A therapeutic perspective of cytokines in tumor management

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Malignant cancer is a serious threat to the health of men and women worldwide, yet no single or combine treatment strategy exists that can effectively eliminate this disease. Recent years, significant interest has been generated in targeting immune system of cancer patients for therapeutic and preventive purposes. Among the several components of immune system, chemokines and cytokines are key potential targets for immunotherapy of cancer. This review provides a brief overview of the current knowledge and recent updates on the use of cytokines or chemokines in cancer therapy and management.

Keywords: Immunosuppression; Malignancy; Tumor microenvironment; Cytokines; Cell death; Immunotherapy

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Introduction

Malignant cancer is one of the most common reasons for human death worldwide. For example, according to a report of World Health Organization (WHO) published in 2004, 12.6%, 10.4%, and 26.6% people died worldwide, developing, and developed countries, respectively, as a result of malignant cancer[1]. In 2008, GLOBOCON reported approximately 12.7 million documented cancer cases worldwide and 7.6 million deaths due to different malignancies [2]. The International Agency for Research on Cancer (IARC), predicts 13.1 million cancer related deaths by the end of 2030 [3]. Based on origin of cancer, there are several types of cancer in humans including adenocarcinoma, carcinoma, glioblastoma multiforme, and acute myeloid leukaemia[4]. The prevalence of cancer is dependent on several factors including socioeconomic status, dietary habits, racial and genetic predisposition, and the surrounding environment [5, 6].

The immune system plays a pivotal role in many malignancies. Several immune molecules including natural killer cells (NK-cells), B-cells, T-cells, and cytokines are involved in different malignancies [7-9]. Components like cluster of differentiation (CD8) T cells play a critical role in the host defense against cancers[10]. Anticancer agents like histone deacetylase inhibitors require immune machinery for the production of IFN-γ in aggressive B-cell lymphoma and colon carcinoma [11]. Pattern recognition receptor agonists and immunostimulatory monoclonal antibodies have been targeted as immunostimulatory drugs [12]. Similarly, monoclonal antibodies that block inhibitory
T-cell pathways have been implicated in leukemia immunotherapy [13]. Among several immune mediators, interleukin and cytokines or chemokines (small molecular weight cytokines) play an important role in tumor progression as well in metastasis. Therefore, these immune mediators represent potential choice for cancer diagnosis and therapeutics.

**Tumor microenvironment and immune system**

Cancer cells thrive in a well-defined environment commonly known as the tumor microenvironment (TME) [14]. The TME is composed of many components including cancer-associated fibroblasts, endothelial and lymphatic cells, pericytes, immune cells, bone-marrow-derived cells, extracellular matrix, blood vessels, fibroblast, and signaling molecules [14-16]. These factors play key role in all aspects of tumorigenesis including tumor initiation, progression, and metastasis [10]. Tumor cells secrete immune components that counter the immune surveillance of host, and protect them from several antitumor agents like natural killer (NK) cells, natural killer T (NKT) cells, dendritic cells (DCs), and effector T-cells. These pro-tumor immune activities are mediated by molecules like cytokines, chemokines, myeloid suppressor cells, and Treg or regulatory T-cells [17]. Tumor derived cytokine and chemokine signals neutralize the immune effector cells, which may be mediated by NF-kB pathway [18, 19]. Surface antigens in tumor cells are tumor specific, and this characteristic has been targeted effectively at clinical level by tumor antigen specific monoclonal antibodies like rituximab, trastuzumab and cetuximab [20]. However, tumor released cytokines in TME disrupt host immune surveillance and this is one of the reasons why tumor cells escape recognition from T-cells [21]. Non-immunogenic neoantigens production, or nonor poor expression of major histocompatibility complex (MHC) antigens also play very important role to protect tumor cells from immune surveillance [22]. Based on this small discussion, it is clear that immune system plays a dual role in cancer. For example: Treg cells have been reported to block anti-tumor immunity of the host [23]; adoptive transfer of CD3+CD25+ T cells from patients to the nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice showed retarded growth of tumor, while simultaneous transfer of Treg cells supported tumor survival [24]. Recently, Burkholder et al. explained that the immunosurveillance may lead to elimination of tumors, equilibrium in the TME and escape of tumor from host immune system. Collectively, these three outcomes are referred to as immunoediting [25]. Together, tumor cells produce/secret/ immunosuppressive entities like cytokines and chemokines, and induce Treg cells which can lead to tumor cell survival and progression.

**Regulatory role of cytokines in TME**

Tumor-derived cytokines cause cancer cell survival and progression [17]. Tumorigenesis is a complex process and initial response of the host immune system involves secretion of cytokines and chemokines that inhibit tumor development [26]. However, tumor derived factors including cytokines and chemokines ultimately suppress host immune system causing failure of anticancer activities of host-derived cytokines and chemokines [27]. Thus tumor cells release several cytokines into their surroundings that favor the growth and survival of tumor cells [28]. The pro-survival function in tumor cells is mediated by multiple cytokines or interleukins, which may function as pro-survival or proapoptotic molecules. Overexpressed of proinflammatory cytokine IL-1β causes cancer cell proliferation including in gastric cancer [29]. In bladder cancer cell lines 5637 and T-24, higher levels of IL-5 and its receptor IL-5Rα are associated with enhanced NF-kB activation indicating pro-survival role of IL-5 [30]. IL-6 promotes cancer cell survival by inhibiting extrinsic apoptotic cell death pathway via IL- 2-independent inhibition of Fas/Fasl. expressions [31]. Another cytokine, IL-8 plays an important role in the angiogenesis and growth of several cancer cells including breast cancer [32, 33]. Further, interferon-gamma (IFN-γ) induces autophagic cell death in some types of cancer cells including human hepatocellular carcinoma [34]. Similarly, TNF-α and TGF-β1 also regulate cancer cell survival and apoptotic cell death [35, 36]. Further, it has been reported that lack of TGF-β signaling and loss of phosphatase and tensin homolog (PTEN) lead to induction of intestinal cancer [37].

**Clinical implications of cytokines in cancer**

Immunotherapy using immune molecules to treat cancer is emerging as a breakthrough therapeutic orientation that involves both passive and active approaches. In active immunotherapy, vaccination (e.g., tumor lysate-pulsed DCs vaccine) is the key consideration that modulates TME against tumor cells [38]. While in passive immunotherapy exogenous antibodies are administered to the cancer patients [39]. Several cytokines have been used for cancer treatment including IFN-α, IFN-β, γ-IFN, IL-1, IL-2, and IL-12. These cytokines demonstrate their efficacy by inducing apoptosis and other anticancer functions in tumor microenvironment. IFN-α exerts its anticancer efficacy by inducing NK cells and DCs against tumor cells by inhibiting cell proliferation and killing cancer cells, thus show anticancer effect in melanoma and Kaposi sarcoma [40-42]. IL-1α shows cytotoxic-cytostatic activity against refractory malignancies and solid tumor cells. A phase I study of recombinant human IL-1α in patients with refractory malignancies showed increased neutrophil and platelet counts [43, 44]. Th1 cytokine IL-2 shows anticancer efficacy against several types of cancer including hematologic malignancies in in-vitro, in-vivo, and clinical studies [45]. Cytokine IL-2 exerts it anticancer efficacy by
enhancing anticancer immunity that is evident by the use of recombinant antibody-IL-2 fusion protein (huKS1/4-IL-2) in colorectal carcinoma [46]. IL-4 has been reported to facilitate its anticancer efficacy by inhibiting growth of some human lung tumor cells [47]. In MCF-7 breast cancer cells, IL-4 showed growth inhibition and induction of apoptosis via insulin receptor substrates and STAT-6 phosphorylation [48]. IL-6 is a platelet growth factor and clinical trials are underway to use it as an antitumor agent [49]. IL-7 in combination with human T cells exerts significant anticancer activity in human colon carcinoma in an in vivo study [50]. The protective function of IL-7 is mediated via activation of the PI3K/AKT pathway [51]. IL-11 is used in myelosuppressive chemotherapy to minimize the chance of thrombocytopenia in patients with malignancies [52]. Being a key player in cellular immunity against tumor, IL-12 is an option for immunotherapy, but presence of severe toxicity minimizes its use in cancer therapy. However, recent study suggests that membrane-bound IL-12 shows minimal risk to patients, and thus IL-12 may play a significant role in cancer treatment and management [53]. Some studies also reported the use of IL-12 therapy with anti-vascular endothelial growth factor receptor-2 monoclonal antibody (VEGFR-2 mAb) for tumor management [54, 55]. IL-15 plays important role in the induction of NK cells, T-cells, and B cells that demonstrate the possible therapeutic potential of this key cytokine in malignancy. However, these reports are positive and encouraging much work needs to be done to assess their potential in multiple cancers.

Conclusions

Together, cytokine-based anticancer agents possess high potential for the development of therapeutic agents to treat or manage various types of malignant cancer. However, the key limitations are the toxic manifestations induced by cytokines therapy. In addition to individual effects of cytokines against tumors, combination of cytokines either with known anticancer drugs or with chemopreventive agents may have high potential to enhance efficacy of anticancer agents or reduce associated toxicity, respectively.

Conflicting interests

The authors have declared that no competing interests exist.

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