seem to either activate or suppress anti-tumor immunity in a context dependent manner (Gunderson et al., 2016; Markiewski et al., 2008; Mauri and

Menon, 2015; Medler et al., 2018; Pylayeva-Gupta et al., 2016) (Figure 3B). However, the ways by which different B cell types manifest their immunosuppressive effects remain poorly understood.

Microbe-Induced Inflammation and Modulation of Tumor Immunity

The microbiota plays a fundamental role in regulating gut immune and tissue homeostasis, nutrient absorption, and energy metabolism. The microbiome also has a central role in induction, training and function of the entire host immune system. Gut microbes can activate and support antigen presentation through TLR signaling and modulate T cell homeostasis through induction of IFNγ, IL-1 and IL-7. Importantly, gut microbes support Treg and Th17 development (Arpaia et al., 2013; Dmitrieva-Posocco et al., 2019; Furusawa et al., 2013; Ivanov et al., 2009; Shalapour et al., 2010) and control humoral immunity, especially IgA production (Gutzeit et al., 2014; Nakajima et al., 2018). Therefore, the microbiota has a pivotal role in modulating anti-cancer immunity as well as gastrointestinal inflammation. Expansion of IL-17 producing cells supports tumor growth in colon, liver and lung and is often elicited by translocation of commensal microbes and their products (Gomes et al., 2016; Grivennikov et al., 2012; Jin et al., 2019). Microbial translocation can lead to chronic inflammation and accumulation of immunosuppressive IgA^+ plasma cells (Rojas et al., 2019; Rosser et al., 2014; Shalapour et al., 2017). However, bacteria can also induce NKT cell activation and stimulate anti-tumor immunity (Ma et al., 2018). Moreover, the gut microbiota was shown to regulate the response to checkpoint inhibitors through APC differentiation and maturation, thereby enhancing T cell priming (Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018).

However, it is still not clear whether the interaction between commensal microbes and the immune system entails innate recognition or whether it also affects adaptive immune recognition, which may support or suppress anti-tumor immunity. In a context dependent manner, bacteria support tumor development, particularly in non-alcoholic steatohepatitis (NASH)-induced hepatocellular carcinoma, colon and lung cancer, by inducing IL-17 and inflammation. However, commensal microbes also support DC and NK cell activation to enhance anti-tumor immunity, particularly in melanomas, but their exact contribution needs to be further analyzed and tested on a case-by-case basis.

Non-Hematopoietic Cells and Fibroblasts that Regulate Adaptive Immunity

Tumor hypoxia caused by either rapid tumor growth or as a result of drug treatment leads to CAF activation in a manner dependent on autocrine TGFβ signaling. Although CAFs have been known to support tumor growth, their ability to recruit immune cells and modulate anti-tumor immunity was discovered only recently. This modulation of tumor immunity by CAFs is very much context dependent and can be either positive or negative depending on the tumor type (Kalluri, 2016; Kato et al., 2018; Lakins et al., 2018; Özdemir et al., 2014). In addition to immunosuppressive TGFβ and IL-6, activated CAF produce CXCL13 and many other chemokines and cytokines, including CXCL12, CXCL19, CCl25, and IL-7 (Ammirante et al., 2014; Shalapour et al., 2010, 2017), that recruit lymphocytes and affect their differentiation and homeostasis. By contrast to their ability to recruit immune cells

through chemokine production, CAFs can physically block the entry of immune cells into the tumor parenchyma and trap them within the collagen-rich peritumoral stroma (Mariathasan et al., 2018)(Figure 4A). The latter effect can be disrupted by using TGFβ neutralizing antibodies.

Roles of Inflammation-Induced Lymphatic Vessels and Tertiary Lymphoid Structures

Lymphatic vessels drain fluids and macromolecules from tissues and take up lipids (chylomicrons) in the intestine. They transport antigens and leukocytes between peripheral tissues, lymph nodes (LNs), and the blood and therefore are important for induction and regulation of immune responses. The lymphatic vasculature enables transport of DC and antigens into tumor-adjacent draining LN, thereby regulating anti-tumor immunity (Figure 4). Lymphatic vessels can also promote tumor tolerance (Lucas et al., 2018; Lund et al., 2016; Vranova, 2014) and even aid in malignant progression by contributing to the dissemination and metastatic spread of many carcinomas (Stacker et al., 2014). Mediators of inflammatory lymphangiogenesis like VEGF-A and VEGF-C/VEGF-D, which signal through VEGFR-2 and/or VEGFR-3, are produced by either leukocytes or stromal cells, and TAMs are important sources of VEGF-A and VEGF-C. Both TAMs and neutrophils can modulate lymphangiogenesis in the inflamed as well as tumor-draining LNs by producing mediators, such as IL-17 or IL-8, that induce lymphangiogenesis. Lymphotoxins (LTα and LTβ) have also been implicated in inflammatory lymphangiogenesis, particularly in the context of tertiary lymphoid organs (TLO), which were described to exert conflicting effects on tumor development (Dieu-Nosjean et al., 2014; Finkin et al., 2015). Importantly, some inflammatory cytokines can inhibit lymphangiogenesis and angiogenesis. IFNγ, in particular, coming from Th1 and NK cells, was shown to inhibit angiogenesis and thereby support tumor regression and probably inhibit metastasis (Kammertoens et al., 2017). IFNγ also inhibits CAF activation and fibrosis (Baroni et al., 1996; Luo et al., 2013). Furthermore, inhibition of TGFβ can induce lymphangiogenesis (Oka et al., 2008).

CODA

Although chronic inflammation generates an immunosuppressive microenvironment that supports tumor development and suppresses anti-tumor immunity, uninflamed tumors do not respond to checkpoint inhibitors, particularly anti-PD(L)1 drugs whose action depends on presence of exhausted $CD8^+$ T cells. Although it is not entirely clear why certain types of cancers are not inflamed, it was suggested that the lack of inflammatory infiltrates may be due to the scarcity of damaged DNA, which is needed for activation of the cGAS-STING pathway and type I IFN production. Alternatively, the absence of chemokine and cytokine production by cancer cells results in poor lymphocyte recruitment and homing to the tumor tissue (Gajewski et al., 2017; Trujillo et al., 2018). It should be noted that only a slight correlation between the tumoral content of T cells (also known as T cell inflammation) and immunogenic peptides has been observed (Spranger et al., 2016). Although production of neo-antigens often correlates with checkpoint inhibitor responses in some cancers, there are additional factors that affect tumor immunogenicity. For instance, chronic inflammation

contributes to resistance to cancer immunotherapy, and resistance to anti-CTLA4 therapy can be conferred by IFNγ-signaling, which induces PD-L1 expression. In this case, responsiveness to immune checkpoint inhibitors (ICI) is restored by combining anti-CTLA4 and anti-PD(L)1 drugs (Benci et al., 2016).

On the other hand, cell death and inflammation induce TGFβ, which promotes CAF activation and fibrosis, resulting in accumulation of a fibrotic tumor stroma that excludes T cells from the tumor and leads to ICI resistance (Mariathasan et al., 2018; Tauriello et al., 2018). Epithelial-to-mesenchymal transition (EMT), which can also be regulated by the TME, inflammatory cytokines, and factors like TGFβ, modulates the response to immunotherapy and contributes to immunosuppression, as mesenchymal tumors are more likely to recruit immunosuppressive cells, have higher PD-L1 expression and downregulate MHCI expression. Thus, mesenchymal tumors are more likely to escape CTL-mediated killing. However, the exact mechanisms by which EMT affects anti-tumor immunity remain unknown (Chae et al., 2018; Dongre and Weinberg, 2019; Dongre et al., 2017). Interestingly, it has been shown both in mouse and human studies that inflammation and TNF can induce reprogramming of melanoma cells (dedifferentiation), resulting in elevated expression of neural crest markers (e.g. NGFR). Dedifferentiated melanoma cells lack expression of melanocytic antigen (MART-1) and therefore acquired resistance to adoptive T cell immunotherapy (Landsberg et al., 2012; Mehta et al., 2018).

Another paradoxical effect of inflammation on anti-tumor immunity is related to obesity-induced metabolic inflammation. Many epidemiological, clinical and animal model studies have confirmed and documented the effects of obesity on cancer incidence and mortality, largely mediated via obesity-induced barrier disruption and chronic inflammation (Nakagawa et al., 2014; Park et al., 2010; Shalapour et al., 2017; Sun and Karin, 2012). However, peripheral adipose depots also have a profound influence on adaptive immunity (DiSpirito and Mathis, 2015; Maurizi et al., 2018), increasing immune ageing and T cell exhaustion and dysfunction (Shalapour et al., 2017; Wang et al., 2019). Moreover, linoleic acid, a fatty acid that accumulates during hepatic steatosis, was suggested to induce oxidative damage and mediate selective loss of intrahepatic $CD4^+$ T cells to support HCC development (Ma et al., 2016). More recent studies, however, showed that obesity is associated with increased efficacy of PD-(L)1 blockade in tumor-bearing mice and cancer patients (Wang et al., 2019). This surprising result may be attributed to obesity-induced immunosuppression which increases PD-L1 expression either in tumors or through effects on PD-$L1^+$ immunosuppressive IgA^+ plasmocytes (Shalapour et al., 2017), macrophages or even adipocytes (Shirakawa et al., 2016; Wu et al., 2018). While suppressing immunosurveillance, such changes may render the obese patient more susceptible to the beneficial effects of anti-PD-(L)1 therapy, but this remains to be validated in the clinic.

In conclusion, the intricate and ever-changing dialogue between inflammation and immunity in the context of cancer development, progression and treatment provides a fertile ground and many challenges for future research. How to boost anti-tumor immunity without losing innate immune defenses or conversely, triggering a cytokine storm, remains to be determined, as well as identifying the best way for dismantling the immunosuppressive aspects of chronic inflammation while leaving its immunostimulatory side intact. Another

important but poorly understood concept in tumor immunology is T cell exhaustion. Why do tumor directed $CD8^+$ T cells become exhausted after chronic antigenic stimulation, but self-directed T cells in autoimmunity remain activated for the duration of the disease? Notwithstanding these mysteries, it has become clear that inflammation-mediated immunosuppression is a major player in cancer biology and its improved understanding is critical for future progress at the translational front.

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Chronic inflammation supports tumor growth and is often immunosuppressive, but under certain conditions, it can enhance anti-tumor immunity. Shalapour and Karin review the intricate and dynamic dialogue between tumor-associated inflammation and anti-cancer immunity, focusing on the impact of inflammatory signals on the adaptive immune response and the implications for cancer immunotherapies.

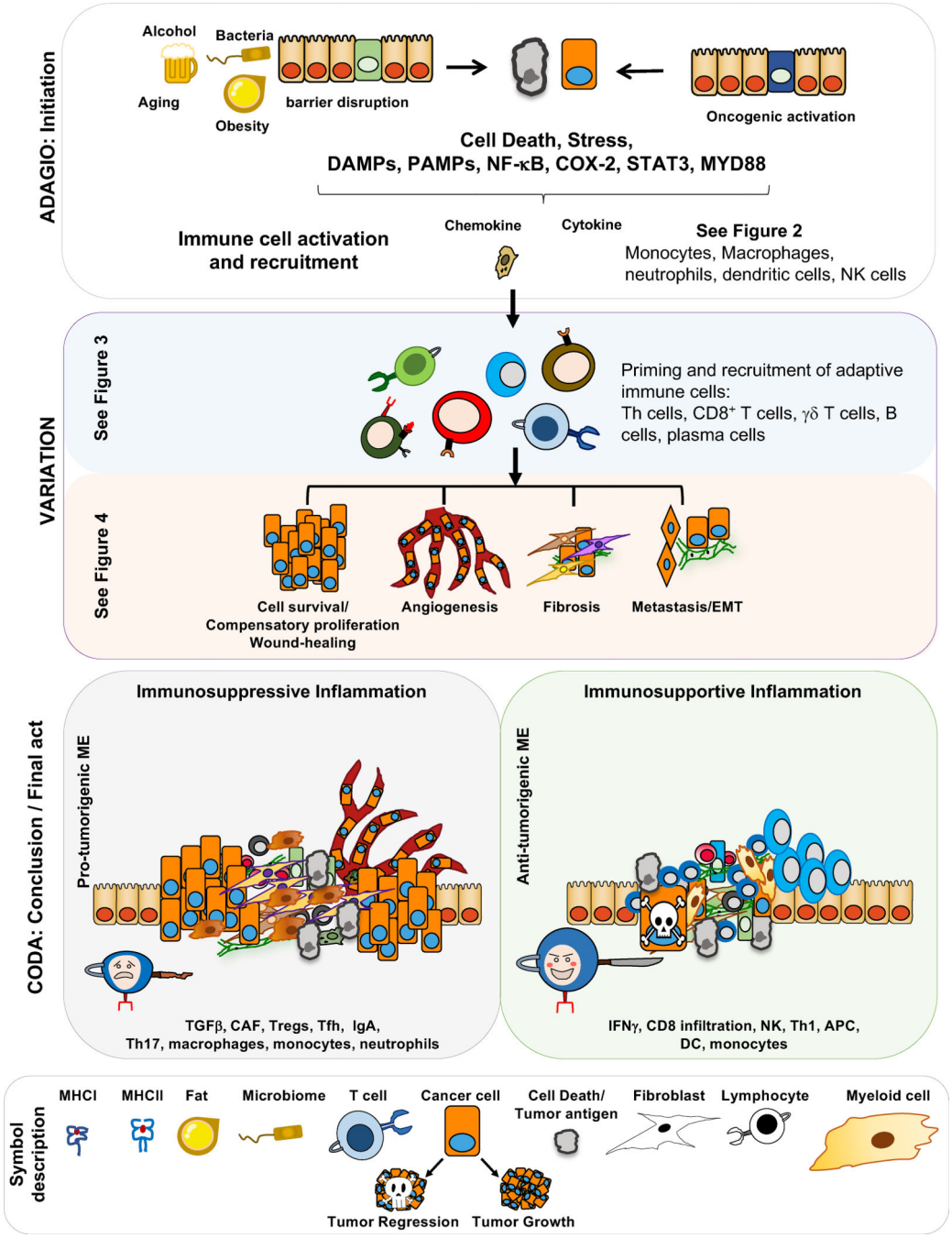

Figure 1: GRAND PAS DE DEUX: Inflammation, Immunity, and Cancer

A schematic description of how cancer-associated inflammation develops, interacts with and modulates anti-tumor immunity. Importantly, inflammation can be either immunosuppressive or immunosupportive. For instance, the extent of myofibroblast activation and TGFβ production can tilt the inflammatory response in a more immunosuppressive direction.

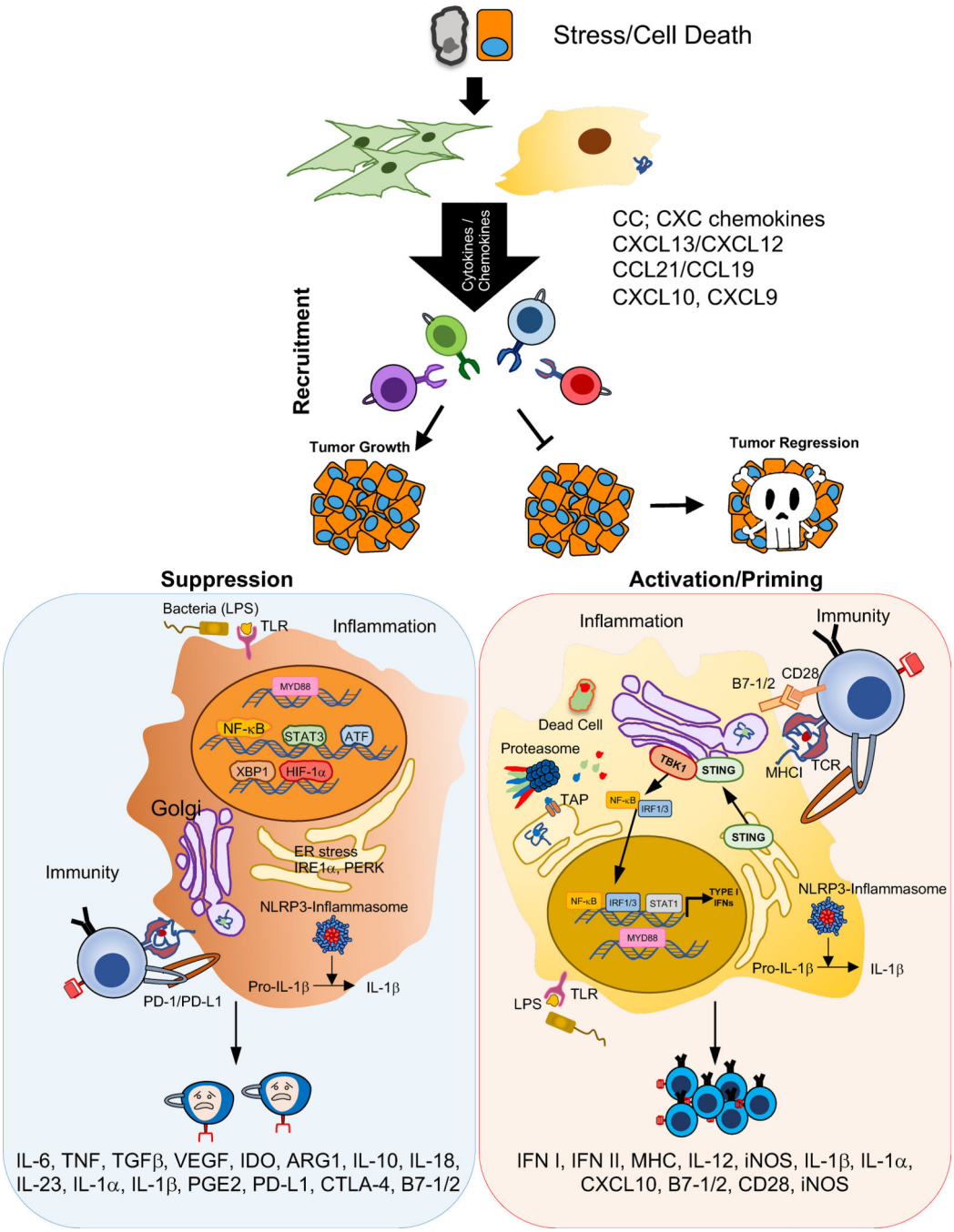

Figure 2: Inflammation in the early stages of cancer.

Stress, cell death, obesity, bacterial infection and translocation of microbial components across disrupted barriers induce innate immune cell activation and increased expression of chemokines and cytokines that promote infiltration of adaptive immune cells to the site of tissue stress or injury. Moreover, myeloid cells, especially DC, take up antigens and present them to T cells to induce CTL activation. Despite increasing antigen release, cell death can also be immunosuppressive and tolerogenic, thereby suppressing CTL activation. In a

similar manner, monocytes and macrophages can suppress CTL-mediated tumor rejection through expression of IL-10, ARG1, IDO, and TGFβ.

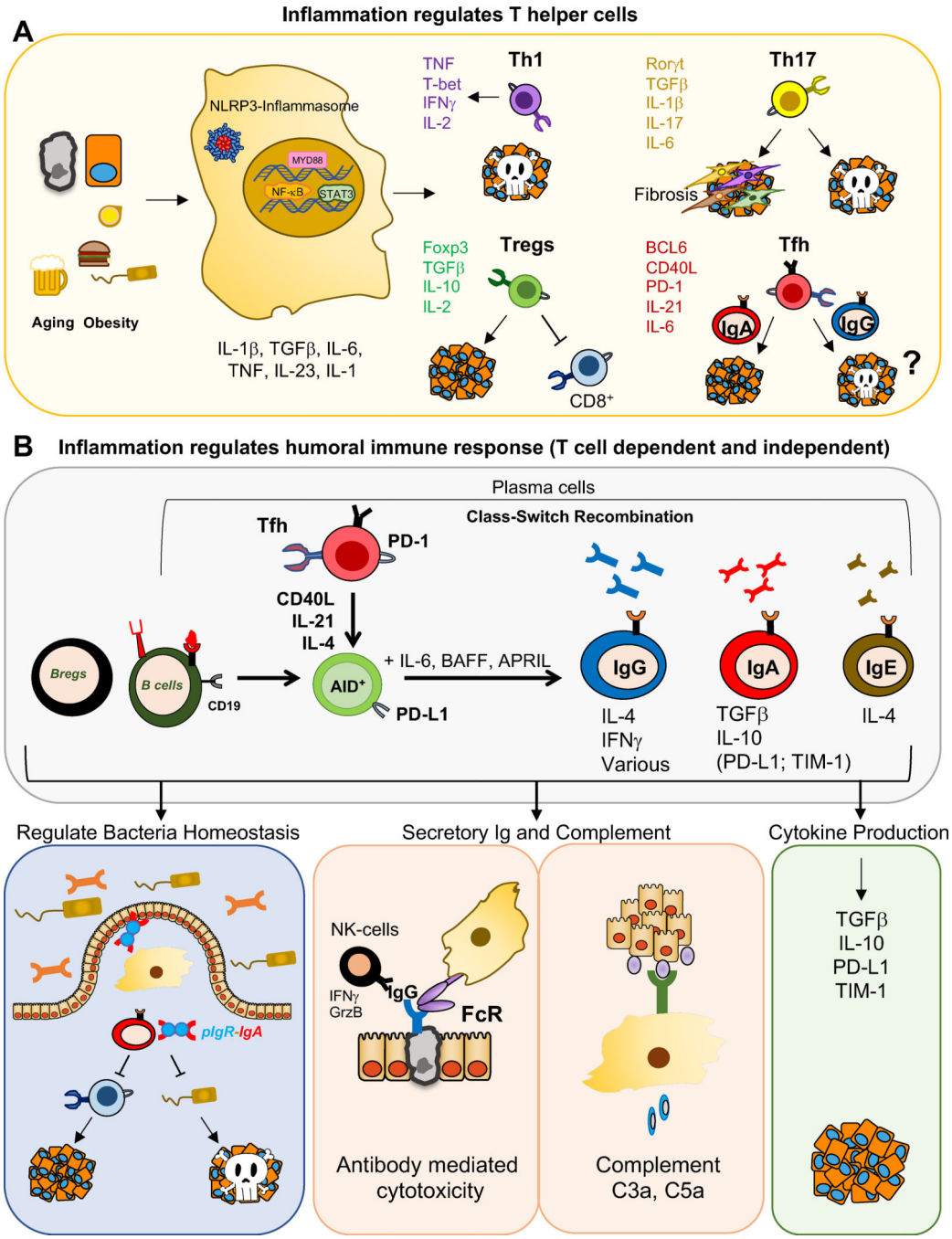

Figure 3: Role of Hematopoietic Cells, Particularly Adaptive Immune Cells in Anti-Tumor Immunity in Inflamed TME.

A) Development of different Th cell subsets in the context of an inflammatory tumor environment. Inflammation supports inhibitors of CTL activation and impairs CTL activators. B) Humoral immunity- good or bad? By-and-large, humoral immunity can suppress CTL activation and thereby support tumor growth, but it can also facilitate NK cell activation, through antibody-mediated cytotoxicity and thereby enhancing anti-tumor immunity.

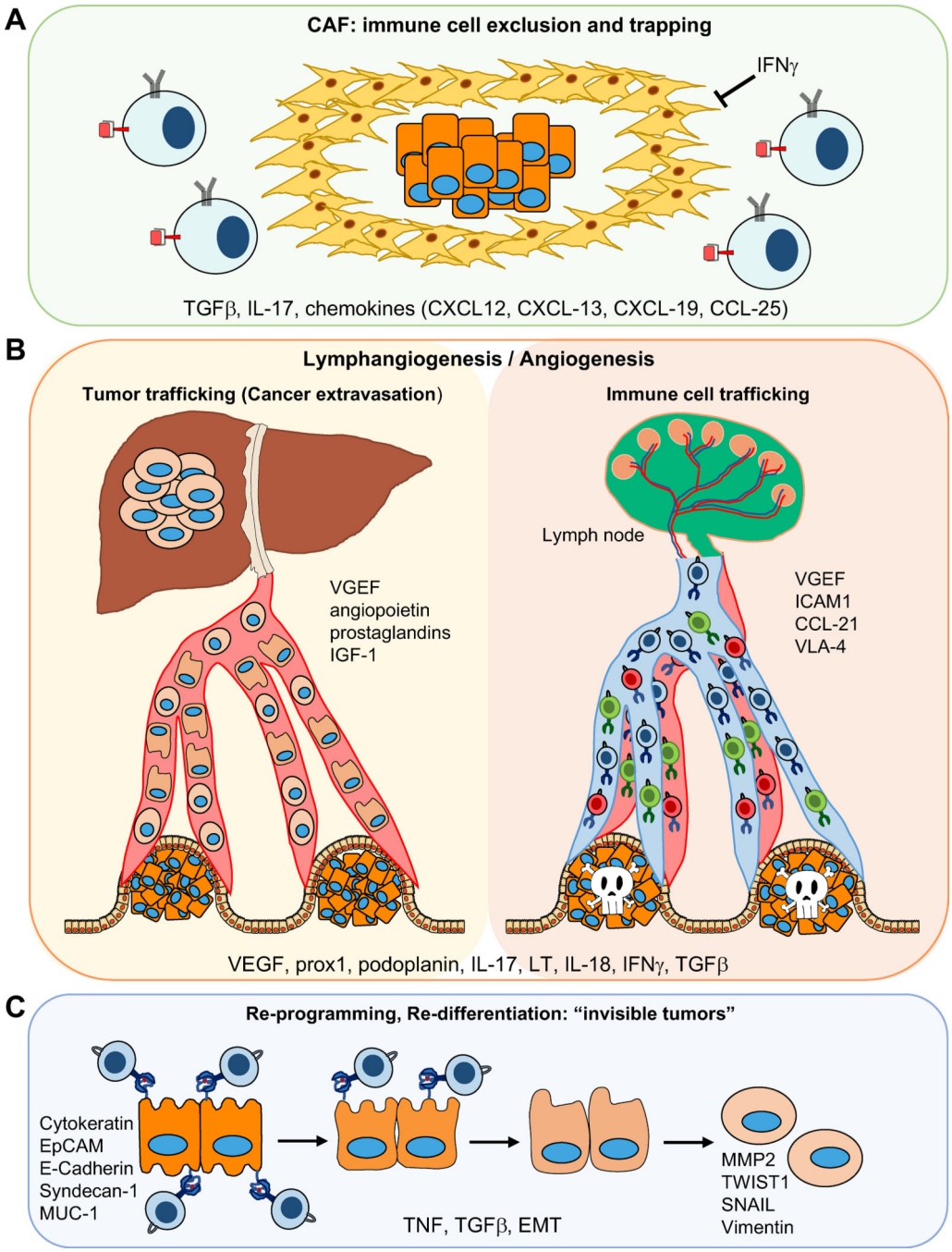

Figure 4: Role of Non-hematopoietic Cells in Anti-Tumor Immunity in the Inflamed TME.

A) Immune cell exclusion by CAFs. B) Angiogenesis and lymphangiogenesis; building the road for tumor and immune cell trafficking. C) Cancer cell re-programming, EMT.