Immunome Research
ISSN: 1745-7580

Ajdukovic, Immunome Res 2018, 14:1
DOI: 10.4172/1745-7580.1000153

Short Communication Open Access

Colorectal Cancer and NLRP-Current Knowledge

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Received date: January 19, 2018; **Accepted date**: February 18, 2018; **Published date**: February 27, 2018

Abstract

Inflammasomes activated by different stimuli in colorectal cancer show dual effect on cancer's destiny. Activation of caspase-1 results in maturation of IL-1β and IL-18. IL-1β suppresses NK and T cells activity against tumor, induces expression of metastatic genes and stimulates the production of proinflammatory leukines, but it also enhances NK cell–mediated death of colon carcinoma cells. IL-18 promoter polymorphisms in humans increase risk for colorectal cancers.

One variant of *NLRP3* gene in human is connected with increased susceptibility to colorectal cancer. Expression levels of NLRP1, NLRP3, NLRC4 were significantly reduced in human CRC compared with healthy controls. Nlrp3 −/−mice exhibited increased colorectal cancer and metastasis in liver.

NLRP3 have an important role in the Epithelial-Mesenchymal Transition (EMT) of colorectal cancer cells, which is necessary for migration and invasion. Absence of NLRP3 in colorectal carcinoma cells diminishes tumor cells migration and invasion.

Keywords: Colorectal cancer; Inflammasome; NLRP; Interleukin-1β; Interleukin-18; EMT

Short Communication

Opposite inflamasomme activity includes both, pro tumoral and anti-tumoral influence on cancer destiny. The aim of this study is to present the result of recent studies which investigate the role of NLRP`s in colorectal cancer (CRC) induction and dissemination.

CRC is connected with inflammation. Inflammation is orchestrated by the inflammasome in many cells (immune, epithel, cancer) [1]. The NLRP3 inflammasome is the most known inflammasome. It is a multiprotein citoplasmic complex activated by pathogen-associated molecular patterns (PAMPs) (such as bacterial and viral nucleic acid), damage-associated molecular patterns (DAMPs) (for example, ATP and uric acid crystals) or environmental irritans [1-3].

Many other NLRPs such as NLRP1, NLRP6, NLRP7 and NLRP12 also can also form inflammasome, and activate caspase-1 in response to different stimuli [4,5]. Different stimuli activate different inflammasomes and mediate many important processes in CLC [3,6].

NLRP1-β, NLRP3, and NLRP6's activation of caspase-1 results in maturation of proinflammatory cytokine interleukin (IL)-1β and IL-18 and pyroptosis [1,7].

Both IL-1β and IL-18 play essential roles in maintaining the integrity of the epithelial barrier in the colon [8].

Role of IL-1β in Colorectal Cancer

IL-1β suppresses NK and T cells activity against tumor [1]. Its level increases during the progression of CRC. IL-1β in tumor induces myeloid-derived suppressor cells (MDSC), stemness and increases resistance to chemotherapy [1,9]. In human colon cancer lines, IL-1 induces expression of metastatic genes and stimulates the production of vascular endothelial growth factor (VEGF), IL-8, IL-6, tumor necrosis factor (TNF) and transforming growth factor (TGF) β [10]. Overexpression of IL-1β induces gastric inflammation and cancer in mice [11].

Role of IL-18 in Colorectal Cancer

IL-18 both promotes (facilitates tumor escape and angiogenesis) oncogenesis and suppresses (induces tumor cell death) oncogenesis [11-14]. IL-18 activates endothelial cell migration and increases angiogenesis *in vivo* [12]. IL-18 inhibits the colonization of colitogenic microbiota [1].

In a murine colon carcinoma cell line IL-18 enhances NK cell–mediated death of colon carcinoma cells [14]. *In vivo*, IL18−/− mice have a higher frequency of tumor growth compared with wild-type mice and administration of rIL-18 results in immune rejection of colon tumors in mice [14]. IL-18 promotes the antitumor activity of eosinophils against a human colon carcinoma cell line [14]. Dupaul-Chicoine showed that mice deficient in Nlrp3 inflammasome had exacerbated colorectal cancer metastasis in liver because of impaired inteleukin-18 [15].

IL-18 promoter polymorphisms increase risk for colorectal cancers [16]. In addition to the results obtained in murine models, clinical trials showed that IL-18 was well tolerated and induced antitumor effects when used alone in patients with advanced cancer [14]. IL-18 and immune checkpoint inhibitors could be useful in cancer patients since they synergistically inhibited the tumor growth without significant adverse events in animal models of peritoneal dissemination of CT-26 colon carcinoma [17].

NLRP´s Role in CLC

Du et al. recently showed that high cholesterol diet (HCD) significantly promoted colon carcinogenesis, through activating the NLRP3 inflammasome. HCD-induced increase of IL-1β secretion, macrophage infiltration. And tumor burden was diminished by deletion of NLRP3 in AOM-treated mice [18].

Mice lacking the inflammasome parts, adaptor protein ASC and caspase-1 have an increased morbidity, in the AOM/DSS model of CRC. The increased tumor burden correlates with attenuated levels of IL-1β and IL-18 at the tumor site. Its suggest that the inflammasome functions as an attenuator of colitis and colitis-driven CRC [10].

In the DSS colitis model and DSS-AOM colitis associated colon cancer murine models, NLRP3, NLRP6 and NLRC4 have a protective role against dysplasia and hyperplasia in the colon [19]. NLRP1 plays a protective role during experimental colitis and colitis-associated tumorgenesis in the mouse [8,13]. NLRP12 has a role in preventing chemically induced colitis and colon tumor associated with inflammation and serves as, a checkpoint protein by negatively regulating the non-canonical NF-kappa B signaling [3,20].

In the DSS colitis model Nlrp3−/− mice had increased polyp numbers and size, but some researchers showed that Nlrp3-deficient mice exhibited attenuated colitis [11,21]. Nlrp1b−/−, Nlrc4−/− and caspase-1−/− mice with CAC had worsened pathology compared to wild type mice. IL-18 levels were dramatically reduced in the colon of Nlrp3 −/−and caspase-1−/− mice [20]. Treatment of caspase-1−/− mice with recombinant IL-18 led to a reduction in disease, demonstrating a crucial role of IL-18 in protection against CAC [19]. Meta-analysis showed that in human, A alele of rs35829419 variant located in exon 3 of the *NLRP3* gene conferred protection against CRC and carriers of the *NLRP3* gene rs35829419 C>A polymorphism displayed a mark increase of susceptibility to colorectal cancer [22].

An analysis of primary patient samples from 40 patients who were newly diagnosed with colon or rectum adenocarcinoma showed that the expression of NLRP3 was reduced in primary CRC samples [19]. Mitchell et al. previously reported the association of genetic polymorphisms in NLRP3 and NLRP12 with gastric cancer in Chinese individuals. Liver cancer study revealed reduced expression of NLRP3 inflammasome components in different stage of hepatocarcinogenesis (HCC).

Expression levels of NLRP1, NLRP3, NLRC4 were significantly reduced in human CRC compared with healthy controls [19]. Williams et al. conducted a retrospective evaluation of eight independent studies that evaluated colon biopsies from areas of cancer versus adjacent tissue or biopsies/tissue from colon cancer patients compared with healthy controls. NLRP3 and NLRC4 were found to be significantly upregulated in cancer biopsies compared with healthy or normal patients, whereas NLRP6 expression was unchanged in all studies [8].

Autophagosomes derived from tumor cells (also named defective ribosomal products in blebs (Dribbles)) act as a cancer vaccine because they induce immunologic response and tumor regression [21,23].

Dribbles induced Nlrp3 inflammasome activation. NLRP3 primes natural killer (NK) cells which express Fas ligand. NK cell connection with Fas receptor on colon carcinoma cells results in apoptosis tumor cell [21,23]. Preclinical cancer models showed efficacy in this NLRP mediated tumor regression. NLRP3 shows more power anticancer activity shows when chemotherapy damaged tumor cells release ATP which is potent NLRP activator. NLRP3 stimulates IFN-γ-production and further damage of tumor cells *via* IL-17 [21].

Recent finding of importance of NLRP3 expression (without activation) in the epithelial-mesenchymal transition (EMT) of colorectal cancer cells necessary for migration and invasion of colorectal cancer cells potentiates the importance of inflammasome role in CLC metastasing, as well as the necessity of IL-18 for prevention of hepatic CLC metastasis [15,24]. IL-18 combined with gene therapy or with combined Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) are investigated in animal colon cancer cells [25,26]. It will probably be the future potential adjuvant therapy for micro metastases in CLC patients [25,26]. To sum up, regulation of NLRP3 expression and activity of IL-18 is a challenge for the future research in the improvement of CLC immunotherapy.

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