LINK TO ORIGINAL ARTICLE

The dichotomy of T helper 17 cells in cancer

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Immunologists have been left with considerable bewilderment by the complexity posed by the brands and flavours of T helper cell subsets. The T helper 17 (T_H17) subset is a recent addition and research has focused extensively on basic biology, lineage development, promotion of inflammation and relevance in autoimmunity, with a critical role being identified for T_H17 cells in host defence against fungal infections. In their timely and insightful Review article (The dichotomous nature of T helper 17 cells. *Nat. Rev. Immunol.* http://dx.doi.org/10.1038/nri.2017.50 (2017))[1], Stockinger and Omenetti discuss T_H17 in non-inflammatory mucosal homeostasis and 'inflammatory' issues surrounding T_H17 pathology, and highlight the beneficial and pathogenic aspects of T_H17 cells. However, emerging evidence reveals the equally dichotomous nature of the T_H17 cell subset in cancer, which the authors do not discuss. Although these cells were initially identified as the mediator of some autoimmune conditions that were previously ascribed to the T_H1 cell subset[2], their importance in cancer is coming to light. There is now strong evidence to support a role, although dichotomous, for T_H17 cells in cancer.

T_H17: anti-tumoural

One of the fundamental questions regarding the T_H17 cell subset is whether tumour-associated T_H17 cells are functional effector T cells with any protective role against cancer. Kryczek *et al.*[3] conducted an extensive study to map the phenotype, mechanism of induction, biological function and clinical relevance of T_H17 cells in tumours from patients with ovarian cancer. This study was one of the first to systemically and mechanistically investigate, using multiple complementary strategies, T_H17 cells in the human tumour microenvironment. Their study documented the presence of T_H17 cells in the tumour microenviroment. T_H17 cells infiltrating the tumour were positively associated with effector immune cells, including interferon-γ (IFNγ)-producing effector T cells, $CD8^+$ T cells and natural killer (NK) cells. Moreover, the tumour-associated T_H17 cells expressed effector cytokines with a profile resembling that of polyfunctional effector T cells, which is similar to what is observed in patients with infectious disease, and contributed to protective tumour immunity[3]. In another study, increased numbers of highly differentiated T_H17 cells in the prostate correlated with slower progression of prostate cancer[4]. In murine models, tumour-specific T_H17 cells protected against various tumours and promoted tumour-specific cytotoxic T cell responses, whereas IL-17-deficient mice were susceptible to tumour development with impaired $CD8^+$ effector T cell differentiation[5,6]. The adoptive transfer of IL-17-secreting $CD8^+$ T cells into mice bearing established vascularized B16F10 melanomas also enhanced anti-tumour immunity, resulting in the regression of established tumours[5].

T_H17: pro-tumoural

The pro-tumoural activity of T_H17 cells is thought to involve angiogenesis and immunosuppressive cytokine and chemokine production in the tumour microenvironment, resulting in the promotion of tumour growth and metastasis[7]. Although tumour-derived T_H17 cells secrete large amounts of pro-inflammatory cytokines (IL-17A, IL-8, tumour necrosis factor (TNF) and IL-6), they also secrete IL-10 and transforming growth factor-β1 (TGFβ1), which suggests that T_H17 cells may perform regulatory functions in the tumour microenvironment[8]. Certain genes involved in the T_H17 differentiation pathway closely map with the TNF signalling pathway in ovarian cancer biopsy samples. These samples show particularly high levels of expression of the genes that encode IL-23, a cytokine that selectively expands IL-17-expressing $CD4^+$ T cell populations[9]. Expression of IL-23 is increased in human tumours, promoting pro-inflammatory processes and reflecting the failure of the adaptive immune cells to infiltrate tumours, which suggests that anti-IL23p19 (a subunit of the IL-23 heterodimer) immunotherapy may prove efficacious for tumour treatment[10]. Tosolini *et al.*[11] also reported poor prognosis in patients with a cluster of T_H17-associated high gene expression on colorectal tumour samples. In animal models, IL-17 was required for the development and tumour-promoting activity of myeloid-derived suppressor cells through the induction of tumour-promoting microenvironments at tumour sites[12].

T_H17 in tumours: bimodal or dichotomous?

Clearly, the 'polyfunctionality' of the T_H17 subset encompasses both effector and regulatory cellular activity in the tumour microenvironment. Chronic inflammation and tumour-associated inflammation share some striking similarities: elevated activity of matrix metalloproteinases and increased angiogenesis and vasculature density[13]. There is also a molecular association between enhanced tumour-associated inflammation and lack of tumour immune surveillance[10]. Although many pro-inflammatory cytokines may function in tumour immune surveillance, it is puzzling that there are startling discrepancies in the function of a single molecule such as IL-17. Whether this reflects the dichotomy of the T_H17 subset or the possibility that T_H17 responses evolve over time and space (a bimodal phase of effector or regulatory function that is dominated by anti-tumoural or pro-tumoural activity at a given time depending on context) is not known. This is certainly indicative of a fundamental caveat in our understanding of the biology of T_H17 cells in cancer, which is further complicated by the ability of T_H17 cells to retain substantial developmental plasticity[14], rendering them able to convert into subsets of both T_H1 and regulatory T cells within the tumour microenvironment.

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