Inflammatory Factors Involved in Cancer Transformation

Subjects: Immunology

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Inflammation, when it became chronic, settles down the body's normal inflammatory process, creating a favorable environment for the development of cancerous cells. There are numerous signaling pathways that are key contributors to generating epigenetic changes outside and inside the cell.

Keywords: cancer ; inflammation ; nanoparticles ; drug delivery ; inflammatory pathways

1. Macrophages and Denticles Cells

Macrophages consist of closely linked bone marrow cells, blood monocytes, macrophages of tissues, and a constituent part of the mononuclear phagocyte system. Macrophages primarily have three major vital roles, phagocytosis, presentation of antigens, and in immunomodulation by producing different cytokinesis and growth factors [1]. Macrophages help in maintaining and initiating inflammation [2]. The secreted pro-inflammatory mediators have a necessary part in the growth of fibroblasts and blood vessels, and in tissue remodeling and regeneration [3]. The process is activated and deactivated by inflammatory processes such as activating signals i.e., cytokinesis and TNF-α are deactivated by removing mediators and inflammatory effector cells. Interleukin 10 helps in the deactivation of activated macrophages [1]. Macrophages are components of innate immunity derived from the myeloid progenitor cell namely known as the granulocyte-macrophage colony forming unit (GM-CFU) inside bone marrow. Tumor-associated macrophages (TAM) are created by cancerous and stroma cells in the tumor and are enlisted by tumor growth factors and chemokines [4].

TAM promotes cancer development mainly by three mechanisms:

- By enhancing the angiogenic tumor potential factors such as IL-8, VEGF, and MIF, and by promoting lymph-angiogenesis
- Progression in the growth of tumor
- Tumor cell invasion, migration, and intravasation at primary sites JAM, and they act on endothelial cells, further promoting the tumor's neovascularization [5].

Macrophages contain antigen-presenting cells, immunomodulators, and phagocytosis that play a vital role in the initiation and maintenance of inflammatory functions [6]. Macrophages that infiltrate the tumor parenchyma have an M1 phenotype and M2 phenotype present in the tumor microenvironment [4]. M2 macrophages are characterized by their anti-inflammatory and wound-healing endotype, and they are further divided into different subtypes: the M2a macrophages subtype, which responds to Interleukin-4 and Interleukin-13 during fungal and helminth infections [7]. They express a high level of mannose receptor (CD206) and are the largest secretor of pro-fibrotic factors, such as TGF-β and GF (growth factors), etc. Further, they are involved in the repair of tissues/cells and the healing of wounds at the time of inflammation [8]. M2b is by bacterial LPS and immune complexes; they secrete IL1β, TNF-α, and IL-6 that consists of anti-inflammatory effects. M2c is stimulated by Interleukin-10, glucocorticoids, and TGF-β. M2d macrophages are activated in response to co-stimulation with adenosine ligands and TLR ligands; they express CD206 at a low rate, however, they highly express vascular endothelial growth factor (VEGF) and Interleukin-10 [9]. Dendritic cells have an important part in antigen-specific immunity activation and tolerance maintenance. They develop a connecting link between innate and adaptive immunity [10]. T-cells are stimulated by tumor-associated dendritic cells (TADCs) and these associated cells are different from TAM (tumor-associated macrophages). TADCs are considered poor inducers for effective tumor responses [11]. Dendritic cells are excellent antigen-presenting cells (APC) as they engulf pathogens and present antigens on major histocompatibility complexes.

2. Proinflammatory Cytokinesis

Inflammatory chemokines and the cytokines that are produced by tumor-associated leukocytes and platelets, participate directly in the progression of malignant cancer. The most basic physiological difference between normal and tumor tissue is that many chemokines and cytokines are induced by hypoxia such as TNF-α, InterLeukin 6, and InterLeukin-1 α and β. They are signaled through type 1 cytokines receptors (CCR1) and are the immune-regulatory cytokinesis that favors inflammation. Inflammatory responses are resolute by the net balance between the anti-inflammatory cytokines and proinflammatory cytokines [12]. Anti-inflammatory cytokines control proinflammatory responses. At the time of chronic inflammation, cytokines can lead to cell malignancy and cell transformation, depending on the tumor microenvironment. Studies found evidence that some cytokines play a key role in promoting and inhibiting cancer [13]. Tumor-promoting cytokines are IL-6, transforming growth factor (TGF-β), TNF-α, and IL-23, they activate STAT proteins, suppress apoptosis, and contribute to EMT [14]. Whereas tumor-inhibiting cytokines including IFN-α, IL-2, and IL-12, inhibit tumor growth and angiogenesis, and expand the functional T-cells and Natural killer cells. Cytokines activate STAT proteins that may increase or decrease inflammation in the case of any viral infection; IFNs trigger and activate STAT 1 and STAT 2. HIF-1 induces inflammation and transcription in genes that process angiogenesis and erythropoiesis; it is a pro-tumorigenic factor that promotes the proliferation of cells and the survival of cancerous cells decreases consumption in VHC-lacking renal carcinoma cells by inhibiting C-Myc.

3. Tumor Necrosis Factor α

TNF-α is an inflammatory cytokine that participates in regulating various signaling processes such as Nuclear factor kB and C-Jun-N-terminal kinase activation contributes to cell death. JNK and NF-kB helps to describe the cellular outcomes. TNF α signals to TNF receptor 1 and 2, TNF receptor 1 activate pro-inflammatory pathways, and TNF receptor 2 binding to membrane-bound TNF that commence tissue regeneration and immune modulation [15]. As a multifunctional cytokine, it plays diverse cellular events such as differentiation, proliferation, and cell death. An inflammatory cell secretes Tumor Necrosis Factor that may have a role in the process, i.e., associated with inflammation-related carcinogenesis. On the other side, TNF could act as a cancer inhibitor/killer [16]. They are also involved in endogenous tumor promotion as they stimulate the metastasis of cancerous cells. In human cancer, Tumor Necrosis Factor can be found in stroma and malignant cells, lungs, breast, prostate, bladder, and colorectal cancer [17]. In a review, it was found that by up-regulating the levels of prion protein (PrP), TNF-α can contribute to malignant cancer [18]. TNF α promotes the formation of inflammatory cytokines and stimulates the permeability of endothelial cells.

4. Interleukin

IL-6 plays a vital part in inflammatory responses as it is a pleiotropic cytokine. They are mainly secreted by monocytes. The secretion of InterLeukin 6 by immune cells is an indication of severe infection or major cell/tissue injuries [19]. Their pro-oncogenic effect has been demonstrated in different types of carcinomas including colorectal, breast, and lung. IL-6, along with the proteins of the STAT family, helps to regulate carcinogenic processes, the inhibition of apoptotic processes, and the release of ROS and RNS. IL-2 and 12 poses an anti-cancer effect, and the clinically effective efficacy of gene-edited lymphocyte transfer has been identified in those patients suffering from lung cancer [20]. IL-12 is capable of activating cytotoxic immune cells [21]. They induce immune responses against different cancers. Thymus and bone marrow cells, mast cells, granulocytes, macrophages, and almost all cells of the immune system secret/produce IL-10, and are considered to have a potent anti-inflammatory cytokine [22]. IL-10 is secreted by tumor cells as a tumor infiltratory macrophage. IL-10 consists of both pro and anti-tumoral effects [23]. It inhibits NF-kB signaling pathways when IL 10 binds to the receptors Jak-1 and TyK-2 tyrosine kinase phosphorylate, which allows it to interact with STAT-1, 3, and 5, preferring STAT translocation in the nucleus, inducing targeted gene expression over there [24]. IL-1 receptor antagonist (IL-1Ra), when used to treat metastasis in mouse models, has shown a sudden decrease in tumor development, because of the inhibition of IL-1 action, while those mice that have low IL-1 were resistant to the development of metastasis experimentally [25].

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