

Tumor Microenvironment and Immune System: Sworn Enemies Living Together

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Introduction

Development of cancer in host either humans or other vertebrate animals has led to the establishment of statement by scientists and researchers involved in this field that it is a multi factorial disease (i.e. genetics, age, ethnic background, environmental factors, incidence of occurrence of specific bacterial and viral infections, exposure to certain drugs and chemicals and immunological status of the host etc.). Out of all these factors, immune system has the responsibility to take care of host against any external pathogen (i.e. bacteria, virus, parasites and fungi etc.) as well as xenobiotics including cancer causing agents (i.e. carcinogens). If anything foreign to the body enters into it, immune system comes in action within minutes via activation of innate immune response comprising of innate immune cells (i.e. Macrophages, Neutrophils, Dendritic Cells (DCs), Mast cells, Myeloid derived suppressor cells (MDSCs), Natural Killer (NK) cells) and its humoral component called complement system to clear it from the body using different fast and robust pathways. If innate immune system proves incapable to do that, then it sends signals (various effector molecules i.e. cytokines and chemokines) to activate adaptive immune response (comprised of T cell and B cell mediated immune response). If this adaptive immune response also fails then host is in danger as its defense system is not working against the invading agent or otherwise host's own modified cells (i.e. cancer cells), which usually occurs during the development of cancer. Thus, immune system has responsibility for providing protection to host from external as well as internal danger causing the development of life threatening cancer.

However, the exact cause of cancer is still unknown but these days much attention is given on the interrelationship between cancer pathogenesis and infection, immunity and inflammation. For example, more than 200,000 women die every year from cervical cancer, which has a close association with Human Papilloma Virus (HPV) infection of female genital tract (i.e. cervix) [1]. Studies have shown 1.9 million cases of cancer per year (2002) are mediated by different types of infections, which comprises about 17.8% of the worldwide cancer burden [2]. Thus, these infection induced cancers occur due to failure of immune response to clear the pathogens from the host system. Even the defect in Pattern Recognition Receptors (PRRs) play important role in the pathogenesis of cancer. For example impairment of TLR9 responsiveness during HIV-1, Hepatitis B Virus (HBV), Hepatitis C virus (HCV) and Human Papilloma Virus (HPV) type 16 infection leads to associated tumors like Kaposi sarcoma, hepatic cancer and cancer of cervix observed during these conditions. Loss of TLR9 responsiveness has also been observed in tumors without any viral diseases (i.e. breast, ovary and head and neck cancers). If it is not enough, even studies have developed an interconnection between persistent inflammation (A state of exaggeratedly activated immune system) and cancer pathogenesis [3]. For example, risks of various types of cancers (i.e. bladder, cervical, gastric, intestinal, esophageal, ovarian, prostate and thyroid cancer) increases with chronic inflammatory diseases and Non Steroidal Anti-Inflammatory Drugs (NSAIDs) decrease the risk of various cancers (like Breast and colon cancers). This is not a new observation, but this interconnection between inflammation and cancer was made in early

nineteenth century, 2000 years ago by a Greek physician Galenus, who described similarity between inflammation and cancer. According to Galenus, it may be possible that cancers may have evolved from inflammatory lesions. Thus, inflammation plays an important role in the cancer pathogenesis was known since 2000 years ago. Hippocratic term cancer was originally applied by Galenus to some types of inflammatory tumors of breast tissue where swollen and radiated superficial veins were observed. Thus, under activation of immune system as well as it's over activation (i.e. chronic persistent inflammation) both play an important role in cancer development. For example, besides escaping from immunological surveillance, these tumor cells are not immunologically silent cells as tumor microenvironment is infiltrated with different immune cells. And these tumor infiltrating immune cells can correlate with tumor prognosis in active progressive tumors.

Immune system plays such an important role in the pathogenesis of cancer that different strategies have been made to target cancer via using immunological tools (i.e. Immunomodulation, Immunotherapy in the form of monoclonal antibodies and tumor vaccines). Even this is not enough; Imatinib, an oncogenic tyrosine kinase inhibitor has its anticancer effect via stimulation of anticancer immune response during Gastrointestinal Stromal Tumors (GISTs) [4]. Thus, immunomodulatory drugs like thalidomide (which has anticancer effect via modulation of immune response) can be used to manipulate the monoclonal antibodies mediated immunotherapeutic approach to increase the efficacy of antitumor treatment. Thus, future studies targeting much deeper interconnection between cancer pathogenesis and immune system will provide better and target oriented therapeutic approach towards cancer diagnosis and treatment.

References

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