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World J Gastroenterol 2006 December 7; 12(45): 7233-7238
World Journal of Gastroenterology ISSN 1007-9327
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EDITORIAL

Colon cancer and the immune system: The role of tumor invading T cells

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Received: 2006-07-18 Accepted: 2006-09-20

Abstract

Colon cancer is still one of the leading causes of cancer death worldwide. Although the host immune system has been shown to react against tumor cells, mainly through tumor infiltrating lymphocytes and NK cells, tumor cells may utilize different ways to escape anti-tumor immune response. Tumor infiltration of CD8+ and CD4+ (T-bet+) effector T cells has been attributed to a beneficial outcome, and the enhancement of T cell activation through T cell receptor stimulation and co-stimulatory signals provides promising strategies for immunotherapy of colon cancer. Growing evidence supports a role for the Fas/FasL system in tumor immunology, although the mechanisms and consequences of FasL activation in colon cancer are not completely understood. In animal models, depletion of regulatory T cells (CD4+ CD25+ T cells) can enhance the anti-tumor immune response under certain conditions. Taken together, recent insights in the immune reaction against colon carcinoma have provided new approaches to immunotherapy, although much remains to be learned about the exact mechanisms.

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Key words: CD4-positive T-lymphocytes; CD8-positive T-lymphocytes; Immunology; Colonic neoplasms therapy; Colorectal neoplasms; Humans; Lymphocytes; Tumor-infiltrating; Tumor escape

Waldner M, Schimanski CC, Neurath MF. Colon cancer and the immune system: The role of tumor invading T cells. *World J Gastroenterol* 2006; 12(45): 7233-7238

http://www.wjgnet.com/1007-9327/12/7233.asp

INTRODUCTION

Colon cancer is still one of the leading causes of cancer death worldwide. In the United States approximately 145 290 new cases of colorectal cancer are diagnosed every year. With more than 56 000 deaths in the United States in 2005, colorectal cancer is responsible for more than 10 percent of all cancer deaths[1]. However, the molecular pathogenesis of colorectal cancer is still poorly understood. Recent studies suggested that different mechanisms such as mutations in cell cycle-[2] and apoptotic-pathways[3], signal transduction[4-6], angiogenesis[7,8], invasion and metastasis[9] significantly contribute to cancer progression (Table 1). Another important mechanism consists of the ability of tumor cells to escape the host immune reaction, as outlined below.

Sir Macfarlane Burnet and Lewis Thomas first proposed the existence of an immunological response to tumors in the cancer immunosurveillance hypothesis in the 1950s[10,11]. However, strong evidence supporting this concept was lacking and the hypothesis was abandoned for many years[12]. In the past two decades, however, the identification of tumor specific antigens and immune modulation leading to tumor regression suggested the existence of cancer immunosurveillance[13-17]. The activation of the host immune system through tumor cells is a complex cascade involving both the innate and adaptive immune systems (Figure 1)[11]. The presence of tumor specific T cells has been correlated with improved clinical outcome in different human cancers[18-21], but does not necessarily result in anti-tumor immunity, since T cells can also promote the progression of tumors through different growth factors[22]. It has been shown that CD8+ T cells and CD4+ effector T cells may have anti-tumor properties, whereas regulatory T cells (CD4+ CD25+ Tregs) may be responsible for immunological hypo-responsiveness observed in cancer[23-26].

The human gastrointestinal tract contains several phenotypically and functionally distinct populations of T cells, which may play a role in anti-tumor immunity[27-29]. Interestingly, T cell activation has been shown in colorectal cancer and proposed as a prognostic factor[30]. The following editorial will discuss recent advantages in our understanding of T cell activation in colorectal cancer and possible therapeutic strategies.

EVIDENCE FOR T LYMPHOCYTE ACTIVATION IN COLON CANCER

Tumor-infiltrating lymphocytes (TILs) have been isolated from a variety of solid human cancers. It has been widely accepted that one of the most promising T cell subsets

for an effective anti-tumor response consists of CD8+ T cells[26]. In a study on 131 patients with colorectal cancer, Naito *et al* showed a positive correlation between CD8+ T-cells within cancer cell nests and patient survival[30]. Another study using 959 specimens of resected colorectal cancer analyzed the correlation between tumor metastasis and T cell activation[31]. Elevated expression of genes, specific for cytotoxic T lymphocytes (CTLs), such as CD8α, granzyme B, or granulysin as well as Th1-associated genes as T-bet, or interferon-γ was significantly higher in patients without signs of early metastatic invasion as compared to those with early invasion (VELIPI+). In addition, the authors proposed the presence of CD45RO+ CCR7- memory cells as an independent, positive prognostic factor in colorectal cancer. The detected cells represented all subpopulations in the differentiation pathway and are characterized by long-term persistence *in vivo* and the ability to rapidly expand upon reencounter with antigen[32].

Interestingly, microsatellite instability in colon cancer results in significantly increased infiltration of tumors with larger numbers of CD8+ T cells and is associated with a favorable prognosis[33,34]. Microsatellite instability is characterized by defective DNA mismatch repair mechanisms, which result in higher rates of mutations and cell-to-cell variability in the length of DNA microsatellites. Tumors revealing extensive microsatellite instability, such as Hereditary Nonpolyposis Colorectal Carcinoma (HNPCC), which is associated with germ-line mutations of DNA mismatch repair genes, are designated as microsatellite instability (MSI)-high. In contrast, sporadic colorectal cancers display MSI-H in only 15%[35]. The better prognosis of MSI-H carcinomas is explained by frequent mutations in oncogenic genes and mutation-dependent abnormal peptides resulting in a cytotoxic immune response against cancer cells and hence increased infiltration by CTLs[36]. Several immunogenic antigens, such as mutated CDX2, TGFβIIR, or Caspase-5, have been identified for MSI-H associated colon cancers[37-39]. In MSI-H negative sporadic colorectal carcinoma, the identification of different tumor associated antigens (TAAs) has also been correlated with the activation of the host immune system to tumor cells[34,40-44].

In some patients, recurrent or persistent inflammation may promote carcinogenesis and trigger cancer growth. For instance, the risk of colorectal cancer in patients with chronic inflammatory bowel disease (ulcerative colitis and Crohn's disease) increases with longer duration of disease[45,46]. In particular, patients with ulcerative colitis have a significant risk for development of colitis associated colon cancer dependent on the extension of the disease, the presence of backwash ileitis and the number of flares suggesting that inflammation drives carcinogenesis. Whereas defined molecular changes in progression of sporadic colon cancer lead to stepwise changes in histology according to the adenoma-carcinoma sequence, carcinogenesis in ulcerative colitis starts with a hyperplastic lesion in the inflamed mucosa and develops through dysplasia into adenocarcinoma, ("inflammation-dysplasia-carcinoma" sequence)[47]. Different molecular mechanisms such as oxidative stress and NF-κB-activation have been attributed to inflammation dependent carcinogenesis[47-49]. Even T cell activation can lead to tumor growth through cytokine secretion. For instance Becker *et al* showed that IL-6 signaling through TILs results in tumor progression, as IL-6 serves as a growth and proliferation factor for tumor cells. This signaling was dependent on tumor derived soluble IL-6 receptor and could be inhibited through TGF-β[50,51].

Table 1 Different pathways of colon cancer progression and possible therapeutic targets

Pathway	Targets
Cell cylce	p53, pRb, p16, p21, D-type cyclins
Apoptosis and survival	Bcl-2, Cox-2
Signal transduction	EGF-R, Akt, AP-1, Her2/neu, NFκB
Angiogenesis, invasion, and metastasis	VEGF, TSP-1, CXCR-4
Immunity	IL-6, TGF-β

Taken together, the immune system may promote progression of colorectal cancer in cases of chronic inflammation, but can also lead to tumor regression through the innate immune system with tumor specific activation of CTLs and effector CD4+ T cells (Figure 2). However, the high incidence and death rate of colorectal cancer suggest an ineffective immune response in many cases. Although it has been shown that CTLs can recognize specific TAAs, many mechanisms of suppression or failure of such recognition do exist[18,21,52].

ESCAPE MECHANISMS IN COLON CANCER

It has been proposed that tumor progression is a result of the natural selection of rapidly growing tumor cell variants leading to a growth advantage of such cells over other cells. This concept has also been applied to the immune escape of tumor cells. The loss or down-regulation of HLA class I antigens, the lack of co-stimulation, defective death receptor signaling, apoptosis of activated T cells, immunosuppressive cytokines, and activation of suppressor T cells are important examples for this phenomenon[53].

Norazmi *et al* described decreased HLA class I antigen in malignant colonic tissues as compared to non-malignant tissues from the same individuals[54], thereby enabling tumor cells to escape CTL-mediated lysis due to circumvention of MHC-restricted, antigen-specific triggering of the T-cell receptor (TCR) complex. On the other hand cross-priming of CTLs through antigen presenting cells (APCs) is ineffective, as powerful APC-activating stimuli are usually absent in tumors[53,55].

Antibody-guided targeting of antigenic MHC class I -peptide tetramers on colon cancer cells results in a destruction of tumor cells by cytotoxic T lymphocytes *in vitro* and *in vivo* and has been proposed as a new form of immunotherapy[56,57]. Otherwise, data from Luo *et al* show a protection of colon carcinoma cells from apoptosis and cytolysis induced by hepatic NK cells through higher MHC

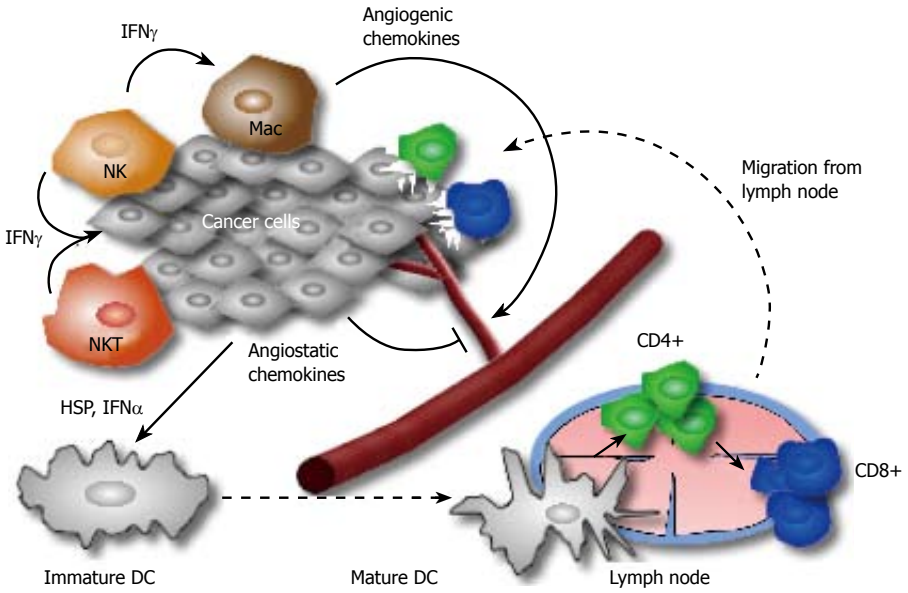

Figure 1 A proposed model for the host immune reaction to cancer cells. At the initiation of the immune reaction lymphocytes and other cells participating in innate immunity (e.g. APCs, NK, NKT cells) recognize transformed tumor cells and produce IFN-γ. This starts a cascade of reactions with production of chemokines (for instance angiogenic or angiostatic chemokines like MIG, IP10 and I-TAC), IFN-γ (antiproliferative mediator for the developing tumor) and direct cytotoxicity of NK cells and macrophages on tumor cells. This cascade may result in partial tumor cell death and tumor cell debris is ingested by dendritic cells, which move to draining lymph nodes and activate CD4+ and CD8+ T cells. Activated and tumor specific T cells move to the tumor along a chemokine gradient and destroy tumor cells expressing a distinctive tumor antigen.

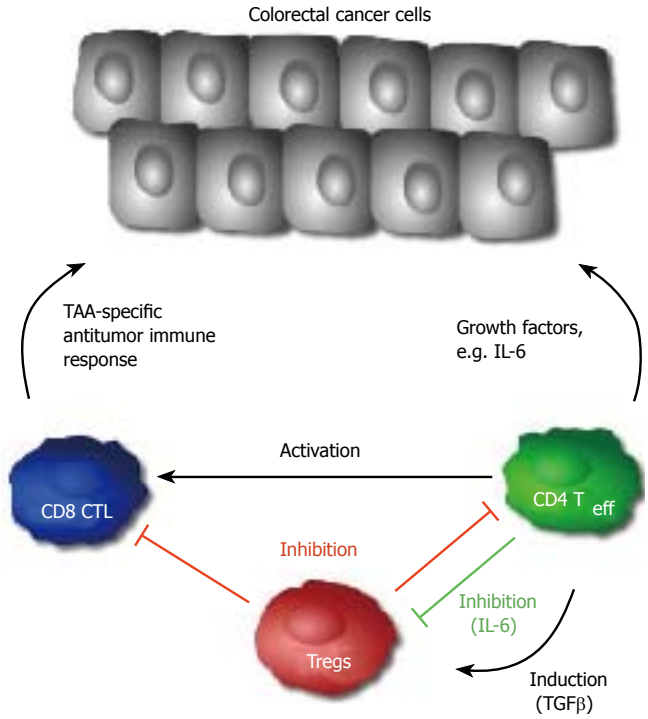

Figure 2 The role of different T cell subsets in colorectal cancer. Activated CD4+ T cells can release growth factors and thereby lead to tumor progression or activate tumor specific CD8+ T cells. Secretion of TGFβ can induce adaptive Tregs, which may suppress the anti-tumor immune response. Once activated, Tregs can be suppressed by IL-6 derived from CD4+ T cells.

class I expression, most likely by blocking the perforin/granzyme pathway[58].

T cell activation is mediated not only by triggering of the T cell receptor complex, but also by antigen-independent mechanisms such as co-stimulation. Co-stimulation induces cytolysis, cytokine secretion, proliferation and protection from apoptosis in CTLs. The poor immunogenicity of tumor cells has been partly ascribed to the lack of expression of co-stimulatory ligands (see Abken *et al*[59] for review). In the past few years, the increasing knowledge about the mechanisms of T cell activation led to new approaches for immunotherapy. Concerning colon carcinoma, the therapeutic amplification of the expression of co-stimulatory molecules as B7.1[60] and CD40L[61], the induction of co-stimulatory molecules as OX40 and 4-1BB[62] on T cells, and the administration of soluble co-stimulator proteins as B7.1-Fc[63], a B7.1 fusion protein consisting of the extracellular domains of human B7.1 and the Fc portion of human IgG1, or Ig-4-1BBL[64], a soluble fusion protein of 4-1BB Ligand and IgG2a, have shown promising results in experimental settings.

Growing evidence supports a relevant role of Fas/Fas Ligand (FasL) interactions in the immune escape of tumors. Fas and FasL belong to the tumor necrosis factor receptor and ligand families and activation of Fas by anti-Fas antibodies results in apoptosis of Fas expressing cells. It has been shown that tumors may provide resistance to Fas-mediated cytotoxicity, and that FasL expression on tumor cells could counterattack the immune system by inducing apoptosis of immune effector cells[65,66].

Several studies gave evidence for a role of the Fas tumor counterattack in colon carcinoma[67-69]. However, in a study with two different Fas-expressing target cell lines and seven different human colon cancer lines Favre-Felix *et al* failed to detect an induction of apoptosis in Fas-expressing target cell lines, namely Jurkat T cells and murine leukemia cells[70]. Recent studies suggest different functions of FasL in the immune response, since it has been shown that FasL is also delivering costimulatory signals to T cells, inducing motility of tumor cells, contributing to liver regeneration and yielding growth stimulatory signals to neurons[65]. The role of FasL in tumor escape is far from being understood and further studies are mandatory to elucidate the mechanisms and consequences of FasL activation.

CD25+CD4+ T CELLS IN COLON CANCER: REGULATORS OF IMMUNE ESCAPE?

While it is generally accepted that CD4+ T cells may

contribute to the host anti-tumor immune response, a small subset of CD4+ T cells, the CD4+ CD25+ regulatory T cells (Treg) have been shown to accumulate in the tumor environment and induce immune escape mechanisms[26,71]. Elevated expression of FOXP3, a transcription factor crucial in the development and function of Tregs, has been associated with a poor prognosis in different types of cancer[72,73].

Depletion of Tregs by specific antibodies has enhanced vaccine-induced anti-tumor immunity in colon cancer and other cancer subsets such as leukemia, plasmocytoma, melanoma, fibrosarcoma, or renal cell carcinoma[24,25,74-80]. On the other hand the addition of Tregs resulted in growth regression of inflammation associated intestinal tumors in two studies provided by Erdman *et al*[81,82]. This is also in agreement with the above-mentioned data about tumor progression through IL-6 signaling, since Tregs can suppress cytokine release. Interestingly enough, TGF-β seems to have a central role in these mechanisms, since the cytokine itself can inhibit IL-6 signaling and lead to FOXP3 expression in tumor infiltrating CD4+ T cells[83]. Accordingly, the role of Tregs in colon carcinoma may also depend on tumor pathogenesis, but the exact mechanisms of Tregs in the regulation of tumor immunology remain undefined.

CONCLUSION

Colon cancer is still one of the leading causes of cancer death worldwide. Although the host immune system can initiate an immune response against colon cancer cells, tumor cells may utilize different ways to escape those defense mechanisms. Detection of tumor associated antigens, stimulation of the T cell receptor, enhancement of costimulatory signals and depletion of regulatory T cells have shown promising results to overcome tumor escape and provide new strategies for immunotherapy of colon cancer.

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