Th1/Th2 balance in cancer, transplantation and pregnancy

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Introduction

The carefully orchestrated events that regulate homeostasis of the immune system and the development of a protective immune response are coordinated to a large extent by cytokines produced by Th1, Th2, and the nominal Th3 lymphocyte subsets. An imbalance of Th1 and Th2 may be responsible for both the occurrence as well as the progression of several diseases and their resultant complications. Patients with advanced cancer often have impaired cell-mediated immunity associated with a switch from Th1 to Th2. On the other hand, shifting from one cytokine pattern to another may be highly beneficial in certain physiological conditions. For instance, IL-10, a Th2-type cytokine, may play a role in pregnancy-associated immune tolerance through the establishment of a Th2 cytokine bias at the maternal-fetal interface. Graft-versus-host disease (GVHD) is the major complication after allogeneic bone marrow transplantation (BMT) and is initiated by Th1 cytokines and resultant dysregulation of the cytokine network. The balance between type 1 and type 2 cytokines governs the extent to which a cell-mediated immune response and a systemic inflammatory response develop after allogeneic BMT. Successful interventions to regulate Th1/Th2 balance and modify the immune response may thus decrease the risk of development or relapse of malignancy, avoid impairment of donor cell engraftment, and allow successful fetal maturation.

Th1/Th2 balance in cancer

It is generally thought that cellular immune responses are induced and maintained by regulatory CD4+ Th1 cells secreting IL-2 and IFN-γ. The induction of effective systemic antitumor immunity, for example, involves priming of both CD4+ and CD8+ cells specific for tumor-associated antigens. The role of Th cells is attributed to providing regulatory signals required for priming of MHC class I-restricted CD8+ cyto-
toxic T lymphocytes (CTL). Activated CTL serve predominantly as immune effectors that induce apoptotic death in tumor cells. Thus, tumor immunity is usually mediated by CTL whose activation and stimulation is supported by Th1-type cytokines. The survival of Th1 cells and CTL is in turn supported by local dendritic cells (DC), providing a source of co-stimulatory molecules and cytokines such as IL-12, IL-15 and IL-18.

**Murine studies**

Several phenotypic and functional abnormalities within the immune system in tumor-bearing hosts have been identified, and suggest interaction between tumor cells and host immune effectors, which results in impaired antitumor immunity. It has been recently demonstrated in a murine B cell leukemia/lymphoma model that animals susceptible to tumor challenge developed a Th2-dominant response, whereas resistant hosts developed a Th1-dominant response [70]. Thus, tumor susceptibility does not necessarily presume the absence of an antitumor immune response. Rather, the nature of the antitumor immune response is critical in determining clinical outcome. Similar data were obtained using a murine melanoma model as well [48]. The data suggest that the failure to generate therapeutic T cells was not due to an inability to recognize tumor antigens per se, but, rather, to the induction of an immune response that was ineffective in mediating tumor regression, i.e., immune deviation. Furthermore, evaluating murine renal cell carcinoma (RCC) and colon adenocarcinoma models in mice, Ghosh et al. [37] demonstrated a gradual loss of Th1 populations and increase in Th2 cytokine profile during progressive tumor growth. Thus, these studies on experimental animals collectively point to the possibility that a shift from Th1- to Th2-type of T cell response may play an important role in the development and progression of cancer. The possibility that tumor growth could be associated with cytokine-induced qualitative alterations in the immune response has also been analyzed in human neoplastic diseases and have been observed to be present in a plethora of different cancers.

**Clinical studies**

Most clinical studies support the finding of an abnormal Th1/Th2 ratio in cancer patients. The flow cytometric analysis of peripheral blood mononuclear cells (PBMC) obtained from patients with advanced cancer indicated that an imbalance of Th1 and Th2 was found not only in the frequency of the subsets in PBMC, but also in the capacity for cytokine production [103]. For instance, tumor-infiltrating lymphocytes (TIL) in non-small cell lung cancer patients express high levels of IL-10 and IL-4, but not IL-2. PBMC isolated from the same patients also expressed high levels of IL-10 mRNA. Alterations of Th1 or Th2 cytokine profile were usually characterized by a decreased Th1/Th2 ratio and were described in virtually all tested patients with cancer including those with glioblastoma [3], lung cancer [13], non-Hodgkin's lymphoma [20], breast cancer [97], urinary bladder, renal cell and prostate cancer [30], head and neck cancer [91], cutaneous T cell lymphoma [46], basal cell carcinoma [134], and other tumor types (Table 1). The expansion of a peculiar subset of 'Th2-like' cells with increased IL-4 production was also found in patients with B cell chronic lymphocytic leukemia (CLL) [25].