Comment on Muranski et al, page 362

Th17 and cancer: friends or foes?

Vincenzo Bronte ISTITUTO ONCOLOGICO VENETO

Adoptive transfer of tumor-reactive CD8+ T lymphocytes is one of the most effective immunotherapy approaches for the treatment of solid tumors.1 Muranski and colleagues show that a recently identified population of CD4+ T lymphocytes called Th17 cells possesses unexpected antitumor therapeutic properties.

In mammals, CD4+ T lymphocytes are central elements of cell-mediated immunity, recruiting and directing other cells of both the innate and the acquired immune system toward antigens. Humans must cope with exposure to many different pathogens, which require diversified effector mechanisms in order to be properly eliminated. Evolution has addressed this environmental complexity by increasing the complexity of effector CD4+ T cells, and at least 4 main subsets have been described to date: Th1, Th2, Th17, and T regulatory cells (Tregs).2 Through the activation of peculiar transcription factors, cytokines mediate the transition from naive CD4+ T cells into one of these subsets, often simultaneously inhibiting other differentiation pathways.2

Th17 cells represent the latest addition to this group. Their differentiation is driven primarily by TGF-β and IL-6 cytokines, whereas IL-23, originally thought to be the master regulator, seems to be important for maintenance of Th17 responses. Th17 cells release IL-17 and IL-22, and are implicated in the induction of numerous autoimmune and inflammatory responses.2 The information about the relevance of this cell subset in cancer biology is scant and contradictory. IL-23 has been shown to promote tumor growth and impair antitumor CD8+ T cells but, on the other hand, dendritic cells transduced with IL-23 have been described as triggering powerful antitumor activity.4 These discrepancies might result from the often-described dichotomous nature of the effects of endogenous production as compared with unregulated engineered release of the same cytokine. However, the effects of IL-23 alone cannot be taken as a bona fide demonstration of Th17 cell involvement. Indeed, few reports have addressed the presence of Th17 cells in experimental and human tumors,3 and none provide a clear indication about either a protumoral or antitumoral activity.

Muranski and colleagues used transgenic mice expressing a high-affinity T-cell receptor (TCR) specific for an epitope of the melanoma antigen known as tyrosinase-related protein 1 (TRP-1). Exploiting different polarizing culture conditions in vitro, the authors drove TRP-1–specific CD4+ T cells toward either Th0, Th1, or Th17 cells. Upon adoptive transfer in mice bearing established cutaneous melanomas, Th17 cells were shown to be superior in mediating both rejection of established melanoma and autoimmune vitiligo. Interestingly, therapeutic activity depended on Th17-cell release of IFN-γ, rather than IL-17 and IL-23 production, even though Th1–polarized cells produced more IFN-γ than Th17 effectors. Muranski and colleagues do not clarify whether the polarizing regimen promoted differentiation of multiple cell subsets; nonetheless, they provide relevant perspectives for adoptive immunotherapy of cancer. Optimization of culture conditions to polarize human CD4+ T cells to Th17 cells with heightened antitumor activity (possibly dependent on high affinity of the TCR) and tumor specificity will require further efforts. It would certainly help to identify the tumor antigens recognized by tumor-infiltrating Th17 cells.

The findings of Muranski and coworkers raise some interesting questions. If Th17 cells are so effective in destroying tissues, what limits their armamentarium during tumor development? Do Tregs play a role, as suggested by some studies?2 For clinical translation, it will also be extremely important to understand whether concomitant autoimmunity can be controlled or mitigated, if this approach is to be extended to tumors other than melanomas.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

Comment on Zhou et al, page 308

Unsweetened Notch leads to myeloproliferation

Robert S. Haltiwanger STONY BROOK UNIVERSITY

The article by Zhou and colleagues in this issue of Blood highlights the importance of Notch glycosylation in suppression of myelogenesis.

The extracellular domain of all 4 mammalian Notch receptors contains 29 to 36 epidermal growth factor (EGF)–like repeats, many of which are predicted to be modified with 2 unusual carbohydrates: O-linked fucose and O-linked glucose. Work in a number of laboratories has revealed that O-fucosylation is essential for Notch function in many contexts,4 and a recent report has shown that O-glucosylation is essential for Notch function in Drosophila.2 In addition, elongation of O-fucose by members of the Fringe family of β1,3,4-acetylgalactosaminyltransferases modulates Notch activity. Several years ago, Smith et al developed a mouse lacking a key enzyme in GDP-fucose biosynthesis (FX−/−).3 These mice lack all forms of fucosylation, including O-fucosylation of Notch, and do not survive long after birth unless fucose is added to their diet. A salvage pathway uses the...
Th17 and cancer: friends or foes?

Vincenzo Bronte