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Perspectives of human gamma/delta T-cells in cancer immunotherapy

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γδ T-cells comprise a numerically small subset of CD3-positive T-cells in peripheral blood but occur at increased frequencies in mucosal tissues. The major subset of human blood γδ T-cells expresses a Vγ9Vδ2-encoded T-cell receptor (TCR) which specifically recognizes pyrophosphate intermediates of the cholesterol synthesis (mevalonate) pathway from microbes and tumor cells. Many tumors have a dysregulated mevalonate pathway and produce increased levels of intermediates (e.g., isopentenyl pyrophosphate, IPP) which are then specifically sensed by γδ T-cells. Recognition of such pyrophosphates is not dependent on HLA presentation but requires the butyrophilin member BTN3A1 (also termed CD277). Due to their HLA-independent killing of many different tumor cells, γδ T-cells have recently raised great interest as potential effector cells for cell-based immunotherapy. In some studies, however, γδ T-cells have also been reported to actually exert pro-tumorigenic activities. I will discuss anti- and pro-tumorigenic activities of γδ T-cells with a focus on strategies how to improve the efficacy of tumor cell killing by human γδ T-cells. This may include the development of bispecific antibodies targeting γδ T-cells to tumor-associated cell surface antigens and the design of other strategies to specifically enhance the cytotoxic capacity of γδ T-cells. On the other hand, it will be important to counteract known inhibitory mechanisms of the tumor microenvironment such as e.g. prostaglandin E2 and certain galectins. Furthermore, the sensitivity of some tumor cells towards γδ T-cell mediated cytotoxicity can be improved by epigenetic modifiers such as histone deacetylase inhibitors. The overall goal is to improve cytotoxic effector activity of γδ T-cells (and therefore to pave the way to clinical application) by enhancing cytotoxic mechanisms while simultaneously inhibiting suppressive mechanisms.

Recent review: Chitadze, Oberg, Wesch & Kabelitz, Trends Immunol 38:668-678,2017.