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Impact of Dietary Components on NK and Treg Cell Function for Cancer Prevention

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Abstract

An important characteristic of cancer is that the disease can overcome the surveillance of the immune system. A possible explanation for this resistance arises from the ability of tumor cells to block the tumoricidal activity of host immune cells such as natural killer (NK) cells by inducing the localized accumulation of regulatory T (Treg) cells. Evidence exists that components in commonly consumed foods including vitamins A, D, and E, water-soluble constituents of mushrooms, polyphenolics in fruits and vegetables, and n-3 fatty acids in fish oil can modulate NK cell activities, Treg cell properties, and the interactions between those two cell types. Thus, it is extremely important for cancer prevention to understand the involvement of dietary components with the early stage dynamics of interactions among these immune cells. This review addresses the potential significance of diet in supporting the function of NK cells, Treg cells, and the balance between those two cell types, which ultimately results in decreased cancer risk.

1. Introduction

NK cells are large granular lymphocytes without B or T cell characteristics and highly effective in destroying tumor cells and virally infected cells without the need for prior sensitization or recognition of a specific antigen (1–3). These cells represent innate immune cells that secrete cytokines participating in the adaptive immune response. For example, NK cells are a major source of protective cytokine IFN- γ that is critical for the development of an appropriate cytotoxic T cell response to the pathogen. The direct and indirect tumoricidal properties of NK cells equip them with the ability to serve as a critical sentinel against invading pathogens. Both experimental and clinical data indicate an important role for NK

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cells in early neoplastic development, possibly by either responding to pathogen-associated molecular patterns (PAMPs) or to various types of extracellular or cell-associated proteinases (4, 5). Cancer cells often evade NK-cell surveillance by producing immunosuppressive molecules and through the recruitment of tolerance-related Treg cells (6, 7).

Treg cells (CD4+, CD25+, fork head box p3 [Foxp3] +) that characteristically express the nuclear transcription factor Foxp3, are known to down-regulate the tumoricidal activity of NK cells and thus maintain immunological self-tolerance and homeostasis. No doubt, it is important to understand the early stage(s) of pathogen-host interactions, and redirect these events from a pro-tumor to an anti-tumor state. Diet may represent a subtle approach to regulating NK cells without losing their homeostasis maintained by regulatory T (Treg) cells. Here, we will discuss our current understanding of the mechanism by which dietary components modulate the function and balance between NK cells and Treg cells for cancer prevention. Papers that do not provide evidence dealing with the effects of specific dietary constituents on the targeted immune-prevention are not included for the discussion.

2. Dietary influence on NK cell properties

Several lines of evidence suggest that a number of bioactive food components can induce tumor cell death, possibly by enhancing NK cell activity. For example, water-soluble extracts of the dried Brazilian sun- (Agaricus Blazei) and Maitake- (Grifola frondosa) mushrooms can enhance the cytolytic activity of NK cells in BALB/c mice (8–10). Likewise, dietary supplementation with vitamin E (250 mg daily for 2 weeks) can enhance NK cell cytolytic activity in advanced colorectal cancer cells obtained from patients (11). Interestingly, the supplementation of vitamin E (administered at 100 mg/day for 8 weeks) restored NK cell activity in a 16 month-old boy with Shwachman-Diamond syndrome which is classically associated with a persistent reduction in NK cytolytic activity (12). Collectively, these findings suggest the involvement of dietary components in the regulation of NK cell tumoricidal activity. In this review, we propose three distinct processes: receptor-ligand interactions, the release of cytokines, and the secretion of lytic enzymes (Figure 1) as possible mechanisms explaining their actions.

2.1 Interaction of bioactive food components with NK cell receptors and their ligands

NK cells are known to exhibit their activity through a diverse repertoire of activating (e.g., NKG2 receptor family) and inhibitory (e.g., killer immunoglobulin-like receptor [KIR] family) receptors that recognize specific ligands on the surface of target cells (13–15). Many of the KIRs recognize major histocompatibility complex (MHC) class I molecules, which in humans are human leukocyte antigen (HLA) class I molecules (16). The inhibitory KIRs block NK cytotoxicity for cells that express normal levels of MHC class I molecules on their surface (17).

There is evidence, admittedly limited, that suggests certain dietary components may modulate the NK cell activity in response to tumor antigen stimuli. For example, when STAV-AB malignant mesothelioma cells are exposed to 7.5 μ M selenite for 24 hours, these cells become highly sensitive to NK cells (18). This event is possibly caused by the

observed selenite-mediated loss of tumor antigen HLA-E on the surface of STAV-AB cells as this molecule can bind to the CD94/NKG2A receptor on NK cells and thereby suppress their tumoricidal activities.

The tumor antigen, HLA-G has tolerogenic properties and provides tumor cells with an efficient way to escape from NK tumoricidal function. This effect of HLA-G appears to be independent of lipid raft integrity that could be modulated by a variety of lipid soluble dietary factors including n-3 polyunsaturated fatty acids (PUFAs) abundant in fish oil and conjugated linoleic acids (CLAs) found in dairy products (19–22). For example, n-3 PUFAs and cis-9, trans-11-CLAs target lipid raft organization in membrane to influence immune cell function (21, 22). However, HLA-G is mainly localized outside the lipid rafts of tumor cells during this process and so remains unaffected by these dietary components.

2.2 Influence of bioactive food components on cytokine release from NK cells

Circulating NK cells, as opposed to dendritic cells, only mature during inflammation or infection (23–25). NK cells, which can lyse tumor cells, provide antigenic cellular debris for mature dendritic cells to present to T cells; in later stages of an immune response, NK cells terminate the process by lysing the dendritic cells and halting their ability for antigen presentation (26, 27). During early onset of inflammation, immature dendritic cells secrete a variety of cytokines including tumor necrosis factor- α (TNF- α), IL-2, IL-12, and IL-18 (24, 25). These cytokines can induce a rapid expression of IFN- γ and subsequently enhance the intrinsic cytolytic activity of NK cells (27). However the response is complex, since T-helper 2 (Th2) cytokines such as IL-4, which are generally viewed as an antagonist of IFN- γ expression in T cells, can induce signal transducer and activator of transcription 6 (STAT6)-dependent IFN- γ secretion by NK cells (28).

Dietary supplementation of 4 month old C57BL/6 mice with 10% (Wt/Wt) white button mushroom powders for 10 weeks increased the production of TNF- α , IL-2, and IFN- γ , which correlated with the increased tumoricidal activity of splenic NK cells (29). Unfortunately, this study does not allow for the determination if the increased production of cytokines is mediated via dendritic cells or from the direct effect of mushroom powders on NK cell function.

Recently, LPS stimulated dendritic cells were found to increase the release of IFN- γ following isoflavone (100 μ M genistein or daidzein), which in turn enhanced the cytolytic effects of NK cells in culture (30). While it appears that soy isoflavones stimulate the release of cytokines from matured dendritic cells, it remains unclear how these cytokines activate the NK cell function.

It is reported that supplementation of mice with galacto-oligosaccharides (5 g/kg b.w. for 2 weeks), a soluble fiber found in human milk, increases the NK cell-mediated protection against *Helicobacter* infection in a Smad3-deficient inflammation model (31). This effect of a milk component on NK cell activity is possibly associated with the increased expression of the NK chemokine receptor CCR 9 as the binding by its ligand CCL25 is known to decrease the severity of pathogen-induced inflammation in the colon. While these results suggest that

specific bioactive food components can modulate the ability of NK cells to respond to various cytokines, the precise mechanism(s) remains unresolved.

2.3 Dietary modulation of release of lytic granules from NK cells

The lysosomal release of cytotoxic granules from NK cells, including two membrane-perturbing proteins such as perforin and granulysin, and a family of serine proteases (also known as granzymes), constitutes the main pathway for the NK-mediated elimination of tumor cells (27, 32–34). A number of studies indicate that dietary habits, including alcohol consumption and caloric restriction, may influence the cytolytic activity of NK cells by down-regulating the release, activity, and expression of perforin and granular proteases (35–38). Restricting calorie intake (starting with 10% restriction at the age of 10 weeks and gradually increased up to 40% at the age of 14 weeks and after) in mice was reported to reduce NK cell number and function particularly cytolytic activity as evident by their decreased ability to resist against influenza virus infection (37). While the mechanism for these changes in NK cells remains unclear, the significance of the PI3K signaling cascade in NK cell biology (39) and the recent finding that inositol (1, 3, 4, 5) tetrakisphosphate (IP₄) suppresses NK cell granule exocytosis and target-cell killing (40), may explain a possible mechanism. IP₄ is a soluble metabolite generated from the membrane lipid phosphatidylinositol- 4, 5-diphosphate [PI(4,5)P₂]. This compound is reported to be critical in immune cell development and function in hematopoietic cells (41). Knocking-out of ItpkB, an enzyme that is essential for the production of IP₄, revealed that this phosphorylated inositol metabolite promotes NK cell maturation and limits NK cell responsiveness (40). It is known that caloric restriction reduces tumor incidence and numbers in animal models. Further studies are warranted to examine how NK cells play a role in these dynamics involving the tumor micro-environment, energy homeostasis, and host immunity.

3. Dietary components modulate Treg cell induction

Treg cells represent 5–10% of total CD4⁺ T lymphocytes in humans and mice, these cells constitute about one fifth of tumor T-cell infiltrates (2, 42, 43) suggesting their active role in the tumor microenvironment. Under normal conditions, Treg cells are known to have a role in developing tolerance to nonpathogenic foreign antigens, (e.g. foods or commensal bacteria) to avoid inappropriate immune responses. Within a tumor site, these regulatory T cells can suppress cancer cell-specific immune reactions, resulting in the cytokine profile that is typically immunosuppressive. For example, transforming growth factor- β (TGF- β), a tumor cell secreted cytokine that can convert antigen-activated peripheral CD4⁺ T cells to CD4⁺CD25⁺ Treg cells, suppresses tumoricidal activity of CD8 (+) cytotoxic T lymphocyte (CTL) and NK cells (44). Through this mechanism, tumor cells escape from either CTL or NK cell-attacks by utilizing Treg cells that are recruited to the tumor by the chemokine ligand CCL22 that is produced by tumor cells and/or tumor-associated macrophages (45).

There are two different types of Treg cells, naturally occurring Treg (nTreg) and inducible Treg (iTreg) (46). The former suppresses T-cell responses by cell contact-dependent mechanisms, whereas the latter secretes inhibitory cytokines, including TGF- β and interleukin-10 (IL-10). While both nTreg cells and iTreg cells are known to modulate NK

cell cytotoxicity *in vitro* and *in vivo* (47, 48), the precise mechanism explaining how this works largely remains unclear.

A few bioactive food components including vitamin A (49, 50), vitamin D (51–53), n-3 fatty acids (54, 55), dietary polyphenolics such as naringenin (56), and epigallocatechin-3-gallate (EGCG, 57) are shown to induce peripheral iTreg cells to escape from immune effector cells including NK cells and thereby prevent autoimmunity and allergy. The effects of iTreg cells are carried out by modulating several processes including the inhibition of dendritic cell (DC) differentiation/maturation (48), stimulation of TGF- β release from the membrane of Treg cells (58), and the modulation of NK-cell perforin and granzyme B expression (59). However, it remains to be revealed which pathway(s) is modulated by these dietary constituents to exert their preventive effects on autoimmunity and allergy. With that limit, this section will focus on the currently known role of dietary constituents in the properties of iTreg cells at peripheral tissues.

3.1 Vitamin A modulates the induction of regulatory T cells in intestine, which promotes NK tolerance against foods and commensal gut bacteria

Antigen presenting cells (APCs) such as DCs harbor retinaldehyde dehydrogenase that metabolizes vitamin A to retinoic acid (RA) (60, 61). RA is reported to be critical for TGF- β -dependent iTreg generation in the intestine where immune tolerance towards foods and commensal microbes is important to maintain homeostasis (62, Figure 2). The conversion to iTreg (CD4+Foxp3+ Treg) cells from naïve T (CD4+Foxp3–) cells may be mediated by a specific population of dendritic cells that are identified by a CD103 marker in the lamina propria of the small intestine (49, 63). It is notable that a conserved non-coding sequence 1 (CNS1) in the Foxp3 locus, which contains TGF- β -Smad/NFAT response elements, has a critical role in iTreg cell generation in gut-associated lymphoid tissues (64, 65). In addition, the inhibitory effects of retinoic acids on the release of pro-inflammatory cytokines such as IL-4, IL-21, and IFN- γ from CD44(hi)CD4(+) memory T cells appears to contribute to the process (50, Figure 2). Interestingly, this cytokine-mediated indirect effect of RA is shown to require the expression of its nuclear receptor retinoic acid receptor- α (RAR- α) (66). The binding of RA to RAR- α can block cytokine production by effector T cells, which in turn facilitates Treg induction and down-regulates NK function. Finally, RA is reported to actively participate in the TGF- β -dependent reciprocal regulation of iTreg (anti-inflammatory) versus Th17 (pro-inflammatory) cells by inhibiting the IL6-driven induction of the latter (67, Figure 2). The priming of naïve T cells by DC in the presence of TGF- β leads to either anti-inflammatory Treg cells or pro-inflammatory Th17 cells (67). Vitamin A metabolite RA was demonstrated as a key determinant driving this pathway toward anti-inflammatory Treg cell induction mediated by mucosal DC. This property of RA seems to be particularly important in the intestine, where efficient immune protection is required to maintain homeostasis in response to constant exposure to exogenous stimuli. Overall, the experimental results suggest that vitamin A may be involved with the fine-tuning of T cell differentiation into Treg in the intestine, which generates NK tolerance against external and internal antigens.

3.2 Vitamin D inhibits dendritic cell maturation and thereby increases the induction of Treg cells

Studies have consistently shown that exposure of DCs to 1,25(OH)₂D₃, the active form of vitamin D, leads to the inhibition of differentiation and maturation of these cells (68–70). *In vitro* treatment of DCs with 1,25(OH)₂D₃ has been shown to decrease IL-12 and enhance IL-10 production, resulting in decreased T-cell activation (68, Figure 2). This effect of vitamin D seems to be mediated by vitamin D receptor (VDR) as shown in the study utilizing VDR knockouts (69). The modulating activities of 1,25(OH)₂D₃ on DCs and T cells were abolished in these mice with limited expression of VDR. Furthermore, 1,25(OH)₂D₃ selectively works on myeloid DCs but not plasmacytoid DCs, suggesting that the differentially produced cytokines in former cells such as IL-12 may play a significant role throughout the process (70, 71). Therefore, the VDR mediated inhibition of myeloid DC maturation, coupled with changes in cytokines such as IL-10 and IL-12 appears to ultimately render the myeloid DCs to be either inactive or tolerogenic (68, 70).

The changes in anti- and pro-inflammatory cytokines in the 1,25(OH)₂D₃ or VDR deficient mice has a key role in favoring Treg induction in peripheral tissues (72). For example, DCs secreting IL-10 induce iTreg cells that do not express Foxp3 (Fox3⁻) (51). These Foxp3⁻ IL-10⁺ Treg cells possess immune suppressive properties and commonly named Tr1 (T regulatory type-1) or Tr1-like cells (73). Vitamin D has also been shown to be able to induce Foxp3⁺ Treg cells though it remains unclear if the changes in cytokines contribute to these events (52, 53). The dynamics between vitamin D and FoxP3⁺ Treg cells was confirmed in the study reporting that Treg induction in peripheral lymphocytes was abolished in VDR knockout mice in which the utilization of this nutrient is limited (74).

3.3 N-3 fatty acids may modulate both antigen-specific Th1/Th17 differentiation and iTreg function

N-3 fatty acids are commonly known to produce anti-inflammatory metabolites and thereby reduce cancer risks (75, 76). Recently, modulating effects of these fish oil components on immune cell development including T cell differentiation have been extensively investigated as a part of the mechanism(s) explaining the observed efficacy of n-3 fatty acids on the inflammatory processes (54, 55, 77). While these findings appear positive, the study results are mixed for which the reason remains unclear. For example, in *Fat-1* transgenic mice where n-6 fatty acids are genetically converted to n-3 fatty acids (78), n-3 fatty acids are shown to suppress differentiation of pro-inflammatory Th1/Th17 cells without altering the expression of Treg cells (55). On the other hand, in *Smad3*^{-/-} inflammatory colon cancer mice, feeding these animals with diet containing various concentrations (0.75% to 6%) of n-3 fatty acids suppressed CD4⁺ CD8⁺T effector cell population and increased Treg cell activity (79). These results suggest that one of the main functions of n-3 fatty acids may be the maintenance of homeostasis between effector T cells and Treg cells that inhibit CD4⁺CD8⁺ T cell function and thereby prevent autoimmunity.

3.4 Modulating effects of dietary polyphenolics on the suppressive activity of iTreg cells

TGFβ, one of the anti-inflammatory cytokines, is actively induced by myeloid immature DCs within the tumor microenvironment (80). When TGFβ works with proinflammatory

cytokine IL6, it primes the differentiation of naïve CD4⁺ T cells into IL17-producing Th17 cells (81, Figure 2). Interestingly, TGFβ is also key to the conversion of peripheral naïve CD4⁺T cells into Foxp3⁺ iTregs with regulatory capacity (82). This fate decision between Th17 and Treg cells during differentiation seems to be determined by a ligand activated transcription factor aryl hydrocarbon receptor (AhR) (83–88) and hypoxia-inducible factor-1α (HIF-1α) (89, 90). Recently, it was shown that AhR-mediated stability and suppressive activity of iTreg cells require both the expression of a lineage-determining transcription factor Foxp3 and epigenetic reprogramming through T cell receptor (TCR) stimulation (91). On the other hand, HIF-1α was reported to mitigate Foxp3 expression by increasing its degradation in the proteasome and thereby fostering Th17 lineage commitment (89, 90). Nevertheless, the relevance of HIF-1α to the T cell differentiation has not been fully elucidated yet.

The AhR-related Treg induction and epigenetic regulation may be modulated by various dietary polyphenolics including naringenin found in citrus fruits and epigallocatechin-3-gallate (EGCG) in green tea (56, 57). These polyphenolics are known to possess the ability to inhibit the expression of proinflammatory cytokine IL6 (92, 93). Naringenin is a natural ligand for AhR and the complex stimulates T cell differentiation toward suppressive Treg cells (56, Figure 2). While this event seems to occur independently from TGFβ, the availability of unoccupied AhR is considered critical for such effects (56). Another dietary polyphenol compound found in tea, EGCG, was shown to significantly increase Treg frequencies (1.8 fold) in Balb/c mice when injected (i.p., 50 mg/kg) for 7 days (57). This effect of EGCG may involve its ability to inhibit DNA methyl transferase (DNMT) activity and thereby increase the expression of Foxp3. The similar effects of other dietary inhibitors of DNMT such as sulforaphane (94) and γ-tocopherol (95) may support this possibility. Regardless, further research on the mechanism elucidating the modulating effects of these dietary components on Treg expression and their ability to suppress other effector cells is warranted.

4. Discussion

The growth and spread of cancer depend not only on the biological characteristics of the tumor per se but also on the host responses. Adaptive immune cells such as B and T cells respond to a specific antigen while innate lymphocytes including NK cells recognize target cells based on the absence of specific cell surface determinants and affect their functions by simple kill/do not kill decisions. Although innate immune cells are less sophisticated than adaptive immune cells in terms of the effector function, these cells nevertheless are early responders and a front-line defense against invading pathogens or malignant non-self molecules. While this tumoricidal activity of NK cells is critical to protect hosts from invading pathogens, these cells could also cause autoimmunity that has been reported to be regulated by Treg cells. No doubt, it is extremely important to understand the early stage(s) of pathogen-host interactions, and redirect these events from a pro-tumor to an anti-tumor state. Diet may represent a subtle approach to regulating NK cells without losing their homeostasis maintained by Treg cells.

The evidence for the antagonizing effect of Treg cells on NK cell function was first reviewed by Zimmer *et al.* in 2008 (96). Treg cells are produced in the thymus (nTreg) and are also induced from conventional CD4(+) T cells at peripheral sites (iTreg). It has been reported that dietary constituents could modulate iTreg cell function through which they enhance immune responses without causing autoimmunity. However, the mechanism explaining the controlling role of diet-induced Treg cells in NK cell tumoricidal activity remains unclear. Furthermore, considering the main focus of this paper is on cancer prevention which usually deals with normal cells and/or pre-malignant stage of normal cells, studies involving cancer animal models that could be used to examine or detect the modulating effects of dietary components on these immune cells have not been covered in this paper.

Available data suggest that certain sites such as in the gastrointestinal tract that is continuously exposed to foods and other exogenous stimuli are dominated by induced Treg cells that arise from peripheral conversion, rather than T cell differentiation in the thymus (6). These iTreg cells appear to be the main target for immune-modulating dietary components such as vitamins A (67), vitamin D (72), n-3 fatty acids (55), and plant polyphenolics (56), which contribute to the fine tuning of immune cells to maintain homeostasis. While these studies suggest the role of diet-derived nutrients in modulating gastrointestinal immunity, several questions including if the effects of dietary components are achievable within the range of physiological concentrations remain unanswered. To clarify this gap existing in research area of nutrition and immunity, the dietary levels along with experimental models adopted in the reported studies are listed with physiological concentrations of the effective bioactive food components in human plasma in Table 1. Interestingly, the effects of RAs and vitamin D on iTreg cells were examined with the physiologically achievable concentrations in humans. In contrast, the influence of other dietary components such as n-3 fatty acids, naringenin, and EGCG was evaluated with exaggerated concentrations either *in vitro* or *in vivo*. Thus, it is suggested to evaluate the study results with caution because it remains unclear how the data generated with high doses in experimental models translate into humans.

In conclusion, immunoprevention of cancer may occur by promoting antitumor effector cells such as NK cells for tumor suppression as well as by counteracting the accompanied autoimmunity through the enhancement of the immunoregulatory mechanisms such as Treg activity that inhibits effector cell cytotoxic properties. When the balance between immunity and autoimmunity is not maintained appropriately as in tumors, the Treg cells alter their polarity and stability to adjust to a new microenvironment. Through these changes, Treg cells are adopted by malignant cells as a mediator to escape from immunity and increase their survival (103, 104). While some studies support the general concept that specific dietary components contribute to immunoprevention by enhancing tumoricidal activity of NK cells and inducing the controlling properties of Treg cells (Figure 3), the evidence largely remains indirect. Therefore, the underlying mechanisms explaining the precise role of dietary components in maintaining the balance between immune surveillance and immune tolerance remain as an emerging research agenda which warrants further investigation.

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Abbreviation

AhR	aryl hydrocarbon receptor
APC	antigen presenting cell
CCL	C-C motif chemokine ligand
CCR	C-C motif chemokine receptor
CNS1	conserved non-coding sequence 1
CLA	conjugated linoleic acid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DNMT	DNA methyl transferase
EGCG	epigallocatechin-3-gallate
Foxp3	forkhead box protein 3
HIF1α	hypoxia-inducible factor 1 α
HLA	human leukocyte antigen
IFN	interferon
IL	interleukin
IP₃	inositol (1, 4, 5)-triphosphate
ItpkB	inositol triphosphate 3-kinase B
iTreg	inducible regulatory T cells
KIR	killer immunoglobulin-like receptor
LPS	lipopolysaccharide
MHC	major histocompatibility complex
NFAT	nuclear factor of activated T cell
NK	natural killer
NKG2	natural killer group 2
nTreg	naturally occurring regulatory T cells
PAMP	pathogen-associated molecular pattern
PI(3,4,5)P₃	phosphatidylinositol (3, 4, 5)-triphosphate
PUFA	polyunsaturated fatty acid

PI3K	phosphoinositide 3-kinase
RA	retinoic acid
RAR-α	retinoic acid receptor- α
ROS	reactive oxygen species
STAT	signal transducer and activator of transcription
TCR	T cell receptor
TGF-β	transforming growth factor- β
Th	T-helper
TNF-α	tumor necrosis factor- α
Treg	regulatory T
Tr1	T regulatory type-1
VDR	vitamin D receptor
Wt	weight

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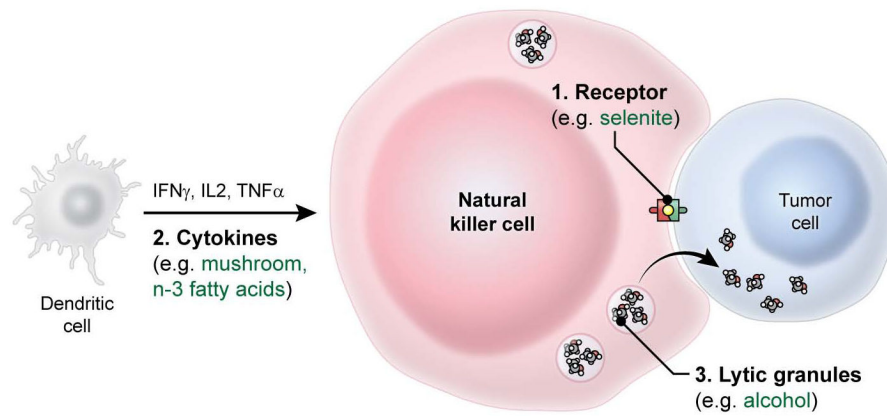


Figure 1. Dietary components modulate tumoricidal activity of NK cells by three distinct processes including receptor-ligand interactions, the release of cytokines, and the secretion of lytic enzymes. Specific examples are discussed in the text under section 2. This figure does not reflect the actual size of cells.

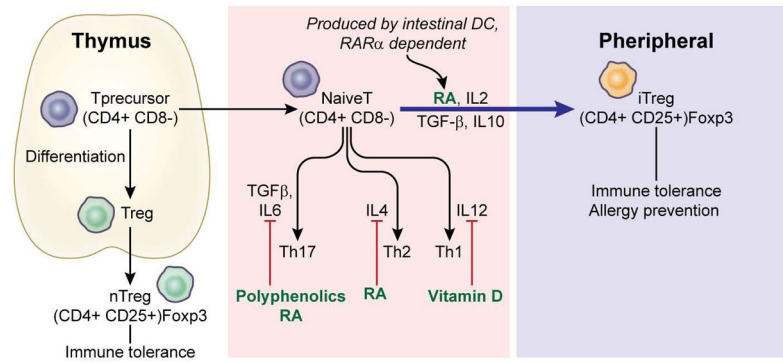


Figure 2.

A naïve T cell can be differentiated into any Th effector cells depending on the cytokines released into the microenvironment. Dietary constituents including vitamin A metabolite retinoic acids, vitamin D, and polyphenolics are shown to inhibit the expression of various cytokines such as IL4, IL6, and IL12, and thereby increase TGF β -dependent peripheral Treg induction.

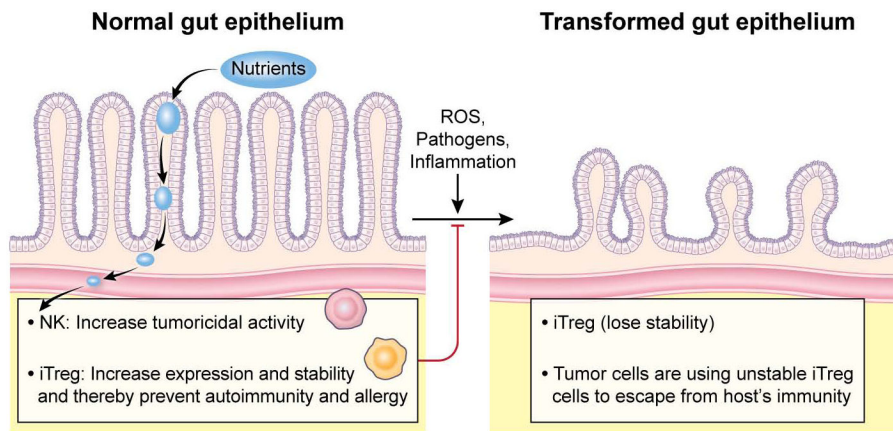


Figure 3.

Nutrients are metabolized to small molecular weight compounds which increase tumoricidal activity of NK cells and induce the controlling properties of iTreg cells. The modulating effects of nutrients on the expression and function of iTreg cells are critical to prevent autoimmunity and allergy. When the gut epithelium is transformed by external stimuli including reactive oxygen species (ROS), pathogens, and inflammatory molecules, iTreg cells lose their stability and function. However, the role of these iTreg cells in tumor microenvironment remains unclear.

Dietary modulation of Treg cell induction with a focus on the concentrations adopted for studies and their human plasma levels

TABLE 1

BFCs*	Effects	Concentration used in studies	Model	Human plasma levels	Reference
Retinoic acids	TGF- β -dependent iTreg generation at the intestine	10–100 nM	C57BL/6 mice	4–14 nM	49, 50, 97
Vitamin D	Inhibits the maturation of myeloid DCs [†] and thereby increases iTreg	15–20 μ M [1, 25 (OH)2D3]	C57BL/6 Rag ^{-/-} mice	30 μ M [25(OH)D3]	51–53, 98
N-3 fatty acids	Modulate Th1/Th17 differentiation and iTreg function	4–6% of diet	Rag ^{-/-} mice	DHA [‡] ~3.5 mol/% EPA [§] ~1.1 mol/%	54, 55, 99, 100
Naringenin	Stimulates AhR-mediated Treg induction	50 μ M	Murine splenic CD4+ T cells	~ 1.0 μ M	56, 101
EGCG [^]	Inhibits DNMT and thereby increases Foxp4 expression	7.8 μ M	Balb/C mice	~ 0.3 μ M	57, 102

* Bioactive food components (BFCs)

[†] Dendritic cells (DCs)

[‡] Docosahexaenoic acid (DHA, 22:6n-3): The value is presented as mol/% of phospholipid

[§] Eicosapentaenoic acid (EPA, 20:5n-3): The value is presented as mol/% of phospholipid

[^] Epigallocatechin 3-gallate (EGCG)