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Relationship between Cancer and Cytokines

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Abstract Cancer is a group of various diseases that involve unregulated cell growth. Inflammation plays an important role in the pathogenesis of cancer. Inflammatory cytokines produced by tumor cells or inflammatory cells in the tumor microenvironment can promote tumor cell survival through the induction of genes encoding nuclear factor-kB–dependent antiapoptotic molecules. Trials with therapies that act on cytokines may represent a new hope for patients with cancer.

Keywords: *cytokines, pathogenesis, cancer*

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1. Introduction

It has been established that cancer can be promoted and/or exacerbated by inflammation and infections. Chronic inflammation provides a tumor supporting environment that participates in the neoplastic process (Kabel et al., 2013). The mechanisms that link infection, immunity, inflammation and cancer include cytokines produced by activated innate immune cells that stimulate tumor growth and progression (Kabel, 2014). In addition, soluble mediators are produced by cancer cells and activate inflammatory cells, which further stimulate tumor progression. However, inflammatory cells also produce cytokines that can limit tumor growth (Lin and Karin, 2007).

2. Mechanisms that Link Inflammation and Cancer

Cancer is a hyperproliferative disorder that involves cellular transformation, dysregulation of apoptosis, uncontrolled cellular proliferation, invasion, angiogenesis and metastasis. Clinical and epidemiologic studies have suggested a strong association between chronic infection, inflammation and cancer (Fox and Wang, 2007). For example, there is strong association between alcohol abuse which leads to hepatitis and pancreatitis and cancers of these organs. Cigarette smoking, asbestos and silica exposure are associated with inflammation of the lung and lung carcinoma; inflammatory bowel disease is associated with colon cancer; chronic viral hepatitis is associated with liver cancer. Such observations suggest that chronic inflammation is involved in tumor initiation, promotion and progression (De Visser et al., 2006).

The inflammatory process occurred by cells such as macrophages, T cells, and natural killer cells. Among these, tumor-associated macrophages (TAMs) and T cells are frequently the prominent leukocytes present in a tumor (Mantovani et al., 2002). Many data indicate that acute inflammation triggered by tumor-infiltrating host leukocytes does not exert normal immunoprotective mechanisms that lead to eradication of cancer. Instead, excessively and chronically produced proinflammatory mediators are thought to contribute to tumor promotion and progression (Lin and Karin, 2007). In the tumor microenvironment, there is a balance between antitumor immunity and tumor-originated proinflammatory activity, which weakens antitumor immunity. When antitumor activity is weaker than tumor-mediated immunosuppressive activity, tumor cells undergo immune escape and grow rapidly. By contrast, when antitumor immunity is stronger than tumor-mediated immunosuppressive activity, tumor cells are eliminated. The net outcome of chronic inflammation is enhanced tumor promotion, accelerated tumor progression, invasion of the surrounding tissues, angiogenesis and metastasis (Kim et al., 2006).

A key molecular link between inflammation and tumor promotion and progression is provided by the inhibition of NF-kB kinase/NF-kB signaling pathway, which is activated by many proinflammatory cytokines (Karin, 2006). NF-kB is a transcription factor that regulates the expression of many genes whose products can suppress tumor cell death, stimulate tumor cell cycle progression, enhance epithelial-to-mesenchymal transition which has an important role in tumor invasiveness and provides newly emerging tumors with an inflammatory microenvironment that supports their progression and invasion of the surrounding tissues (Luo et al., 2005).

3. Tumor Necrosis Factor Alpha (TNF-α)

The critical role of TNF- α in chronic inflammatory diseases is well established and its tumor-promoting

effects have been demonstrated. TNF-α produced by tumor cells or inflammatory cells in the tumor microenvironment can promote tumor cell survival through the induction of genes encoding NF-kB–dependent antiapoptotic molecules (Luo et al., 2004).

In asbestos-induced malignant mesothelioma, macrophages phagocytose asbestos and then release TNF-α. This TNF-α promotes cell survival and thereby reduces asbestos-induced cytotoxicity increasing the pool of asbestos-damaged mesothelial cells that are susceptible to malignant transformation (Lin and Karin, 2007). TNF-α has also been proposed to contribute to tumor initiation by stimulating the production of genotoxic molecules that can lead to DNA damage and mutations, such as nitric oxide and reactive oxygen species (Hussain et al., 2003).

Genetic polymorphisms that enhance TNF-α production are associated with increased risk of bladder cancer, hepatocellular carcinoma, gastric cancer and breast cancer, as well as poor prognosis in various hematological malignancies. Other actions of TNF-α include promotion of angiogenesis and metastasis as well as impairment of immune system by strongly suppressing many T cell responses and the cytotoxic activity of activated macrophages (Mocellin et al., 2005). Studies have suggested a role for keratinocyte-produced TNF-α in mouse models of skin carcinogenesis. Reduced tumorigenesis was also found in mice deficient in TNF-α receptors (Arnott et al., 2004).

A tumor-promoting role for TNF-α has also been found in cholestatic liver cancer, which develops as a result of chronic liver inflammation in mice lacking the drug and phospholipid transporters. Treatment with TNF-α–specific neutralizing antibody during the tumor promotion stage resulted in apoptosis of transformed hepatocytes and failure to progress to hepatocellular carcinoma (Pikarsky et al., 2004). Another study had indicated that TNF-α signalling is crucial for promoting liver metastasis of colon adenocarcinoma (Kitakata et al., 2002). In another study, lipopolysaccharide administration to tumor-bearing mice induced production of TNF-α and stimulated metastatic tumor growth in the lung. Taken together, TNF-α released by host and tumor cells is an important factor involved in initiation, proliferation, angiogenesis and metastasis of various types of cancers (Luo et al., 2004).

4. TRAIL

The TNF superfamily member TRAIL can bind five different receptors, two of which, death receptor 4 (DR4) and DR5, deliver caspase-dependent apoptotic signals to the cell on which they are expressed. TRAIL is mainly produced by activated T cells and NK cells and is one of the major mediators of antitumor immunity. Unlike TNF-α, TRAIL is able to induce apoptosis in various tumor cells but has negligible effects on normal cells. TRAIL-deficient mice or mice treated with TRAIL-specific neutralizing antibody exhibit increased susceptibility to experimentally induced and spontaneous tumors suggesting an important role for endogenous TRAIL in tumor surveillance (Le Blanc and Ashkenazi, 2003).

5. Interleukin-6 (IL-6)

IL-6 is a potent inflammatory cytokine that is considered a key growth-promoting and antiapoptotic factor. Activation of IL-6 receptor triggers phosphorylation of the STAT proteins; STAT1 and STAT3. STAT3 has a predominant role in malignant cell proliferation while STAT1 inhibits tumor cell growth. Most IL-6 target genes are involved in cell cycle progression and suppression of apoptosis which lead to tumorigenesis (Haura et al., 2005). IL-6 is suggested to have a pivotal role in the pathogenesis of Kaposi sarcoma. Other studies suggest an association between circulating IL-6 and elevated risk of developing Hodgkin lymphoma (Cozen et al., 2004).

6. IL-17

Th17 cells are characterized by production of IL-17 which plays a role in the inflammatory responses. The production of IL-17 relies on STAT3 activation triggered by IL-23. IL-17 induces the migration of immune cells to peripheral tissues, a response that requires NF-kB activation after IL-17 receptor engagement. IL-17 also leads to the induction of many proinflammatory factors, including TNF-α and IL-6, suggesting an important role for IL-17 in localizing and amplifying inflammation (Cho et al., 2006). Furthermore, TNF-α and IL-6, which are both produced by Th17 cells, synergize with IL-17 to enhance the production of proinflammatory mediators. There is evidence that IL-17 might be involved in tumor surveillance in immunocompetent mice (Benchetrit et al., 2002).

7. IL-12 and IL-23

They are mainly produced by phagocytes. The receptors for both IL-12 and IL-23 are mainly expressed on T cells, NK cells, monocytes, macrophages, and DCs. Both cytokines activate STAT protein (Watford et al., 2004). The antitumor activity of IL-12 has been reported in mouse models of cancer, where it has been shown to inhibit tumorigenesis and induce regression of established tumors by activation of Th1 adaptive immunity and increasing interferon production which has a direct toxic effect on cancer cells and antiangiogenic activity (Trinchieri, 2003).

IL-23 can enhance the proliferation of memory T cells and the production of IFN and IL-12 by activated T cells (Hao and Shan, 2006). However, it can drive Th17-mediated responses, induce IL-17 production, induce the production of TNF-α by macrophages and promote end-stage inflammation which may lead to the development of cancer. It was found that the growth of transplanted tumors was restricted in hosts deficient in IL-23 (Langowski et al., 2006).

8. IL-10

The effects of IL-10 are opposite to those of IL-6, as IL-10 is immunosuppressive and anti-inflammatory. IL-10 inhibits NF-kB activation and consequently inhibits the production of proinflammatory cytokines, including TNF-

α, IL-6, and IL-12. IL-10 has also been shown to modulate apoptosis and suppress angiogenesis during tumor regression. Expression of IL-10 in mammary and ovarian carcinoma xenografts inhibits tumor growth and spread (Lin and Karin, 2007).

9. Conclusion

There are many cytokines that play an important role in the pathogenesis and management of cancer by different ways including TNF-α, TRAIL, IL-6, IL-10, IL-12, IL-17 and IL-23. The drugs acting as agonists or antagonists to some of these cytokines may represent a new hope for cancer therapy.

Competing Interests

The author has no competing interests.

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