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Mini review

IL-10 in cancer: Just a classical immunosuppressive factor or also an immunostimulating one?

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Abstract: It is generally well-accepted and established the IL-10-mediated protumor function in cancer, based on its immunosuppressive properties. However, new evidences from *in vitro* and *in vivo* murine models have emerged showing a potential immunostimulating activity of this cytokine, which may sustain IL-10-mediated antitumor function in cancer, hence favoring tumor regression. Here, we attempt to clarify IL-10's role in cancer, by conducting a literature review of previously published studies, presenting information about IL-10 immunosuppressive and/or immunostimulating properties. Different and contradictory IL-10 effects leading to tumor growth (e.g., suppression of pro-inflammatory cytokines or inhibition of immune response recognition steps) or tumor regression (e.g., stimulation of cytotoxic and cytolytic activities of immune cells or inhibition of angiogenic factors) were found in distinct scenarios, hindering the establishment of a general role for IL-10 in cancer. Such definition is still a challenge, maybe due to a lack of sufficient information to support it, or perhaps based on the fact that IL-10 role in distinct cancer contexts may vary, switching from a classical immunosuppressive factor to an immunostimulating one.

Keywords: IL-10; cancer; immunosuppression; immunostimulation; protumor activity; antitumor activity

Abbreviations: ATM/ATR: Ataxia telangiectasia mutated/Ataxia telangiectasia and Rad3-related protein; CTL: Cytotoxic T lymphocyte; DC: Dendritic cell; HLA-G: Human leukocyte antigen-G; HSP70: 70 kilodalton heat shock protein; ILT: Ig-like transcripts; IL-2: Interleukin-2; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-10R: Interleukin-10 receptor; IL-10RA: Interleukin-10 receptor subunit alpha; IL-10RB: Interleukin-10 receptor subunit beta; IL-12: Interleukin-12; IL-27: Interleukin-27; IFN-γ: Interferon gamma; KIR: Killer Ig-like receptors; LPS: lipopolysaccharide; MCA: 3'-methylcholanthrene; MHC: Major histocompatibility complex; MICA A: MHC class I chain-related A; MICA B: MHC class I chain-related B; MMP-9: Matrix metallopeptidase 9; NK: Natural killer; NKG2D: Natural killer group 2D; NKT: Natural killer T; NFIL3: Nuclear factor interleukin-3; Treg: Regulatory T cell; STAT1: Signal transducer and activator of transcription 1; STAT3: Signal transducer and activator of transcription 3; Th1: T helper 1; Th17: T helper 17; TGF-β: Transforming growth factor beta; TAM: Tumor-associated macrophage; TAMC: Tumor associated myeloid cell; TNF-α: Tumor necrosis factor alpha; TNF-β: Tumor necrosis factor beta; Tr1: T regulatory type 1 cell; ULBP: Unique long 16 binding proteins; VEGF: Vascular endothelial growth factor.

1. Introduction

The cytokine network balance is a determinant factor in homeostasis maintenance and is pivotal to solve or avoid distinct pathological processes. As a consequence, any disruption of cytokine network results in a wide range of events that may lead to a specific microenvironment, favorable to develop several diseases, including cancer. In cancer, the role of different cytokines are intrinsically related to its natural history and also to metastasis occurrence, especially because tumor cells modulate cytokine network on its own favor, propitiating tumor progression and immune system evasion [1].

Cytokine network impairment may alter the production of tumor-inducing or tumor-inhibiting factors, cause DNA damage, promote or inhibit angiogenesis, among other effects. Therefore, cytokine network plays a determinant role in the development or regression of different cancers [2].

One of the several important cytokines involved in cancer development and sustenance is interleukin-10 (IL-10). Despite its importance, the role of IL-10 in cancer is still controversial and poorly understood, and even considered paradoxical by some authors [3,4]. Thus, based on accumulating data, at the present work we aimed to discuss the role of IL-10 in cancer and showed different effects of this cytokine, depending on the cancer context involved.

2. Material and methods

For literature review, we conducted a PubMed search using "IL-10", "cancer" and "immunostimulating" or "immunosuppressive" as keywords and selected studies published between January 2000 and January 2018, bringing information about IL-10 immunostimulating and/or immunosuppressive role.

3. Results and discussion

In tumor microenvironment, IL-10 production can be induced and maintained by several cellular populations through distinct stimulus. Among those, we highlight tumor cells stimulated by IL-6 derived from M2 macrophage; macrophages and monocytes in response to tumor necrosis factor beta (TNF-β) (i.e., as a negative feedback inhibiting the inflammatory response); T helper 17 (Th17) cells by transforming growth factor beta (TGF-β) alone or with interleukin-6 (IL-6) (i.e., between TGF-β and IL-10 there is a positive feedback loop); and other T cells, stimulated by several cytokines as interleukin-12 (IL-12), interleukin-27 (IL-27) and TGF-β, with Regulatory T cells (Treg) being one of the major tumor cellular sources of IL-10 [1,5].

Often, patients with distinct cancer types present increased IL-10 levels, both in serum and locally, within the tumor microenvironment. Several studies have shown a positive association between elevated IL-10 levels with advanced disease stage or with negative prognosis in those patients [6]. IL-10 levels tend to increase in parallel to clinical disease progression in patients with independent cancers, including metastatic melanoma, colon cancer and cervical cancer. Additionally, serum levels of IL-10 could predict the chance of recurrence of certain cancer types [7].

Although known as a classic inhibitory factor, data based on experimental models have shown both IL-10 immunosuppressive and immunostimulatory effects considering distinct immune cells, as well as different contexts of stimulation and concentration of the multiple factors involved. In some contexts, IL-10 induces immunosuppression and tumor immune escape, favoring tumor growth. In others, however, IL-10 promotes an antitumor cytotoxic response, thus favoring tumor regression (i.e., which is also favored by IL-10 antiangiogenic property). Therefore, apparently IL-10's effects vary greatly relying on both experimental context and cell types involved (Figure 1) [3,4].

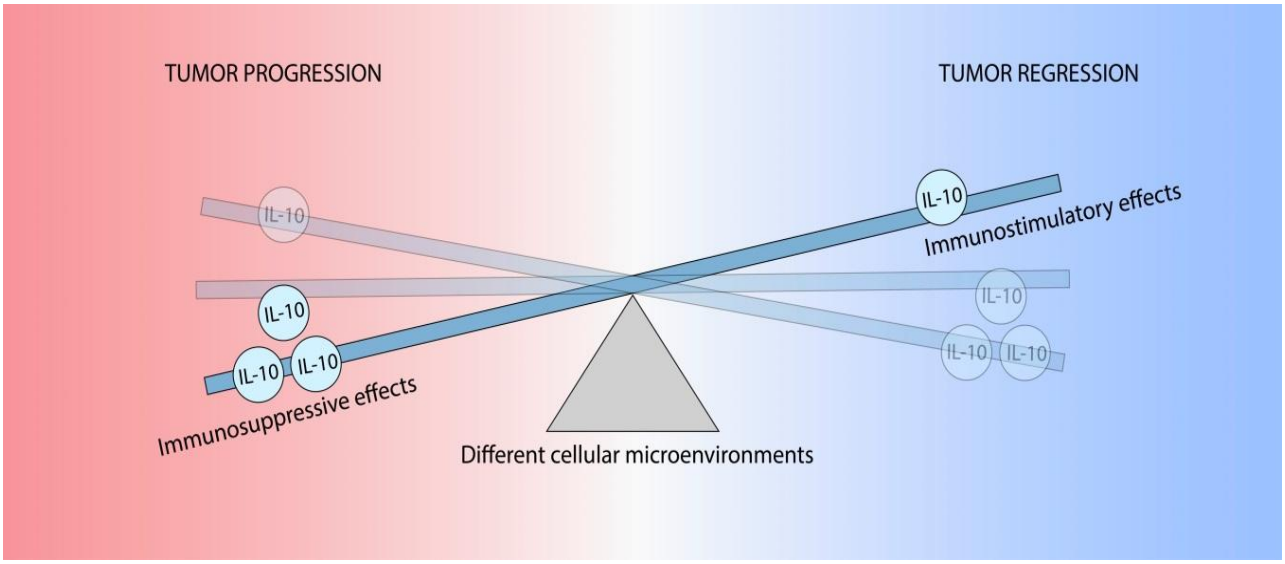

Figure 1. IL-10 balance in distinct microenvironments. IL-10 balancing in different cancer microenvironments leading to tumor progression or tumor regression according to IL-10 effects.

3.1. IL-10-mediated protumor function in cancer

The immunosuppressive properties of IL-10 are well established in the literature, being consistent with the high levels of IL-10 observed in the great majority of patients with different sorts of cancers. By diminishing pro-inflammatory and anti-tumor immune response in tumor microenvironment, IL-10 promotes tumor immune surveillance escape and tumor progression [7]. In addition to significantly inhibiting a Th1-polarized phenotype and suppressing pro-inflammatory cytokines, IL-10 presents other immunosuppressive and protumor actions. This cytokine has the ability to inhibit essential steps in immune detection, such as the expression of major histocompatibility complex (MHC) class II expression in antigen-presenting cell (APC), MHC class I in tumor cells, and co-stimulatory molecules on dendritic cells (DC), along with its acting on DC and macrophages, repressing their differentiation and antigen presenting properties [3].

IL-10 also inhibits natural killer group 2D (NKG2D) ligand expression on tumor cells and suppresses cytotoxicity mediated by natural killer (NK) cells, in addition to inducing human leukocyte antigen-G (HLA-G) molecules expression, preventing NK cells effects [1,8]. NKG2D is a homodimeric C-type lectin activating receptor expressed by several cells, including NK [9]. Ligands for NKG2D include stress-induced proteins, such as MHC class I chain-related A and B (MICA and MICB) and unique long 16 binding proteins (ULBP). Conditions such as malignant transformation, induces NKG2D ligands upregulation [9,10], leading to NKG2D receptor recognition, activation of several signaling pathways, as the 70 kilodalton heat shock protein (HSP70) mediated cellular stress [11] and the ataxia telangiectasia mutated/ataxia telangiectasia and Rad3-related protein (ATM/ATR) mediated DNA damage pathways [12], triggering effector functions of NK cells against tumor cells. Additionally, blocking of NKG2D pathways seems to increase the susceptibility of mice to induced carcinogenesis [13]. Experiments conducted in mice, using a 3'-methylcholanthrene (MCA) induced model, demonstrated that tumor outgrowth did not occur when monoclonal antibodies that block natural killer cell recognition (anti-NKG2D) were used [14]. However, in the presence of IL-10, NKG2D ligand expression seems to be hindered, as well as NKG2D-mediated NK cell cytotoxicity, thereby influencing on tumor immune surveillance [1]. On the other hand, while IL-10 downregulates cell surface MHC class I, it upregulates the non-classical class I molecule HLA-G [15]. HLA-G is the best-characterized non-classical HLA-class Ib molecule, which includes HLA-E, HLA-F and HLA-H, as well as other HLA-G isoforms that can be generated by alternative splicing. HLA-G molecules are expressed on trophoblastic cells and placental chorionic endothelium and play an important role in immune tolerance during pregnancy [16]. Moreover, it can be expressed in pathological conditions including cancer. HLA-G expression has been observed in various malignancies, being strongly associated with tumor immune escape, metastasis and poor prognosis [17]. HLA-G could lead to tumor evasion by several mechanisms as inhibition of immune cell cytolysis, differentiation and proliferation and inhibition of cytokine production and induction of immune cell apoptosis [18,19]. HLA-G interacts with inhibitory receptors such as the killer Ig-like receptors (KIR) and Ig-like transcripts (ILT), which are expressed on NK cells and T lymphocytes, thus inhibiting NK cell-mediated lysis, suppressing $CD8^+$ T cell and $CD4^+$ T cell function while also regulating cytokine production [8,18–20].

Furthermore, IL-10 has the ability to act as a negative regulator between innate and adaptive antitumor immunity. For instance, IL-10 secreted by T cells suppresses NK and natural killer T (NKT), leading to an impaired activation of cytotoxic T lymphocytes (CTL) and T helper 1 (Th1) $CD4^+$ T cells and tumor immune privilege. Additionally, IL-10 has been shown to mediate the immunosuppressive activity of Treg cells, including the expansion of T regulatory type 1 (Tr1) cells, which seems to down-modulate immune responses through the production of IL-10 [21,22].

Myeloid cells exposed to tumor microenvironment participate in tumor progression, promoting immunosuppression, matrix degradation and angiogenesis by secreting soluble factors, including IL-10. Among different tumor associated myeloid cells (TAMC), a significant amount of IL-10 is secreted by M2-activated macrophages, which correspond to the great majority of tumor-associated macrophages (TAMs) within a tumor [23]. Nowadays, plenty of evidence suggests that high TAM infiltration within the tumor generally correlates with a poor outcome. Besides TAM, IL-10 is additionally produced by tumor cells, which apparently co-express IL-10 and interleukin-10 receptor (IL-10R) [3].

Moreover, in experimental models, the IL-10 production by T cells or impaired tumor cells (e.g., through anti-IL-10-/IL-10R-blocking antibodies) resulted in an antitumor immune response [1]. Thus, all these findings and the previously exposed above support a strong IL-10-mediated immunosuppressive and protumor function (Figure 2).

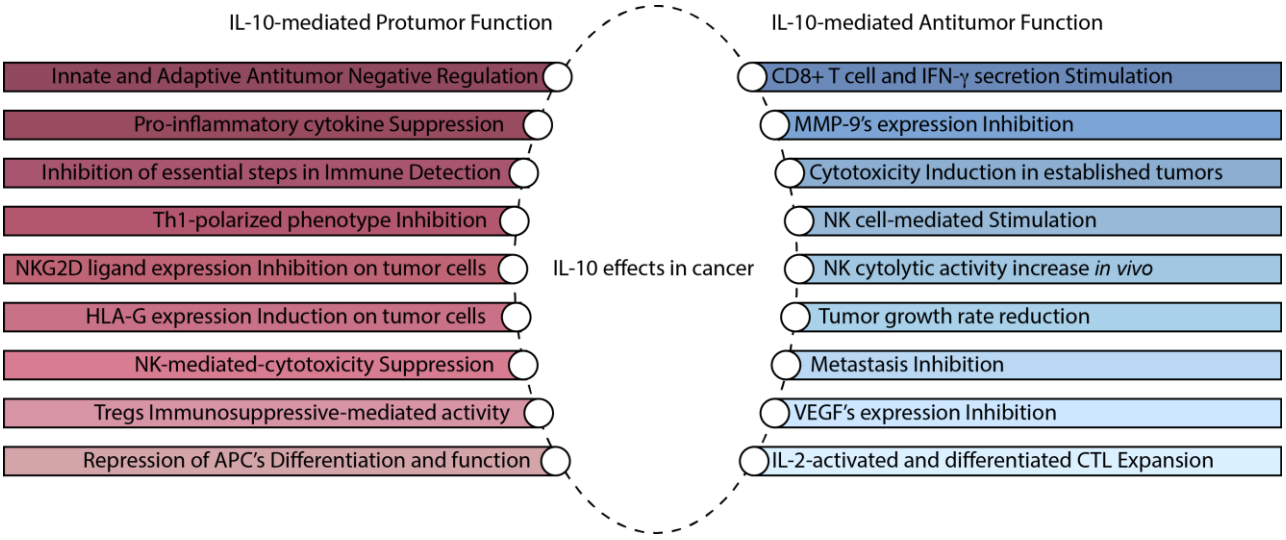

Figure 2. IL-10 effects in Cancer. Effects supporting IL-10-mediated Protumor Function (left) or IL-10-mediated Antitumor Function (right) in cancer.

3.2. IL-10-mediated antitumor function in cancer

Undoubtedly, in the context of inflammatory diseases and bacterial responses, IL-10 plays a clear role as an immunosuppressive factor. The same cannot be said in all cancer contexts, especially when taking into account the evidence based on murine tumor models that bring a clearly contradictory role of IL-10, presenting IL-10 as an immunostimulatory cytokine, leading to tumor regression and metastasis inhibition [4]. Although IL-10 has been associated with tumor regression

in different settings, the molecular mechanisms underlying its effects have not been fully characterized [24].

Among the distinct immunostimulatory effects that IL-10 exerts on different cells, the ability of IL-10 to increase $CD8^+$ T cell numbers, interferon gamma (IFN-γ) secretion, and induce cytotoxicity in established tumors are far the most related [1,3,4]. Lauw et al. [25] during clinical trials studying human endotoxemia used IL-10 as an anti-inflammatory agent and found an unexpected upregulation of IFN-γ by IL-10. In the serum of normal healthy volunteers injected with IL-10 and lipopolysaccharide (LPS), IFN-γ was increased rather than decreased. Such effect came as a contradictory role, since, in most inflammatory and infectious disease models, IL-12-induced IFN-γ expression is upregulated in the absence of IL-10. IL-10 seems to suppress the expression of the IL-12p40 chain of the heterodimeric cytokine IL-12 by upregulating the transcriptional repressor nuclear factor interleukin-3 (NFIL3) consequently, compromising the inflammatory response and the IFN-γ induction [26].

Mumm et al. [27] showed that IL-10 induces several essential mechanisms for effective antitumor immune surveillance, including an IFN-γ-dependent tumor immune surveillance. IL-10 seems to induce antigen-specific $CD8^+$ T cell responses in tumor-bearing mice, elevating IFN-γ in $CD8^+$ T cells. In addition, the authors confirmed that IL-10 regulates cytotoxic enzymes and the Th1 cytokine IFN-γ in human $CD8^+$ T cells, suggesting that IL-10 regulation of cytotoxic activity and IFN-γ expression is similar in $CD8^+$ T cells from both mice and man. Besides that, other mechanisms for IL-10's effective antitumor immune surveillance were also described, as infiltration and activation of intratumoral tumor-specific cytotoxic $CD8^+$ T cells and granzyme expression by those cells. They showed that IL-10 deficiency increases tumor incidence and decreases immune surveillance, and also that MHC molecules and cytotoxic mediators are increased by IL-10 in the tumor but not in secondary lymphoid organs (i.e., IL-10 induces upregulation of MHC molecules through induction of T cell-derived IFN-γ), with $CD8^+$ T cells activation in the tumor being essential to IL-10-mediated tumor immune surveillance. Additionally, they showed that IL-10 directly induces cytotoxicity of human $CD8^+$ T cells and its expression correlates with the expression of cytotoxic enzymes. Moreover, they found that IL-10 receptor subunit alpha (IL-10RA) was highly expressed on tumor-infiltrating $CD8^+$ T cells. The expression of the IL-10R seems to be required on $CD8^+$ T cells to facilitate IL-10-induced tumor rejection as well as *in situ* expansion and proliferation of tumor-resident $CD8^+$ T cells.

Additionally, Emmerich et al. [28] demonstrated that IL-10 exerts direct effects on mature T cells, acting as a cytotoxic T cell differentiation factor promoting an elevated number of interleukin-2 (IL-2) activated CTL to proliferate and differentiate into effector CTL. Treatment with IL-10 induces specific activation of tumor-resident $CD8^+$ T cells as well as their intratumoral expansion in distinct mouse tumor models, with this specific cellular population expressing increased levels of the IL-10R, that were directly activated by a unique combination of STATs in tumor-resident $CD8^+$ T cells, resulting in phosphorylation of signal transducer and activator of transcription 3 (STAT3) and signal transducer and activator of transcription 1 (STAT1). Moreover, they confirmed that IL-10R expression on $CD8^+$ T cells was necessary and sufficient for $CD8^+$ T cells activation by IL-10, that IL-10RB expression was required on endogenous $CD8^+$ T cells for activation and IFN-γ induction by IL-10 and that IL-10R induced accumulation of antigen-specific

tumor-resident $CD8^+$ T cells. Additionally, they observed that the frequency of $CD8^+$ T cells producing IFN-γ increased on average 3-fold upon IL-10 treatment, showing that IL-10 treatment led to an increase in the frequency of IFN-γ producing $CD8^+$ T cells in the tumor. Besides increasing the effector cytokine IFN-γ expression, IL-10 also seems to increase the expression of effector molecules as granzymes. The mRNA analysis of tumors from control and IL-10-treated mice revealed that IL-10 induces a strong increase in the expression of cytotoxic effector molecules, such as granzyme B and perforin. Thus, despite a seemingly unlikely candidate, IL-10 appears to stimulate the immune system in a particularly efficacious way, delivering an equally potent immune stimulation.

Furthermore, IL-10 also seems to mediate NK cells stimulation, increasing NK cytolytic activity *in vivo*, which was not demonstrated *in vitro*, where IL-10 has been shown to suppress NK expression of pro-inflammatory cytokines such as TNF-α and IFN-γ [3,29]. In the context of experimental cancer models, IL-10 seems to promote local effector mechanisms, such as NK cell activation and the enhanced expression of cytotoxic molecules [30,31]. Mocellin et al. [30] proposed that NK cells serve to "link" innate immunity to adaptive immunity, which may be a crucial step in tumor escape. As IL-10 acts as a potent stimulator of NK cells (i.e., IL-10 can induce NK cell activation and facilitate target-cell destruction), it may facilitate antigen acquisition from dead cells for cross-priming by activated APCs, providing this link. IL-10 seems to enhance the susceptibility of target cells to NK cell lysis by reducing the surface expression of MHC antigens [30,32–34]. Although some mechanisms have been proposed to explain IL-10-mediated NK stimulatory effect, it is not completely clear how this activation occurs. IL-10 seems to indirectly stimulate NK cells, based on the fact that TAMs have been shown to deactivate NKs by releasing reactive oxygen species, which secretion in macrophages is known to be inhibited by IL-10. Moreover, IL-10 seems to reduce the expression of MHC/HLA molecules in APC, which may activate NK cells and increase cytotoxic function [3]. The effects of IL-2 and IL-10 on the proliferative and cytotoxic function of NK cells were tested, demonstrating that despite IL-10's absent effect over NK cell proliferation, it significantly increased the lysis of a human lymphoma cell line, as a result of the combination of IL-2 and IL-10 actions. In addition, it appears that IL-10 has the ability to stimulate an intrinsic NK cell activity through distinct pathways, with the combination of IL-2 and IL-10 administration specifically inducing the differential expression of several genes, mostly promoting inflammation and increased NK cell migration and function. Thus, once IL-10 is secreted constitutively by tumor cells, it may pre-condition the immune responsiveness of tumors to proinflammatory stimuli, activating NK cells, leading to tumor cell killing, antigen release and APC stimulation by damaged cells [30].

Another important property of IL-10 that corroborates to its antitumor role is the possible effect of IL-10 over important angiogenic factors. Tumor cells expressing IL-10 were rejected and established tumors displayed reduced growth rates upon injection of IL-10, as well as inhibition of metastasis. In addition a decrease in mRNA of vascular endothelial growth factor (VEGF), an important angiogenic factor, as well as matrix metallopeptidase 9 (MMP-9), which is important for both angiogenesis and metastasis, was demonstrated, supporting IL-10 antiangiogenic action [1,3]. Therefore, these evidence and others previously mentioned, support an IL-10-mediated immunostimulant and antitumor function in cancer (Figure 2).

4. Conclusions

If, on the one hand, it is well established the fact that higher expression of IL-10 correlates with tumor progression and metastasis in patients with several cancer types, indicating that IL-10 production in the clinical setting may be detrimental, its role in tumorigenesis facilitating tumor eradication should not be excluded. Even considering the fact that literature reports are based on *in vitro* and *in vivo* murine models, whereas *in vivo* findings in humans are restrict, we still find plenty of evidence supporting IL-10-mediated antitumor action. Indeed, until the present moment, we still have not enough information to completely determine IL-10's role in cancer, with further research being required to define particular roles of this intriguing cytokine in different particular cancer contexts. However, we have evidence to support the fact that this cytokine acts not just as a classical immunosuppressive factor, behaving sometimes as an immunostimulating one.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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