REVIEW

Modulators affecting the immune dialogue between human immune and colon cancer cells

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Abstract

The link between chronic inflammation and colorectal cancer has been well established. The events proceeding along tumorigenesis are complicated and involve cells activated at the cancer microenvironment, tumor infiltrating polymorphonuclears, immune cells including lymphocyte subtypes and peripheral blood mononuclear cells (PBMC), as well as tumor-associated macrophages. The immune cells generate inflammatory cytokines, several of them playing a crucial role in tumorigenesis. Additional factors, such as gene expression regulated by cytokines, assembling of tumor growth- and transforming factors, accelerated angiogenesis, delayed apoptosis, contribute all to initiation, development and migration of tumor cells. Oxygen radical species originating from the inflammatory area promote cell mutation and cancer proliferation. Tumor cells may over-express pro-inflammatory mediators that in turn activate immune cells for inflammatory cytokines production. Consequently, an immune dialogue emerges between immune and cancer cells orchestrated through a number of activated molecular pathways. Cytokines, encompassing migration inhibitory factor, transforming growth factor beta 1, tumor necrosis factor-α, Interleukin (IL)-6, IL-10, IL-12, IL-17, IL-23 have been reported to be involved in human cancer development. Some cytokines, namely IL-5, IL-6, IL-10, IL-22 and growth factors promote tumor development and metastasis, and inhibit apoptosis *via* activation of signal transducer activator transcription-3 transcription factor. Colon cancer environment comprises mesenchymal, endothelial and immune cells. Assessment of the interaction between components in the tumor environment and malignant cells requires a reconsideration of a few topics elucidating the role of chronic inflammation in carcinogenesis, the function of the immune cells expressed by inflammatory cytokine production, the immunomodulation of cancer cells and the existence of a cross-talk between immune and malignant cells leading to a balance in cytokine production. It is conceivable that the prevalence of anti-inflammatory cytokine production by PBMC in the affected colonic mucosa will contribute to the delay, or even to halt down malignant expansion. Targeting the interplay between immune and cancer cells by mediators capable to alter cytokine secretion toward increased anti-inflammatory cytokine release by PBMC and tumor associated macrophages, may serve as an additional strategy for treatment of malignant diseases. This review will focus on the inflammatory events preceding tumorigenesis in general, and on a number of modulators capable to affect colon cancer cell-induced production of inflammatory cytokines by PBMC through alteration of the immune cross-talk between PBMC and cancer cells.

Core tip: The substantial number of studies that soundly demonstrated the close relationship between chronic inflammation and colon carcinogenesis has encouraged researchers to investigate the pathways interrelated with this process. The results point-out to various fac-

tors, molecules and genes that may jointly enhance or inhibit tumor development. The close linkage between immune and colon cancer cells resulting in a cross-talk between them with a consequent equilibrium in inflammatory cytokines release opens a new window for understanding the complicated stages of cancer initiation and progression. Moreover, the capability of emerging modulators to target the dialogue between immune and cancer cells indicates that immunomodulation may serve as a promising addition to the drug armamentarium for colorectal cancer.

INFLAMMATION AND CANCER

Colon cancer is one of the common malignancies observed in clinical practice and it is one of the frequent causes of human death. No wonder therefore, that extensive efforts have been made, and are still carried on to enlighten the grounds providing suitable conditions for initiation, development, proliferation and spreading of this malignant process. Therefore, to mention even a part of the studies on the subject is beyond the scope of the present review. However, it seems reasonable to focus on a topic that has gained a wide interest, *i.e.*, the relation between chronic inflammation and cancer in general and colorectal malignant tumors in particular. Clinical observations based on the increased rate of colorectal cancer in patients with chronic colitis and Crohn's disease support this concept[1,2]. According to Rogler[3], thirty five percent of the patients suffering from ulcerative colitis for more than 35 years are at an increased risk for development of colorectal cancer, although population based studies point toward a lower risk. Factors, such as enhanced activation of the inflammatory cells by malignant cells and by the tumor microenvironment may initiate, and further promote cancer development[1,4]. Nguyen *et al*[5] have reported data suggesting that incitement of epithelial signal transducer activator transcription-3 (STAT3) in the inflamed colon plays a significant role in tumor progression by increasing mobilization and infiltration with CD8$^+$ lymphocyte population in the large intestine. Furthermore, according to the authors, activated STAT3 restrains the recruitment of regulatory Treg lymphocytes that possess the ability to suppress host immune responses with a subsequent enhancement of tumor progression. To make the issue more complicated, there are suggestions supporting the possibility of cancer-related inflammation, *i.e.,* the prospect that alterations inflicted by the tumor itself are those to provoke the inflammatory process[6]. Shigdar *et al*[7] emphasize the role of tumor associated immune cells that secrete cytokines capable to promote development of tumor stem

cells. The activated stem cells from their part produce factors building a microenvironment ready to facilitate tumor growth and spreading. The connection between the immune activity of mononuclear cells and inflammation has been demonstrated by Leung *et al*[8] who have examined interleukin (IL)-12A and IL-22 cytokine production and the number of T helper cells from colon of patients with ulcerative colitis and Crohn's disease. The results showed an increased release of IL-17$^+$ and an elevated number of CD4$^+$ cells in patients with Crohn's disease compared to healthy individuals and patients with ulcerative colitis. On the other hand, patients with ulcerative colitis had decreased number of IL-22$^+$ cells. The role of bacteria in colon cancer etiology has been considered. Based on the fact that colonic mucosal cells from colorectal carcinoma are colonized by intracellular *Escherichia coli* (*E. coli*) and that the DNA repair gene *MUTYH* being blamed for cancer development is a homologue of *E. coli* gene mutY, Khan *et al*[9] have suggested that *mutY* gene and *E. coli* themselves might be involved in colorectal carcinoma development. Aggarwal *et al*[10] have reviewed in detail the links that build the chain of events leading to cancer and consist of pro-inflammatory substances that suppress apoptosis, enhance neovascularization and promote an increased activity of the immune system with a subsequent generation of pro-inflammatory cytokines. As for the relationship between chronic inflammation and carcinogenesis Basnet *et al*[11] divide the pro-inflammatory factors in two groups *i.e.*, external, that include pollutants, viruses, bacteria and even foods, as well as internal, comprising free radicals and the cytokines IL-1β, tumor necrosis factor (TNF)-α, NF-κB and NSAID-activated gene-1. It should be emphasized that cancer-associated inflammation plays not only an etiological role, but has also a therapeutic and even a prognostic potential. Thus, Laird *et al*[12] have shown that an inflammation score based on C-reactive protein level and albumin concentration on one hand and patient's performance status on the other hand, predicts fairly well the survival of patients with advanced stage cancer. A review on the relationship between innate immunity, inflammation and cancer, detailing the function of inflammatory cytokines as mediators of inflammation-related carcinogenesis has been reported by Lin *et al*[13].

PERIPHERAL BLOOD MONONUCLEAR CELLS AND CYTOKINE PRODUCTION

In regard to the link between chronic inflammation and carcinogenesis, the mononuclear cells appear to be persuasive warriors expressing a vivid phagocytic capacity[14], to encompass Toll-like receptors able to recognize pathogen molecules and to be capable to modulate both innate and adoptive immune responses[15-17]. Studies have shown that the number of Th1 and Th17 cells is increased in patients with inflammatory bowel disease and correlates well with its severity[18], whereas the number of CD14$^+$ and CCL11$^+$ mononuclear cells has been found to be

increased in colonic biopsies from patients with ulcerative colitis[19]. According to van Dooren *et al*[20] there is a difference between cytokine production by whole blood with CCL11, IL-23 and IL-12p40 solely presented, and lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells (PBMC) producing IL-20, vascular endothelial growth factor (VEGF) and GM-colony stimulating factor (CSF). Endogenous type interferon 1 (IFN-1) released by colon mononuclear cells in mice with T-cell colitis has been demonstrated to be essential for stimulated production of the anti-inflammatory cytokines IL-10, IL-1ra and IL-27[21]. Inflammasomes are closely related to chronic inflammation since they act as activators of IL-1β and IL-18 release by PBMC[22,23]. Moreover, activation of inflammasomes may stimulate cancer development[24]. The ability of PBMC to produce inflammatory cytokines plays a major role in the modulation of chronic inflammatory responses associated with carcinogenesis. This particular function is promoted by various factors, such as amorphous silica particles capable to increase IL-1β and IL-8 production[25], and cortisol that have been shown to suppress secretion of IL-1β, IL-6, IL-17 and G-CSF[26]. Recently, Veinalde *et al*[27] have reported that double stranded RNA has the capacity to induce PBMC to produce a considerable number of both pro- and anti-inflammatory cytokines. Metal particles, such as titanium and stainless steel originating in patients with implanted medical devices have been shown to enhance increased production of IL-6 and IL-1 by PBMC, but to lower the level of TNF-α[28]. Even mental conditions, such as post-traumatic stress disorders, may affect the immune activity of PBMC causing an increased spontaneous release of the pro-inflammatory cytokines IL-1β and TNF-α[29]. Finally, it should be noted that there is no obligatory correlation between the level and type of cytokines produced by PBMC and those in the whole blood[20].

COLON CANCER CELLS AND CYTOKINE PRODUCTION

Concerning the role of chronic inflammatory process as a basis for carcinogenesis, the question if colon cancer cells possess the capacity for cytokine production comes up. In that sense the reports in the literature are rather scarce. It is our experience that HT-29 and RKO cells from human colon cancer lines do not produce cytokines unless they are exposed to various stimuli. Yoshimoto *et al*[30] have shown that HT-29 carcinoma cells stimulated with LPS, IFNγ and epithelial growth factor (EGF) expressed a modulation of the Hedgehog (Hh) pathway signaling. Hh agonists exerted a decrease of IL-8 and monocytic chemotactic protein-1, compared to its antagonists such as dopamine, LPS, IFNγ and EGF. The connection between chronic inflammation, cytokine release and colon cancer has been reviewed by Klampfer *et al*[4] and by Lin *et al*[13]. According to the authors, the inflammatory process is initiated and further driven to carcinogenesis by soluble factors and cytokines released by

both cancer-and recruited immune cells, including those at the tumor environment. TNF-α, IL-6, IL-12 and IL-23 from the group of pro-inflammatory cytokines are of particular importance, since they are involved not only in maintaining the inflammatory process, but they promote tumor cell survival by exerting an anti-apoptotic activity, induce angiogenesis and are crucial for further tumor development and tumor cell migration.

IMMUNE CROSS-TALK BETWEEN PBMC AND CANCER CELLS

Accepting the presumption that carcinogenesis is closely linked to chronic inflammation, it is conceivable that immune, stromal and mast cells mobilized to an affected area will interfere with tumor cells and will establish an immune dialogue resulting in a prompt release of a number of inflammatory cytokines, as it is graphically shown in Figure 1. It has been reported that unstimulated PBMC release a small amount of inflammatory cytokines[31]. On the other hand, PBMC exposed to HT-29 or RKO cells from human colon cancer lines or their supernatants were able to release both pro-and anti-inflammatory cytokines, in some cases in a dose-dependent matter. However, the release of the pro-inflammatory cytokines TNF-α, IL-1β and IFNγ was more pronounced[31]. It is notable that direct exposure of PBMC to cancer cells resulted in higher cytokine secretion compared to cytokine levels released by PBMC incubated with cancer cells' supernatants, a finding similar to that observed by Ma *et al*[32] in co-cultures of PBMC with gastric cancer cells. In their hands the release of transforming growth factor (TGF)-β by PBMC was markedly increased when they were co-cultured with gastric carcinoma cells. Cytokines secreted during immune-cancer cells communication may affect the process of carcinogenesis. Combination of the pro-inflammatory cytokines IL-32 and TNF-α restrained the growth of HCT116 and SW620 human colon cancer cells by inhibition of TNF-α dependent DNA synthesis[33]. PBMC co-cultured with cells from an AGS human gastric epithelial line expressed a decreased TGF-β1 and an increased TGF-β2 cytokine secretion. On the other hand, incubation of PBMC with cells from a gastric cancer line (MKN45) caused enhancement in TGF-β1 production, a cytokine known to move forward cancer development. It is of interest that cancer cells incubated with PBMC showed an increase in TGF-β1 mRNA level up to 3-fold higher than cancer cells cultured alone[32]. The way PBMC and cancer cells create an immune dialogue is intriguing. Studies have shown that intercellular communication between tumor-associated leukocytes and malignant cells proceeds through exosomes released from tumor cells and results in enhanced production of pro-inflammatory cytokines and metalloproteinases[34]. Redzic *et al*[35] have underlined the capacity of extracellular vesicles purified from various cancer cell lines to stimulate PBMC to release a number of tumor promoting factors including IL-6. The role of autophagy in inflection of both innate
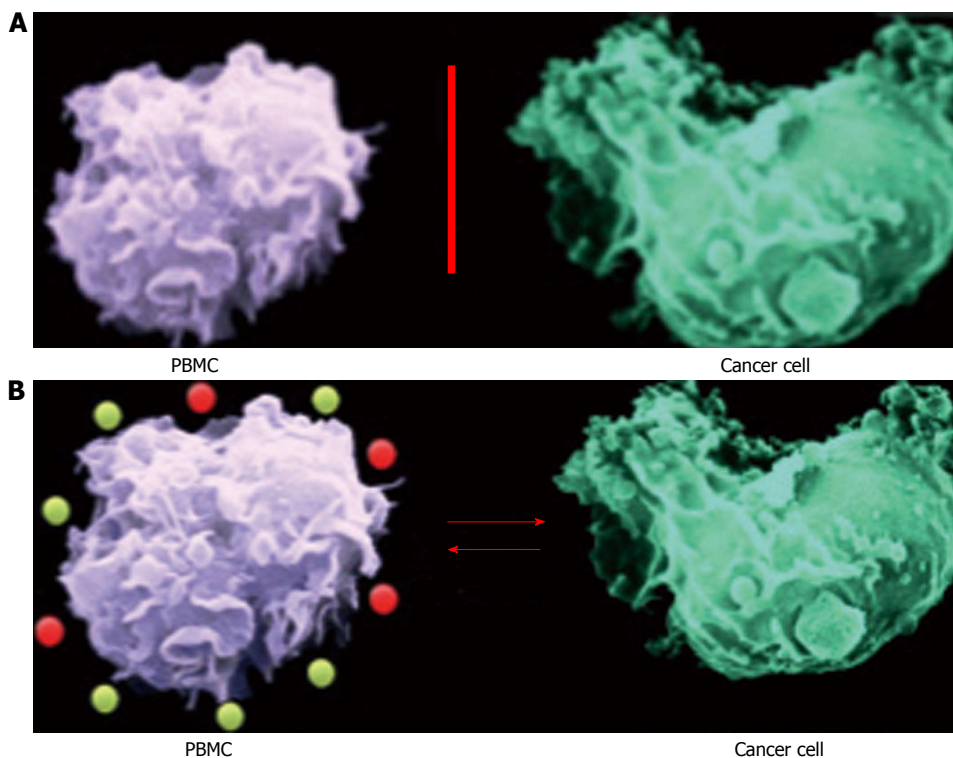
Figure 1 Interrelationship between peripheral blood mononuclear cells and human colon cancer cells. A: Unstimulated peripheral blood mononuclear cells (PBMC) do not release significant amount of inflammatory cytokines. B: Following direct contact with cancer cells PBMC are stimulated for pro-inflammatory (red dots) and anti-inflammatory (yellow dots) cytokine production.

and adaptive immunity is gaining importance. Autophagy modulates production of the pro-inflammatory cytokines IL-1β and IL-18 that consecutively enhance the functional expression of B and T lymphocytes, as well as that of the IL-2 receptor[36]. Reduced expression of IL-1β, IL-18 and IL-21 in mice with colitis-associated cancer resulted in achievement of a higher clinical score[37,38]. Conversely, cytokines released by immune cells participated in regulation of autophagy. Thus, IFNγ being a Th1 helper cytokine induced enhanced autophagy in macrophages, whereas IL-4 and IL-13, which are Th2 cytokines, exerted an inhibitory effect[39]. Similar findings have been reported by Schmeisser *et al*[40] who have shown that IFNγ and TGF-β enhance autophagy in human cancer lines derived from uterus cervix, breast, glioblastoma and alveolar carcinoma. The role of autophagy in regulation of immune responses has been described in details by Valdor *et al*[39].

MODULATORS OF THE CROSS-TALK BETWEEN IMMUNE AND COLON CANCER CELLS

It has been shown that during the inflammatory process, the vicinity of the tumor comprises tumor-associated macrophages and a significant number of white blood cells producing various cytotoxic mediators, enzymes linked with tumor development and cytokines, such as IL-1, IL-6, IL-8 and IFNs[41]. A considerable number of drugs, vitamins, nutrients and spices have been shown

to exert anti-cancerous effect *via* various pathways. Relying on observations that immune cells maintain chronic inflammatory processes by cytokine release, and the ability of cancer cells to alter the type and level of cytokine production following direct cell contact, the question arises if intercellular communication may be directed by immune modulators in a way capable to increase production of anti-inflammatory cytokines, as schematically presented in Figure 2. Table 1 summarizes our experience and findings with modulators that target the communication between immune and cancer cells.

Aspirin
It is conceivable that anti-inflammatory drugs may play a major role in both abolishing inflammation and restraining cancer development. Indeed, a substantial number of experimental data indicates that non-steroidal anti-inflammatory drugs (NSAID) may inhibit colon cancer development. The anticancer activity of most of them is based on their selective inhibitory effect on cyclooxygenase-2 (COX-2) activities, that play a crucial role in colon cancer development and progress[42]. In that sense, aspirin has drawn particular attention since it expresses an inhibitory activity on both COX-1 and COX-2 enzymes. However, studies have showed that NSAID anti-cancer properties may proceed also through COX-independent pathways, such as inappropriately Delta1/Notch1 signal transduction pathway, and upregulation of *NAG-1* gene that is a member of the TGF-β superfamily[42-44]. Bergman *et al*[45] have found that addition of aspirin to PBMC
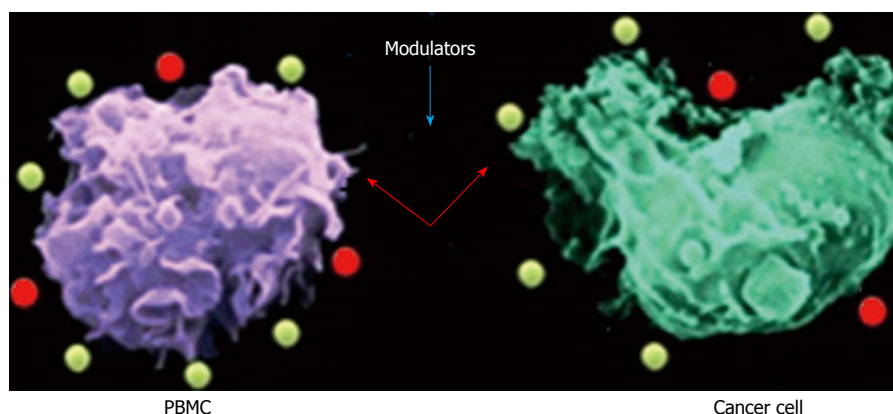
Figure 2 Schematic presentation of the way immune modulators modify the cross-talk between peripheral blood mononuclear cells and cancer cells. Following alteration of the immune dialogue between these two cell types, the modulators inhibit cancer cell-stimulated peripheral blood mononuclear cells (PBMC) to generate pro-inflammatory cytokine (red dots), acting as cancer promoters.

Table 1 Modulators acting on cross talk-induced cytokine secretion

	Ref.	Pro-inflammatory cytokines				Anti-inflammatory cytokines	
		IL-1β	IL-6	TNFα	IFNγ	IL-1ra	IL-10
PBMC + colon cancer cells	Bessler *et al*[31] (2010)	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑
Modulator							
Aspirin	Bergman *et al*[45] (2011)	↑ slightly	↓	ND	↓/↑[1]	0/↓[1]	↓
Colchicine	(Submitted for publication)	↑	0/↑[1]	↓	ND	0	↓/↑[1]
Statins	Bergman *et al*[66] (2011)	↓	0	ND	↓	↓	↓
Caffeine	Bessler *et al*[75] (2012)	0	0	↓	↓	↓	↓
Resveratrol	Bergman *et al*[82] (2013)	↓	↑ /0[1]	↓	↓	↓	↓
Curcumin	Bessler *et al*[92] (2012)	↓	↓	↓	ND	↓	↓
Vit. D3	Bessler *et al*[99] (2012)	↓	0	↓	ND	0	↓

[1]Respresents results for HT-29-induced/RKO-induced cytokine secretion by PBMC. ND: Not determined; 0: No change in cytokine secretion; PBMC: Peripheral blood mononuclear cells; IFN: Interferon; TNFα: Tumor necrosis factor-α; IL-6: Interleukin-6; Vit. D3: Vitamin D3.

co-cultured with HT-29 or RKO cells from human colon cancer lines, affected the immune equilibrium between immune and cancer cells by inducing inhibited production of the pro-inflammatory cytokines IFNγ and IL-6. Notably, the secretion of anti-inflammatory cytokines was somewhat depressed. Skeen *et al*[46] have stressed the role of the cross-talk between the anti-inflammatory cytokine TGF-β1 and factors critical for colorectal tumorigenesis. A decreased TGF-β1 expression is linked to both increased inflammation and colorectal cancer evolution. The expansion of colon-cancer is closely related to the pro-inflammatory cytokines IL-6, IL-8, TNF-α, and VEGF. Aspirin has been shown to reduce the pro-inflammatory IL-6 expression with a subsequent reduction of CRP, an important protein for the maintenance of chronic inflammation[47]. Since cancer cells' apoptosis and death are mediated through TNF-α and IL-1-induced transcription factor NF-κB activation, aspirin may increase the apoptotic rate of the malignant cells by inhibited expression of these cytokines[48]. On the other hand, NF-κB activation can promote production of pro-inflammatory cytokines in colon cancer cells and particularly IL-8 with a further enhancement of the gastrointestinal inflammation that may explain the undesirable effect of aspirin on the alimentary system[49]. Lang *et al*[50] have found that monocytes incubated with supernatants from human carcinoma cell lines showed a down-regulation of the chemokine receptor CCR5, and beta 2-integrin Mac-1, resulting in impaired monocyte migration and adhesion, functions important for exertion of their anti-cancer activity. The authors have observed that administration of a selective COX-2 inhibitor, rofecoxib, to cancer patients improved markedly their reduced monocyte CCR5 levels and migration capacities. Using SW480 colorectal cells, Lai *et al*[51] have reported that aspirin, in a concentration-dependent manner, was able to inhibit their proliferation and promote cancer cell apoptosis and necrosis by cell arrest at the G_0/G_1 phase. The proportions of cells at the S- and G_2/M phases was decreased.

Colchicine

Colchicine is an anti-inflammatory agent, known since long as the drug of choice for management of gout. It is gaining increased interest for treatment of other conditions, such as familial Mediterranean fever and Behçet disease. It has been shown that its anti-inflammatory effect proceeds *via* inhibition of the pro-inflammatory cytokines IL-1 and IL-1β release[52]. Moreover, by restrain of the NF-κB pathway and blocking cell mitosis, colchicine may exert an inhibitory effect on tumorigenesis. Addition of colchicine to human LPS stimulated PBMC exerted a disruptive effect on cellular microtubules with a consequent increased IL-1β and a decreased TNF-α release[53]. In a recent study it has been shown that colchicine added to co-cultures of PBMC with either HT-29 or RKO human colon cancer cells promoted cancer cells-stimulated PBMC to produce IL-1β and to inhibit the release of TNF-α and IL-10[54]. It is conceivable that colchicine may

act on tumor development by modulation of the immune balance between immune and cancer cells with a subsequent interference in production of inflammatory cytokines by cancer cells-activated PBMC. A similar tumor cell-macrophage cross-talk has been observed in other studies. TNF-α released from colon cancer cells stimulated TNF-α and CSF-1 production by mouse macrophages indicating the existence of an immune intercellular communication between these cell types[55]. Furthermore, it has been shown that monocytes interacting with cancer cells differentiate into tumor-associated macrophages that may be associated with angiogenesis and metastasis[56].

Statins

Although statins, branded as 3-hydroxy-methylglutaryl coenzyme (HMG-CoA) reductase inhibitors, have been introduced as potent anti-cholesterol agents in cardiovascular diseases, a substantial number of studies indicate that these drugs possess additional attributes including anti-inflammatory[57,58] and anti-cancer activities[59,60]. It is notable that statins enhance cytokine production by acting directly on PBMC. The hydrophobic statins lovastatin and simvastatin increased the production of IL-1β and decreased IL-2 and IFNγ secretion[61]. Simvastatin, atorvastatin, fluvastatin and pravastatin reduced IL-6 production by human PBMC co-cultured with human vascular smooth muscle cells by 53%, 50%, 64% and 60% respectively[62]. Simvastatin induced increased production of IL-18, TNF-α and IFNγ by human PBMC[63]. Bessler *et al*[64] have shown that the effect of statins on malignant cell proliferation depends on their dosage, physiochemical properties and the type of cancer cells. Both hydrophilic and hydrophobic statins inhibited proliferation, but not apoptosis in cells from HuCC human colon carcinoma line. However, this effect differed when statins were incubated with EHEB, K562 and Raji-cells (B chronic lymphocytic leukemia, human erythroleukemia, and Burkitt lymphoma cell lines, respectively). EHEB and K562 cell proliferation was inhibited by hydrophobic but not by hydrophilic statins. The hydrophobic statins enhanced cell apoptosis in the hematological lines. Similar observations have been reported by Kato *et al*[60] who have found that hydrophobic, but not hydrophilic statins, induced apoptosis in cells from gynecological cancers expressing high levels of HMG-CoA reductase. Simvastatin caused a decreased release of IL-6 and IL-8 from HT-29 and Caco-2 cells derived from colorectal cancer lines[65]. The capacity of statins to modulate inflammation-induced colon cancer proliferation by alteration of the equilibrium between pro- and anti-inflammatory cytokines secreted by tumor cells-stimulated PBMC is of particular interest. Statins added to PBMC stimulated for cytokine secretion by direct contact with HT-29 or RKO cells from human colon carcinoma lines induced a decreased expression of the anti-inflammatory cytokines IL-1ra and IL-10[64,66].

Nutrients

Nutrients and naturally-occurring phytochemicals are gaining positive reputation based on their beneficial prop-

erties on health and their carcino-preventive capacities[67]. The number of studies on the potential inhibitory activity of these substances on colorectal cancer development is rapidly mounting; hence to encompass the mechanisms by which all of them influence tumorigenesis is beyond the scope of the present review. Having a personal experience with a few of them, we therefore will concentrate on phytochemicals and nutrients with substantiated anti-inflammatory and anti-cancer activities.

Caffeine

The xanthine alkaloid caffeine is the main compound of coffee, one of the most popular beverages renowned for its long history. Apart from its beneficial effect on a lengthy list of diseases[68], studies demonstrate that coffee possesses anti-cancer properties. Clinical studies indicate that prolonged coffee consumption abolishes the risk for colorectal cancer[69,70]. The ways caffeine exerts its carcino-preventive effect have been reviewed in details[71,72]. It is noteworthy that caffeine is involved in modulation of the immune system. It has been reported that addition of caffeine to concanavalin A-stimulated mouse lymphocytes inhibited the generation of TNF-α, IFNγ and IL-2[73]. Caffeine, being a potent adenosine receptor antagonist, has been found to be able to decrease TNF-α release from LPS stimulated cord blood monocytes[74]. Due to its inhibitory activity on adenosine receptors caffeine has been capable to alter the stability of hypoxia-inducible factor 1-alpha, VEGF and IL-8 expression in tumor cells[72]. Bessler *et al*[75] have suggested an additional mechanism based on the capacity of caffeine to alter the immune balance between PBMC and HT-29 or RKO cells derived from human colon cancer lines. The authors have observed that caffeine inhibited secretion of the pro-inflammatory cytokines TNF-α and IFNγ by PBMC stimulated for cytokine production through a direct contact with cancer cells. The fact that caffeine did not enhance cytokine production by PBMC co-cultured with both types of cancer cells and that supernatants derived from cancer cells incubated with caffeine did not affect this activity, brought the authors to the conclusion that caffeine, at least *in vitro*, exerts its anti-inflammatory and anti-cancer effects *via* increasing anti-inflammatory cytokine production by PBMC, but only subsequent to a direct contact between immune and cancer cells.

Resveratrol

Resveratrol, a phenolic compound present in grapes and their seeds has been shown to exert a favorable effect on a number of diseases[76]. Moreover, studies have shown that it may act as an inhibitor of cancer development[77-79]. The mechanisms explaining resveratrol's anti-inflammatory properties have been reviewed by de la Lastra *et al*[80]. According to Richard *et al*[81] resveratrol added to stimulated PBMC brought to an impaired early expression of IL-8 and TNF-α. Bergman *et al*[82] have reported that resveratrol, while added to non-stimulated PBMC expressed a minimal activity for cytokine production, it did not enhance cytokine release by HT-29 and RKO human

colorectal cells. However, resveratrol added to PBMC co-cultured with cancer cells inhibited the release of IL-1β, IL-6, TNF-α, IFNγ, IL-1ra and IL-10. Here again, this is an example of the way a modulator targets the immune dialogue between immune and cancer cells by affecting inflammatory cytokine production with a consequent impact on tumorigenesis. It should be stressed that a substantial number of dietary polyphenols have been found to express anti-inflammatory and anti-cancer properties. Thus, ellagic acid present in pomegranates was shown to reduce the expression of NF-κB, COX2, TNF-α and IL-6 and to exert both anti-inflammatory and carcino-preventive effects[83,84]. Polyphenol-rich apple diet administered to rats inhibited TNF-α, iNOS, IL-1β and IL-6 mRNA expression in the colon and diminished the number of CD68 cells[85]. Diet supplemented with cocoa polyphenols feed to rats with experimentally induced colon inflammation decreased the level of the nuclear NF-κB and of the pro-inflammatory enzyme COX-2[86]. The role of natural products and their phytochemicals in modulation of molecular pathways involved at various stages of tumorigenesis has been summarized by Rajamanickam *et al*[87].

Curcumin

The natural spice curcumin, extracted from the Curcuma longa plant has been recognized as an effective anti-inflammatory and anti-cancer agent[11,88]. As an inhibitor of tumorigenesis, curcumin acts as an anti-oxidant, apoptotic promoter and by expressing antifungal and immunomodulatory activities. As an immunomodulator curcumin is capable to modify T and B cell activities and to downregulate the release of the pro-inflammatory cytokines TNF, IL-1, IL-2, IL-6, IL-8, and IL-12 *via* NF-κB inactivation[89]. It has been reported that curcumin modulates DNA methylation in HCT116, HT-29 and RKO colorectal cancer lines[90]. Curcumin enhances the differentiation of myeloid-derived suppressor cells that are actively involved in tumor angiogenesis, tumor growth and metastasis[91]. Administration of curcumin to a mouse-colon cancer allograft model resulted in a decreased percentage of myeloid-derived suppressor cells in the peripheral blood and organs, reduced IL-6 levels and significantly inhibition of tumor growth. Similar findings were obtained when curcumin was added to myeloid-derived suppressor cells co-cultured with cancer cells. Bessler *et al*[92] have reported that curcumin caused a dose-dependent inhibition of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6 produced by HT-29 or RKO stimulated human PBMC. The generation of IL-1ra, IL-10 and the proliferation of the cancer cells from both lines were also inhibited. These results were observed after co-culture of immune and cancer cells, indicating the likelihood of a direct interaction between immune and cancer cells, a plausible mechanism for explaining the inhibitory effect of curcumin on tumorigenesis. It is not wonder therefore, that efforts are ventured to synthesize compounds that are more efficient and less toxic than

curcumin for augmentation the possibilities for colon cancer therapy[93].

1α, 25-Dihydroxyvitamin D3

Recently, a number of studies indicate that vitamin D (vit. D) exerts a protective action against colon cancer by several mechanisms, such as modifying cancer angiogenesis, cell differentiation, and proliferation, as well as apoptosis[94]. Moreover, due to presence of vit. D receptors in the PBMC the vitamin plays a significant role as an immune system regulator[95]. Mice lacking vit. D receptors developed inflammatory bowel disease and their CD4+ cells produced more IFNγ and less IL-2, IL-4 and IL-5 compared to cells from wild type animals[96]. Mice that spontaneously developed symptoms of inflammatory bowel disease due to IL-2 deficiency showed reduced mortality after vit. D supplementation[97]. It should be stressed however, that IL-6 and TNF-α, two pro-inflammatory cytokines that are crucial for development of inflammatory bowel disease and colorectal cancer, may impair the anti-inflammatory activity of vit. D[98]. The prospect that vit. D may affect carcinogenesis by interfering with the immune relationship between immune and cancer cells has been examined by Bessler *et al*[99]. Incubation of PBMC with either HT-29 or RKO cells induced a marked enhancement of both pro- and anti-inflammatory cytokine production. Vit. D added to the incubation mixture containing PBMC and cells from both colon carcinoma lines caused a significant inhibition of TNF-α and IL-6 generation and to a lesser extent of the IL-10. In view of the key role of both TNF-α and IL-6 in maintaining chronic inflammation and promoting colorectal tumorigenesis, these findings suggest the existence of an additional mechanism for explaining the beneficial role of vit. D as an anti-cancer agent.

It should be underscored that the above-mentioned compounds illustrate a list of potential anti-cancer drugs, nutrients and spices that are gaining increased appreciation as modulators of the immune interaction between PBMC and cancer cells, and offer therefore an additional therapeutic opportunity for malignant diseases.

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