**Name of journal: World Journal of Gastrointestinal Oncology**

**ESPS Manuscript NO: 7562**

**Columns: REVIEW**

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

Djaldetti M *et al.* Modulators of immune and colon cancer cells’ crosstalk

Meir Djaldetti, Hanna Bessler

**Meir Djaldetti, Hanna Bessler,** The Laboratory for Immunology and Hematology Research, Rabin Medical Center, Hasharon Hospital, Petah-Tiqva, and the Sackler School of Medicine, Tel-Aviv University, 699780 Ramat-Aviv, Israel

**Author contributions:** Djaldetti M and Bessler H contributed equally to this work.

**Correspondence to: Meir Djaldetti, MD, Professor of Medicine,** The Laboratory for Immunology and Hematology Research, Rabin Medical Center, Hasharon Hospital, Petah-Tiqva, and the Sackler School of Medicine, Tel-Aviv University, 7 Keren Kayemet St., 699780 Ramat-Aviv, Israel meird@clalit.org.il

**Telephone**: +972-3-9372397 **Fax**: +972-3-9372398

**Received:** November 24, 2013 **Revised:** January 3, 2014

**Accepted:** April 11, 2014

**Published online:**

**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 (MIF), transforming growth factor beta 1 (TGF-β1), TNF-, IL-6, IL-17, 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 STAT-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.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key words:** Cytokines; Immune dialogue; Colon cancer; Peripheral blood mononuclear cells; Cross-talk

**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 factors, 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.

Djaldetti M, Bessler H. Modulators affecting the immune dialogue between human immune- and colon cancer cells.

**Available from:**

**DOI:**

**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 in 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 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 and Cash[9] have suggested that mutY gene and *E. coli* themselves might be involved in colorectal carcinoma development. Aggrawal *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 neovascularisation 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 and Skalko-Basnet[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, TNF-, NF-kB 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 and Karin[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 LPS stimulated PBMC producing IL-20, VEGF and GM-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-1R 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 cancerogenesis. This particular function is promoted by various factors, such as amorphous silica particles capable to increase IL-1β and IL-8 production[25], polysaccharides (LPS) 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-[28]. Even mental conditions, such as posttraumatic stress disorders, may affect the immune activity of PBMC causing an increased spontaneous release of the pro-inflammatory cytokines IL-1β and TNF-[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 (MCP-1), compared to its antagonists such as cydopamine, 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 and Karin[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-, 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-, 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 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- 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 metaloproteinases[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 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, glyoblastoma and alveolar carcinoma. The role of autophagy in regulation of immune responses has been described in details by Valdor and Macian[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.

***Apirin***

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 indicate 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 transforming growth factor-beta (TGF-β) superfamily[42-44]. Bergman *et al*[45] have found that addition of aspirin to PBMC 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- and IL-1-induced transcription factor NF-kappaB activation, aspirin may increase the apoptotic rate of the malignant cells by inhibited expression of these cytokines[48]. On the other hand, NF-kappaB activation can promote production of pro-inflammatory cytokines in colon cancer cells and particularly IL-8 with a further enhancement of the gastro-intestinal 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 a 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-kB 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 cell stimulated PBMC to produce IL-1β and to inhibit the release of TNF- 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 colony stimulating factor-1 (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 cardio-vascular 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 H-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 properties 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-, 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 (HIF1-), vascular endothelial growth factor (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-. 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-, 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-kappaB, COX2, TNF- and IL-6 and to exert both anti-inflammatory and carcino-preventive effects[83,84]. Polyphenol-rich apple diet administered to rats inhibited TNF-, iNOS, IL-1β and IL-6 m-RNA 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-kB 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 and Agarwal[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-kappaB inactivation[89]. It has been reported that curcumin modulates DNA metilation 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 and Djaldetti[92] have reported that curcumin caused a dose-dependent inhibition of the pro-inflammatory cytokines TNF-, 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 (vit.D)***

Recently, a number of studies indicate that 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-, 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 and Djaldetti[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- 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.

**REFERENCES**

1 **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867 [PMID: 12490959]

2 **Viennois E,** Chen F, Merlin D. NF-κB pathway in colitis-associated cancers. *Transl Gastrointest Cancer* 2013; **2**: 21-29 [PMID: 23626930]

3 **Rogler G**. Chronic ulcerative colitis and colorectal cancer. *Cancer Lett* 2014; **345**: 235-241 [PMID: 23941831 DOI: 10.1016/j.canlet.2013.07.032]

4 **Klampfer L**. Cytokines, inflammation and colon cancer. *Curr Cancer Drug Targets* 2011; **11**: 451-464 [PMID: 21247378]

5 **Nguyen AV**, Wu YY, Liu Q, Wang D, Nguyen S, Loh R, Pang J, Friedman K, Orlofsky A, Augenlicht L, Pollard JW, Lin EY. STAT3 in epithelial cells regulates inflammation and tumor progression to malignant state in colon. *Neoplasia* 2013; **15**: 998-1008 [PMID: 24027425]

6 **Mantovani A,** Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436-444 [PMID: 18650914 DOI: 10.1038;/nature07205]

7 **Shigdar S**, Li Y, Bhattacharya S, O'Connor M, Pu C, Lin J, Wang T, Xiang D, Kong L, Wei MQ, Zhu Y, Zhou S, Duan W. Inflammation and cancer stem cells. *Cancer Lett* 2014; **345**: 271-278 [PMID: 23941828 DOI: 10.1016/jcanlet.2013.07.031]

8 **Leung JM,** Davenport M, Wolff MJ, Wiens KE, Abidi WM, Poles MA, Cho I, Ullman T, Mayer L, Loke P. IL-22-producing CD4+ cells are depleted in actively inflamed colitis tissue. *Mucosal Immunol* 2013; [Epub ahead of print]

[PMID: 23695510 DOI: 10.1038/mi.2013.31]

9 **Khan AA**, Cash P. E. coli and colon cancer: is mutY a culprit? *Cancer Lett* 2013; **341**: 127-131 [PMID: 23933175 DOI: 10.1016/j.canlet.2013.08.003]

10 **Aggarwal BB**, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? *Biochem Pharmacol* 2006; **72**: 1605-1621 [PMID: 16889756]

11 **Basnet P**, Skalko-Basnet N. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. *Molecules* 2011; **16**: 4567-4598 [PMID: 21642934 DOI: 10.3390/molecules]

12 **Laird BJ**, Kaasa S, McMillan DC, Fallon MT, Hjermstad MJ, Fayers P, Klepstad P. Prognostic factors in patients with advanced cancer: a comparison of clinicopathological factors and the development of an inflammation-based prognostic system. *Clin Cancer Res* 2013; **19**: 5456-5464 [PMID: 23938289]

13 **Lin WW,** Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest* 2007; **117**: 1175-1183 [PMID: 17476347]

14 **Djaldetti M**, Salman H, Bergman M, Djaldetti R, Bessler H. Phagocytosis--the mighty weapon of the silent warriors. *Microsc Res Tech* 2002; **57**: 421-431 [PMID: 12112425]

15 **Gupta SK**, Deb R, Gaikwad S, Saravanan R, Mohan CM, Dey S. Recombinant flagellin and its cross-talk with lipopolysaccharide--effect on pooled chicken peripheral blood mononuclear cells. *Res Vet Sci* 2013; **95**: 930-935 [PMID: 23937992 DOI: 10.1016/j.rvsc.2013.07.015]

16 **Belmont L**, Rabbe N, Antoine M, Cathelin D, Guignabert C, Kurie J, Cadranel J, Wislez M. Expression of TLR9 in tumor-infiltrating mononuclear cells enhances angiogenesis and is associated with a worse survival in lung cancer. *Int J Cancer* 2014; **134**: 765-777 [PMID: 23913633 DOI: 10.1002/ijc.28413]

17 **Rodríguez-Fandiño O**, Hernández-Ruíz J, López-Vidal Y, Charúa L, Bandeh-Moghaddam H, Minzoni A, Guzmán C, Schmulson M. Intestinal recruiting and activation profiles in peripheral blood mononuclear cells in response to pathogen-associated molecular patterns stimulation in patients with IBS. *Neurogastroenterol Motil* 2013; **25**: 872-e699 [PMID: 23937411 DOI: 10.1111/nmo.12204]

18 **Dai J**, Zhang GB, Gao N, Xi QH, Li YQ, Pang Z, Zhao Y, Zhao JM, Nie JS, Chen WC. [The expression of peripheral Th1 and Th17 cells in inflammatory bowel disease and its potential clinical value]. *Zhonghua Nei Ke Za Zhi* 2013; **52**: 375-378 [PMID: 23945300]

19 **Lampinen M**, Waddell A, Ahrens R, Carlson M, Hogan SP. CD14+CD33+ myeloid cell-CCL11-eosinophil signature in ulcerative colitis. *J Leukoc Biol* 2013; **94**: 1061-1070 [PMID: 23904440]

20 **van Dooren FH**, Duijvis NW, te Velde AA. Analysis of cytokines and chemokines produced by whole blood, peripheral mononuclear and polymorphonuclear cells. *J Immunol Methods* 2013; **396**: 128-133 [PMID: 23994257 DOI: 10.1016/j.jim.2013.08.006]

21 **Kole A**, He J, Rivollier A, Silveira DD, Kitamura K, Maloy KJ, Kelsall BL. Type I IFNs regulate effector and regulatory T cell accumulation and anti-inflammatory cytokine production during T cell-mediated colitis. *J Immunol* 2013; **191**: 2771-2779 [PMID: 23913971 DOI: 10.4049/jimmunol.1301093]

22 **Tang A**, Sharma A, Jen R, Hirschfeld AF, Chilvers MA, Lavoie PM, Turvey SE. Inflammasome-mediated IL-1β production in humans with cystic fibrosis. *PLoS One* 2012; **7**: e37689 [PMID: 22649552 DOI: 10.1371/journal.pone.0037689]

23 **Plantinga TS**, Joosten LA, Netea MG. Assessment of inflammasome activation in primary human immune cells. *Methods Mol Biol* 2013; **1040**: 29-39 [PMID: 23852595 DOI: 10.1007/978-1-62703-523-1\_4]

24 **Kolb R,** Liu GH, Janowski AM, Sutterwala FS, Zhang W. Inflammasomes in cancer: a double-edged sword. *Protein Cell* 2013; [Epub ahead of print] [PMID: 23943320]

25 **Yang EJ**, Choi IH. Immunostimulatory effects of silica nanoparticles in human monocytes. *Immune Netw* 2013; **13**: 94-101 [PMID: 23885223 DOI: 10.4110/in.2013.13.3.94]

26 **Chovanova L**, Vlcek M, Krskova K, Penesova A, Radikova Z, Rovensky J, Cholujova D, Sedlak J, Imrich R. Increased production of IL-6 and IL-17 in lipopolysaccharide-stimulated peripheral mononuclears from patients with rheumatoid arthritis. *Gen Physiol Biophys* 2013; **32**: 395-404 [PMID: 23817641 DOI: 10.4149/gpb\_2013043]

27 **Veinalde R**, Petrovska R, Brūvere R, Feldmane G, Pjanova D. Ex vivo cytokine production in peripheral blood mononuclear cells after their stimulation with dsRNA of natural origin. *Biotechnol Appl Biochem* 2014; **61**: 65-73 [PMID: 23941496 DOI: 10.1002/bab.1143]

28 **Cachinho SC**, Pu F, Hunt JA. Cytokine secretion from human peripheral blood mononuclear cells cultured in vitro with metal particles. *J Biomed Mater Res A* 2013; **101**: 1201-1209 [PMID: 23349093 DOI: 10.1002/jbm.a.34410.]

29 **Gola H**, Engler H, Sommershof A, Adenauer H, Kolassa S, Schedlowski M, Groettrup M, Elbert T, Kolassa IT. Posttraumatic stress disorder is associated with an enhanced spontaneous production of pro-inflammatory cytokines by peripheral blood mononuclear cells. *BMC Psychiatry* 2013; **13**: 40 [PMID: 23360282 DOI: 10.1186/1471-244x-13-40]

30 **Yoshimoto AN**, Bernardazzi C, Carneiro AJ, Elia CC, Martinusso CA, Ventura GM, Castelo-Branco MT, de Souza HS. Hedgehog pathway signaling regulates human colon carcinoma HT-29 epithelial cell line apoptosis and cytokine secretion. *PLoS One* 2012; **7**: e45332 [PMID: 23028941 DOI: 10.1371/journal.pone.0045332]

31 **Bessler H**, Djaldetti M. Role of the equilibrium between colon cancer and mononuclear cells in cytokine production. *Biomed Pharmacother* 2010; **64**: 706-711 [PMID: 20880664 DOI: 10.1016/j.biopha.2010.08.006]

32 **Ma GF**, Miao Q, Zeng XQ, Luo TC, Ma LL, Liu YM, Lian JJ, Gao H, Chen SY. Transforming growth factor-β1 and -β2 in gastric precancer and cancer and roles in tumor-cell interactions with peripheral blood mononuclear cells in vitro. *PLoS One* 2013; **8**: e54249 [PMID: 23342108 DOI: 10.1371/journal.pone.0054249]

33 **Deng Z**, Cheng Z, Xiang X, Yan J, Zhuang X, Liu C, Jiang H, Ju S, Zhang L, Grizzle W, Mobley J, Roman J, Miller D, Zhang HG. Tumor cell cross talk with tumor-associated leukocytes leads to induction of tumor exosomal fibronectin and promotes tumor progression. *Am J Pathol* 2012; **180**: 390-398 [PMID: 22067905 DOI: 10.1016/jajpath.2011.09.023]

34 **Park ES**, Yoo JM, Yoo HS, Yoon DY, Yun YP, Hong J. IL-32γ enhances TNF-α-induced cell death in colon cancer. *Mol Carcinog* 2014; **53** Suppl 1: E23-E35 [PMID: 23255489]

35 **Redzic JS**, Kendrick AA, Bahmed K, Dahl KD, Pearson CG, Robinson WA, Robinson SE, Graner MW, Eisenmesser EZ. Extracellular vesicles secreted from cancer cell lines stimulate secretion of MMP-9, IL-6, TGF-β1 and EMMPRIN. *PLoS One* 2013; **8**: e71225 [PMID: 23936495 DOI: 10.1371/journal.pone.0071225]

36 **Bhattacharya A**, Eissa NT. Autophagy and autoimmunity crosstalks. *Front Immunol* 2013; **4**: 88 [PMID: 23596443 DOI: 10.3389/fimmu.2013.00088.]

37 **Long TM**, Chakrabarti A, Ezelle HJ, Brennan-Laun SE, Raufman JP, Polyakova I, Silverman RH, Hassel BA. RNase-L deficiency exacerbates experimental colitis and colitis-associated cancer. *Inflamm Bowel Dis* 2013; **19**: 1295-1305 [PMID: 23567782 DOI: 10.1097/MIB.0b013e318281f2fd]

38 **Stolfi C**, Rizzo A, Franzè E, Rotondi A, Fantini MC, Sarra M, Caruso R, Monteleone I, Sileri P, Franceschilli L, Caprioli F, Ferrero S, MacDonald TT, Pallone F, Monteleone G. Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. *J Exp Med* 2011; **208**: 2279-2290 [PMID: 21987656 DOI: 10.1084/jem.20111106]

39 **Valdor R,** Macian F. Autophagy and the regulation of the immune response. *Pharmacol Res* 2012; **666**: 475-483 [PMID: 23063674 DOI: 10. 1016/j.phrs.2010.10.003]

40 **Schmeisser H**, Fey SB, Horowitz J, Fischer ER, Balinsky CA, Miyake K, Bekisz J, Snow AL, Zoon KC. Type I interferons induce autophagy in certain human cancer cell lines. *Autophagy* 2013; **9**: 683-696 [PMID: 23419269 DOI: 10.4161/auto.23921]

41 **Vendramini-Costa DB**, Carvalho JE. Molecular link mechanisms between inflammation and cancer. *Curr Pharm Des* 2012; **18**: 3831-3852 [PMID: 22632748]

42 **Zhang H**, Ye Y, Bai Z, Wang S. The COX-2 selective inhibitor-independent COX-2 effect on colon carcinoma cells is associated with the Delta1/Notch1 pathway. *Dig Dis Sci* 2008; **53**: 2195-2203 [PMID: 18320325 DOI: 10.1007/s10620-007-0139-0]

43 **Gurpinar E**, Grizzle WE, Piazza GA. COX-Independent Mechanisms of Cancer Chemoprevention by Anti-Inflammatory Drugs. *Front Oncol* 2013; **3**: 181 [PMID: 23875171 DOI: 10.3389/fonc.2013.00181]

44 **Stolfi C**, De Simone V, Pallone F, Monteleone G. Mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs) and mesalazine in the chemoprevention of colorectal cancer. *Int J Mol Sci* 2013; **14**: 17972-17985 [PMID: 24005861 DOI: 10.3390/jims140917972]

45 **Bergman M**, Djaldetti M, Salman H, Bessler H. Inflammation and colorectal cancer: does aspirin affect the interaction between cancer and immune cells? *Inflammation* 2011; **34**: 22-28 [PMID: 20349206 DOI: 10.1007/s10753-0109203-6]

46 **Skeen VR**, Paterson I, Paraskeva C, Williams AC. TGF-β1 signalling, connecting aberrant inflammation and colorectal tumorigenesis. *Curr Pharm Des* 2012; **18**: 3874-3888 [PMID: 22632753]

47 **Slattery ML**, Wolff RK, Herrick JS, Caan BJ, Potter JD. IL6 genotypes and colon and rectal cancer. *Cancer Causes Control* 2007; **18**: 1095-1105 [PMID: 17694420]

48 **Kutuk O**, Basaga H. Aspirin inhibits TNFalpha- and IL-1-induced NF-kappaB activation and sensitizes HeLa cells to apoptosis. *Cytokine* 2004; **25**: 229-237 [PMID: 15036249]

49 **Mladenova D**, Pangon L, Currey N, Ng I, Musgrove EA, Grey ST, Kohonen-Corish MR. Sulindac activates NF-κB signaling in colon cancer cells. *Cell Commun Signal* 2013; **11**: 73 [PMID: 24083678]

50 **Lang S**, Lauffer L, Clausen C, Löhr I, Schmitt B, Hölzel D, Wollenberg B, Gires O, Kastenbauer E, Zeidler R. Impaired monocyte function in cancer patients: restoration with a cyclooxygenase-2 inhibitor. *FASEB J* 2003; **17**: 286-288 [PMID: 12490541]

51 **Lai MY**, Huang JA, Liang ZH, Jiang HX, Tang GD. Mechanisms underlying aspirin-mediated growth inhibition and apoptosis induction of cyclooxygenase-2 negative colon cancer cell line SW480. *World J Gastroenterol* 2008; **14**: 4227-4233 [PMID: 18636671]

52 **Tougeron D**, Fauquembergue É, Latouche JB. [Immunotherapy for colorectal cancer]. *Bull Cancer* 2013; **100**: 871-885 [PMID: 23917703]

53 **Allen JN**, Herzyk DJ, Wewers MD. Colchicine has opposite effects on interleukin-1 beta and tumor necrosis factor-alpha production. *Am J Physiol* 1991; **261**: L315-L321 [PMID: 1928366]

54 **Salman H,** Bergman M, Blumberger N, Djaldetti M, Bessler H.Do androgen deprivation drugs affect the immune cross-talk between mononuclear and prostate cancer cells? *Biomed Pharmacother* 2014; **68**: 21-24 [PMID: 24406295 DOI: 10.1016/j.biopha.2013.12.007]

55 **Zins K**, Abraham D, Sioud M, Aharinejad S. Colon cancer cell-derived tumor necrosis factor-alpha mediates the tumor growth-promoting response in macrophages by up-regulating the colony-stimulating factor-1 pathway. *Cancer Res* 2007; **67**: 1038-1045 [PMID: 17283136]

56 **Honda T**, Yamamoto I, Inagawa H. Angiogenesis-, metastasis- and signaling pathway-related factor dynamics in human colon cancer cells following interaction with monocytes. *Anticancer Res* 2013; **33**: 2895-2900 [PMID: 23780976]

57 **Shovman O**, Levy Y, Gilburd B, Shoenfeld Y. Antiinflammatory and immunomodulatory properties of statins. *Immunol Res* 2002; **25**: 271-285 [PMID: 12018465]

58 **Sun D,** Fernandes G. Lovastatin inhibits bone marrow-derived dendritic cell maturation and upregulates proinflammatory cytokine production. *Cell Immunol* 2003; **223**: 52-63 [PMID: 12914758]

59 **Jakobisiak M**, Golab J. Potential antitumor effects of statins (Review). *Int J Oncol* 2003; **23**: 1055-1069 [PMID: 12963986]

60 **Kato S**, Smalley S, Sadarangani A, Chen-Lin K, Oliva B, Brañes J, Carvajal J, Gejman R, Owen GI, Cuello M. Lipophilic but not hydrophilic statins selectively induce cell death in gynaecological cancers expressing high levels of HMGCoA reductase. *J Cell Mol Med* 2010; **14**: 1180-1193 [PMID: 19432822 DOI: 10.1111/j.1582-4934.2009.00771.x]

61 **Bessler H**, Salman H, Bergman M, Straussberg R, Djaldetti M. In vitro effect of statins on cytokine production and mitogen response of human peripheral blood mononuclear cells. *Clin Immunol* 2005; **117**: 73-77 [PMID: 16051523]

62 **Loppnow H**, Zhang L, Buerke M, Lautenschläger M, Chen L, Frister A, Schlitt A, Luther T, Song N, Hofmann B, Rose-John S, Silber RE, Müller-Werdan U, Werdan K. Statins potently reduce the cytokine-mediated IL-6 release in SMC/MNC cocultures. *J Cell Mol Med* 2011; **15**: 994-1004 [PMID: 20158569 DOI: 10.1111/j.1582-4934.2010.01036.x]

63 **Takahashi HK**, Mori S, Iwagaki H, Yoshino T, Tanaka N, Nishibori M. Simvastatin induces interleukin-18 production in human peripheral blood mononuclear cells. *Clin Immunol* 2005; **116**: 211-216 [PMID: 15936988]

64 **Bessler H**, Salman H, Bergman M, Djaldetti M. On the factors modulating the effect of statins on malignant cell proliferation. *Cancer Invest* 2007; **25**: 279-284 [PMID: 17661201]

65 **Malicki S**, Winiarski M, Matlok M, Kostarczyk W, Guzdek A, Konturek PC. IL-6 and IL-8 responses of colorectal cancer in vivo and in vitro cancer cells subjected to simvastatin. *J Physiol Pharmacol* 2009; **60**: 141-146 [PMID: 20065508]

66 **Bergman M**, Salman H, Djaldetti M, Bessler H. Statins as modulators of colon cancer cells induced cytokine secretion by human PBMC. *Vascul Pharmacol* 2011; **54**: 88-92 [PMID: 21440087]

67 **Madka V**, Rao CV. Anti-inflammatory phytochemicals for chemoprevention of colon cancer. *Curr Cancer Drug Targets* 2013; **13**: 542-557 [PMID: 23597198]

68 **Higdon JV,** Frei B. Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr* 2006; **46**: 101-123 [PMID: 16507475]

69 **Larsson SC**, Bergkvist L, Giovannucci E, Wolk A. Coffee consumption and incidence of colorectal cancer in two prospective cohort studies of Swedish women and men. *Am J Epidemiol* 2006; **163**: 638-644 [PMID: 16443798]

70 **Naganuma T**, Kuriyama S, Kakizaki M, Sone T, Nakaya N, Ohmori-Matsuda K, Nishino Y, Fukao A, Tsuji I. Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study. *Am J Epidemiol* 2008; **168**: 1425-1432 [PMID: 18974083 DOI: 10.1093/aje/kwn282]

71 **Merighi S**, Benini A, Mirandola P, Gessi S, Varani K, Simioni C, Leung E, Maclennan S, Baraldi PG, Borea PA. Caffeine inhibits adenosine-induced accumulation of hypoxia-inducible factor-1alpha, vascular endothelial growth factor, and interleukin-8 expression in hypoxic human colon cancer cells. *Mol Pharmacol* 2007; **72**: 395-406 [PMID: 17488804]

72 **Sabisz M,** Skladanowski A. Modulation of cellular response to anticancer treatment by caffeine: inhibition of cell cycle checkpoints, DNA repair and more. *Curr Pharm Biotechnol* 2008; **9**: 325-236 [PMID: 18691092]

73 **Ritter M**, Hohenberger K, Alter P, Herzum M, Tebbe J, Maisch M. Caffeine inhibits cytokine expression in lymphocytes. *Cytokine* 2005; **30**: 177-181 [PMID: 15863391]

74 **Chavez-Valdez R**, Wills-Karp M, Ahlawat R, Cristofalo EA, Nathan A, Gauda EB. Caffeine modulates TNF-alpha production by cord blood monocytes: the role of adenosine receptors. *Pediatr Res* 2009; **65**: 203-208 [PMID: 19047957 DOI: 10.1203/PDR.0b013e31818d66b1]

75 **Bessler H**, Salman H, Bergman M, Djaldetti M. Caffeine alters cytokine secretion by PBMC induced by colon cancer cells. *Cancer Invest* 2012; **30**: 87-91 [PMID: 22149008 DOI: 10.3109/07357907.2011.636113]

76 **Yadav M**, Jain S, Bhardwaj A, Nagpal R, Puniya M, Tomar R, Singh V, Parkash O, Prasad GB, Marotta F, Yadav H. Biological and medicinal properties of grapes and their bioactive constituents: an update. *J Med Food* 2009; **12**: 473-484 [PMID: 19627194 DOI: 10.1089/jmp.2008.0096]

77 **Udenigwe CC**, Ramprasath VR, Aluko RE, Jones PJ. Potential of resveratrol in anticancer and anti-inflammatory therapy. *Nutr Rev* 2008; **66**: 445-454 [PMID: 18667005 DOI: 10.1111/J.1753-4887.2008.00076.x]

78 **Kaur M**, Agarwal C, Agarwal R. Anticancer and cancer chemopreventive potential of grape seed extract and other grape-based products. *J Nutr* 2009; **139**: 1806S-1812S [PMID: 19640973 DOI: 10.3945/jn.109.106864]

79 **Kountouri AM**, Gioxari A, Karvela E, Kaliora AC, Karvelas M, Karathanos VT. Chemopreventive properties of raisins originating from Greece in colon cancer cells. *Food Funct* 2013; **4**: 366-372 [PMID: 23211994 DOI: 10.1039/c2fo30259d]

80 **de la Lastra CA**, Villegas I. Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications. *Biochem Soc Trans* 2007; **35**: 1156-1160 [PMID: 17956300]

81 **Richard N**, Porath D, Radspieler A, Schwager J. Effects of resveratrol, piceatannol, tri-acetoxystilbene, and genistein on the inflammatory response of human peripheral blood leukocytes. *Mol Nutr Food Res* 2005; **49**: 431-442 [PMID: 15779068]

82 **Bergman M**, Levin GS, Bessler H, Djaldetti M, Salman H. Resveratrol affects the cross talk between immune and colon cancer cells. *Biomed Pharmacother* 2013; **67**: 43-47 [PMID: 23218986 DOI: 10.1016/j.biopha]

83 **Umesalma S**, Sudhandiran G. Differential inhibitory effects of the polyphenol ellagic acid on inflammatory mediators NF-kappaB, iNOS, COX-2, TNF-alpha, and IL-6 in 1,2-dimethylhydrazine-induced rat colon carcinogenesis. *Basic Clin Pharmacol Toxicol* 2010; **107**: 650-655 [PMID: 20406206 DOI: 10.1111/j.1742-7843.2010.00565.x]

84 **Rosillo MA**, Sánchez-Hidalgo M, Cárdeno A, Aparicio-Soto M, Sánchez-Fidalgo S, Villegas I, de la Lastra CA. Dietary supplementation of an ellagic acid-enriched pomegranate extract attenuates chronic colonic inflammation in rats. *Pharmacol Res* 2012; **66**: 235-242 [PMID: 22677088 DOI: 10.1016/j.phrs.2010.05.006]

85 **Femia AP**, Luceri C, Bianchini F, Salvadori M, Salvianti F, Pinzani P, Dolara P, Calorini L, Caderni G. Marie Ménard apples with high polyphenol content and a low-fat diet reduce 1,2-dimethylhydrazine-induced colon carcinogenesis in rats: effects on inflammation and apoptosis. *Mol Nutr Food Res* 2012; **56**: 1353-1357 [PMID: 22715065 DOI: 10.1002/mnfr.201200122]

86 **Rodríguez-Ramiro I**, Ramos S, López-Oliva E, Agis-Torres A, Bravo L, Goya L, Martín MA. Cocoa polyphenols prevent inflammation in the colon of azoxymethane-treated rats and in TNF-α-stimulated Caco-2 cells. *Br J Nutr* 2013; **110**: 206-215 [PMID: 23186731 DOI: 10.1017/S0007114512004862]

87 **Rajamanickam S,** Agarwal R. Natural products and colon cancer: current status and future prospects. *Drug Dev Res* 2008; **69**: 460-471 [PMID: 19884979]

88 **Zhou H**, Beevers CS, Huang S. The targets of curcumin. *Curr Drug Targets* 2011; **12**: 332-347 [PMID: 20955148]

89 **Jagetia GC**, Aggarwal BB. "Spicing up" of the immune system by curcumin. *J Clin Immunol* 2007; **27**: 19-35 [PMID: 17211725]

90 **Link A**, Balaguer F, Shen Y, Lozano JJ, Leung HC, Boland CR, Goel A. Curcumin modulates DNA methylation in colorectal cancer cells. *PLoS One* 2013; **8**: e57709 [PMID: 23460897 DOI: 10.1371/journal.pone.0057709]

91 **Tu SP**, Jin H, Shi JD, Zhu LM, Suo Y, Lu G, Liu A, Wang TC, Yang CS. Curcumin induces the differentiation of myeloid-derived suppressor cells and inhibits their interaction with cancer cells and related tumor growth. *Cancer Prev Res (Phila)* 2012; **5**: 205-215 [PMID: 22030090 DOI: 10.1158/1940-6207.carp-11-0247]

92 **Bessler H,** Djaldetti M. Curcumin affects the cross-talk between immunocytes and colon carcinoma cells. *Recent Res Devel Nutrition* 2012; **8**: 81-93

93 **Ahmed MM**, Khan MA, Rainsford KD. Synthesis of thiophene and NO-curcuminoids for antiinflammatory and anti-cancer activities. *Molecules* 2013; **18**: 1483-1501 [PMID: 23353121 DOI: 103390/molecules]

94 **Kang W**, Lee S, Jeon E, Yun YR, Kim KH, Jang JH. Emerging role of vitamin D in colorectal cancer. *World J Gastrointest Oncol* 2011; **3**: 123-127 [PMID: 22007275 DOI: 10.4251/wjgo.v3.i8.123]

95 **Cantorna MT**, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. *Am J Clin Nutr* 2004; **80**: 1717S-1720S [PMID: 15585793]

96 **Froicu M**, Weaver V, Wynn TA, McDowell MA, Welsh JE, Cantorna MT. A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. *Mol Endocrinol* 2003; **17**: 2386-2392 [PMID: 14500760]

97 **Bemiss CJ**, Mahon BD, Henry A, Weaver V, Cantorna MT. Interleukin-2 is one of the targets of 1,25-dihydroxyvitamin D3 in the immune system. *Arch Biochem Biophys* 2002; **402**: 249-254 [PMID: 12051670]

98 **Hummel DM,** Fetahu IS, Gröschel C, Manhardt T, Kállay E. Role of proinflammatory cytokines on expression of vitamin D metabolism and target genes in colon cancer cells. *J Steroid Biochem Mol Biol* 2013; [Epub ahead of print] [PMID: 24120915 DOI: 10.1016/j.jsmb.2013.09.017]

99 **Bessler H**, Djaldetti M. 1α,25-Dihydroxyvitamin D3 modulates the interaction between immune and colon cancer cells. *Biomed Pharmacother* 2012; **66**: 428-432 [PMID: 22795808 DOI: 10.1016/j.biopha.2012.06.005]

**P-Reviewers:** Stanojevic GZ, Zhu YL **S-Editor:** Qi Y

**L-Editor: E-Editor:**

**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.

**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 | ↓/↑\* |
| Statins | Bergman *et al*[66] (2011) | ↓ | 0 | ND | ↓ | ↓ | ↓ |
| Caffeine | Bessler *et al*[75] (2012) | 0 | 0 | ↓ | ↓ | ↓ | ↓ |
| Resveratrol | Bergman *et al*[82] (2013) | ↓ | ↑/01 | ↓ | ↓ | ↓ | ↓ |
| Curcumin | Bessler *et al*[92] (2012) | ↓ | ↓ | ↓ | ND | ↓ | ↓ |
| Vit D3 | Bessler *et al*[93] (2012) | ↓ | 0 | ↓ | ND | 0 | ↓ |

1Respresents resultsfor HT-29-induced / RKO-induced cytokine secretion by PBMC. ND: Not determined; 0: No change in cytokine secretion.