Pancreatic cancer and innovative treatment: the seeming paradox to block the immune response

Pancreatic cancer (PC) is the 5th leading cause of cancer?related death in the developed world with more than 260,000 annual deaths worldwide and with a dismal 5?year survival (5%). The lethality of pancreatic cancer is due to its aggressive nature, its tendency to remain asymptomatic until the tumour reaches an advanced stage, and its resistance to conventional chemotherapy. Hence the need to find a more effective therapy to improve prognosis of this dreadful cancer. The causes of pancreatic cancer remain unknown, although increasing evidence has shown that the host immune response and related inflammatory and immune mediators, such as cytokines, instead of being protective, can contribute to human PC development.

Interleukin 22 (IL?22), which belongs to the IL?10 cytokine family, is a T cell?derived cytokine that targets cells of the digestive system including pancreatic cells. $CD4^+$ T helper (Th) lymphocytes and $CD8^+$ cytotoxic T (Tc) cells can produce IL-22 alone (named Th22 or Tc22 respectively) or together with other cytokines, such as IL?17 or interferon?? (IFN??). IFN??-producing T cells play a key role in tumour suppression, but little is known regarding the clinical relevance of IL?22-producing cells. We know that physiologically IL-22 orchestrates mucosal immune responses and tissue regeneration through pleiotropic effects, including pro?survival signaling, cell migration, dysplasia and angiogenesis. While this functions can prevent the initial establishment of tumors, they can also be exploited by aggressive cancers to enhance tumour growth and metastasis. In fact, recent studies have shown a pro?tumour role of IL-22 in cancers of the gastrointestinal tract and, moreover, an increased infiltration of Th22 correlates with tumour stage and poor prognosis in colorectal and gastric cancer patients.

Intra?tumoural IL?22 levels have been shown to be elevated also in PC patients, so we decided to investigate the role of IL-22 in pancreatic cancer carcinogenesis. In these study we have observed that the percentage of Th22 cells in the peripheral blood of PC patients was significantly higher compared to age?matched healthy donors. Moreover the number of IL?22?producing CD4+ and CD8+ T cells isolated from PC patients was significantly elevated in PC tissues compared with the surrounding healthy pancreas. So, we have investigated the properties of IL22 producing cells and we found that IL-22 favors the PC progression by inhibiting the cytotoxic activity of protective immune T cells. Furthermore, an increased frequency of Th22 cells correlated with TNM staging and with an unfavorable outcome of the disease; thus, we demonstrated that the number of IL?22?producing T cells negatively correlated with PC patient survival. These novel findings support the dual role of the anti?tumor immune system and that IL?22?producing cells may participate in PC pathogenesis. Therefore, monitoring Th22 levels could be a good diagnostic parameter and blocking IL?22 signaling may represent a viable method for innovative anti?PC therapies.

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