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Review Article

AK-5 TUMOR: THE EXPERIMENTAL MODEL TO STUDY INTERACTION BETWEEN CANCER CELL AND THE HOST IMMUNE SYSTEM: A REVIEW

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Abstract: Mammalian immune system being very efficient performs the most crucial function by keeping our body free from a large variety of infections. Because of its long memory, it can recognize the antigens even after several decades. Based on these findings a large number of vaccines for several diseases have been developed which keep us protected from such diseases. Similarly, there is a strong interaction between a cancer cell and the host immune system. The outcome of this interaction decides if the cancer will grow or disappear in a host. In this short review we demonstrate a positive interaction between the cancer cell and the host immune system and the role of different immune effectors in this interaction.

Key words: Cancer cell, Host immune system

INTRODUCTION

Abnormal or altered cells are generated constantly in our body, however, our humoral and cell mediated immune responses are capable of clearing such cells. These cells develop into tumor or cancer when the immune system fails to recognize and kill such cells. The immune system discriminates between the normal cells and the malignant cells because of the presence of unique or altered antigens present on the tumor cell surface. On the other hand tumor cells have evolved mechanisms by which they evade both recognition and killing by the immune effectors. Due to the complex and heterogeneous nature of the disease, successful cancer immunotherapy is still a dream for the immunologists, inspite of tremendous progress in this field. Immunotherapeutic approaches in cancer have been mainly aimed at the activation

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Dedication: I would like to dedicate this review to the celebrations of 81st birth anniversary of my CCMB colleague and friend Dr P.D. Gupta.

of the host immune system to fight the growing neoplasm. One recent approach has been the use of monoclonal antibodies where a large amount of data are now available regarding the clinical trials and use of monoclonals against different types of cancers [1]. Approaches in cancer therapy have focused on different arms of the immune system that get activated in response to cancer and mediate the destruction of the malignant neoplasm. Our group at the Centre for Cellular and Molecular Biology has been studying the interaction between the host immune system and the cancer cell using the rat histiocytoma – AK-5 as the tumor model [2].

Immune system: Immune system needs to be sufficiently activated for the host to mount a rejection response against a tumor. The failure of many spontaneous tumors to escape destruction is due to the down regulation of antitumor immunity; or to the induction of escape strategies by the tumor cells [3]. It has been earlier shown in several studies that the immunity to the growth of a tumor is mainly cell-mediated in nature [4] since it could be adoptively transferred from immunized donors to normal syngeneic recipients with lymphoid cells, but not with immune serum. Thus the cellular response against a tumor is considered to be more important and effective in eliminating the tumor.

Molecular mechanisms: We have been studying the molecular mechanisms of host-tumor interactions leading to the rejection of a highly immunogenic rat histiocytoma AK-5, which arose spontaneously in our laboratory [5]. AK-5 tumor grows as solid tumor when transplanted subcutaneously and as ascites when injected intraperitoneally. About 70% animals reject the tumor when transplanted s.c. and 100% animals succumb to the tumor when injected i.p. Animals that have rejected the tumor have been shown to be resistant to the subsequent challenges of AK-5 tumor, however, other rat tumors grow uninhibited suggesting that the immunity imparted in the tumor rejected animals is specific to only AK-5 [5].

Tumor model: The rat histiocytoma AK-5, that developed in our laboratory has been thoroughly characterized for its markers, chromosomal make-up and histopathology and ultrastructure [2,6,7] and its myeloid lineage was established. AK-5 provided us a very useful tumor model in studying the death of the host caused by the ascitic tumor and also the mechanisms involved in the rejection and regression of the subcutaneous tumors. Tumor rejection in syngeneic host involves both humoral and the cell mediated immune responses. In addition the role of several molecules like cytokines, interleukins etc. has been established in the immunological rejection of the AK-5 tumor. AK-5 tumor rejecting animals possessed high levels of specific antitumor antibodies in circulation, which could fix the complement and also participate in NK cell mediated antibody dependant cellular cytotoxicity (ADCC) [8]. The role of NK cells, their activation by IL-12 and the killing of the AK-5 tumor cells in the presence of anti-AK-5 antibody was established *in vitro* and also *in vivo* [9].

Immunotherapy: IL-12 plays an important role in the activation of NK cells [10] and in our studies mature dendritic cells (DCs) are involved in secreting IL-12 which in turn activates host NK cells [11]. Adoptive transfer of DCs isolated from AK-5 tumor bearing animals into normal animals also induced activation of NK cells in normal animals [11]. The interaction between NK cells and the DCs has been shown to be through NKR-P2/ NKG2D present on DCs suggesting NKR-P2 to function as an activating receptor on DCs [12]. Dendritic cells are shown to have tremendous potential in cancer immunotherapy and several approaches have been tried where DCs were used in treating a growing cancer in animals and humans [13]. In our studies we have identified a putative NKR-P2 ligand on AK-5 cell surface which interacts with Irp94-NKR-P2 on the DCs leading to the production of IL-12 which in turn augments NK cell cytotoxicity [14].

Cancer biologists, based on their hypothesis that a cancer cell which develops from its normal progenitor as a consequence of the transformation event, carries a foreign or altered antigen which could be recognized by the host immune system. Therefore, tumor antigens remain interesting molecules to immunologists, primarily due to the role they play in modulating the immune response evoked. The classical definition of tumor-specific antigens implied their presence only on tumors, but not on normal cells. Many of the tumor-specific antigens known are from cells that have been transformed either by viruses or chemical carcinogens [15]. The primary interest in tumor specific antigens has been to develop specific cancer vaccines; however this approach has not been very easy. We have cloned and sequenced a tumor

rejection antigen from AK-5 cells. The recombinant antigen induced antibody response against the AK-5 cells and the immunized animals showed significant resistance to AK-5 tumor challenge [16].

Similarly cytokines play an important role in the host immune response against a wide variety of infections and cancers. The characteristics of the immune response to tumors are significantly influenced by the activity of T-helper (Th) cell populations and their cytokine products. Cytokines are involved in the activation of effector cells and other immune cells that participate in the effector function. Spontaneous regression of AK-5 tumor in syngeneic hosts is mediated by IL-2, IL-12 [10], IFN-gamma [17] and TNF-alpha [18].

CONCLUSION

A successful cancer immunotherapy approach is dependent on the interaction between the cancer cell and the host immune system. Immunogenic nature of the cancer cell and the successful activation of both the humoral and the cell mediated arms of the immune system determine the outcome of the cancer in the host. Immune system has tremendous potential in combating the onslaught of the cancer cell however, cancer cells have also developed mechanisms to supress the immune mechanisms at various levels. Thus the host immune system has to remain always on guard like a soldier on the front, to clear the cancer cell from the system as and when it confronts one.

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