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IMMUNOBIOLOGY

Comment on Samudio et al, page 2575

Virus fuels NK cell killing of leukemia

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In this issue of *Blood*, Samudio et al found that inactivated herpes simplex virus (HSV) particles provide a potent adjuvant capacity to enhance natural killer (NK) cells' killing of leukemic cells, an effect driven by Toll-like receptor (TLR)–mediated activation of glycolysis in the NK cells.[1]

NK cell transplants have emerged as a potentially powerful approach to treating acute myeloid leukemia.[2] Approaches that could be applied to enhance the NK-mediated killing of leukemic cells would therefore have direct clinical importance. Oncolytic viral therapies have also shown promise in the treatment of a variety of solid cancers, leading to the recent approval of the oncolytic HSV talimogene laherparepvec (IMLYGIC) for the treatment of metastatic melanoma.[3] It appears that these vectors act primarily as immunotherapies; however, their use against hematopoietic malignancies has been limited. In a recent report, Samudio et al have demonstrated the use of oncolytic HSV to activate peripheral blood mononuclear cells to lyse leukemic cells. This activation was found to at least partly depend on TLR-2 and acted primarily through activation of NK cells.

Several further interesting and important observations were made that demonstrated the future clinical potential of this approach, including the fact that (1) the increased NK-mediated killing was selective for leukemia, and healthy lymphocytes were not targeted; (2) UV light-inactivated HSV provided as potent activation as live virus; (3) these effects could be enhanced even further through combination with interleukin 15; and (4) ex vivo exposure of peripheral blood mononuclear cells to the UV-inactivated viral particle provided a survival benefit in a murine xenograft model. A clear path to safely translating this approach is therefore feasible. It will be of interest to further define what factors on the viral particle are responsible for this effect, and whether the effects are exclusively mediated through TLR-2 signaling, or if other pathways also contribute. In this way, a less complex approach to NK cell activation may be delineated for clinical translation.

Of particular interest was the observation that UV-inactivated HSV stimulated glycolysis in NK cells, and that this effect was required for the enhanced killing of leukemic cells. The importance of the metabolic profile of immune cells in driving their functional capacity has become clear recently, primarily in providing effector and effector memory T cells the potential for rapid proliferation. The potential to prime NK cells for rapid expansion upon exposure to leukemic targets provides a potent approach to enhancing this therapeutic strategy. Interestingly, fatty acid oxidation was also increased in NK cells after exposure to UV-inactivated HSV, yet this was not critical for enhanced leukemic cell killing. This observation was similar to effects recently reported in CD8 memory cells,[4] but its role remains unclear.

The realization that oncolytic viral therapies are primarily acting as immunotherapies has raised many questions as to how these effects are mediated and how they might be enhanced. It will be intriguing to find out if the role of HSV viral particles in NK cell activation observed here might also apply in activation of NK and T cells in solid tumors, and the specificity of these effects (which were not observed with several other viruses) may provide insight into the potential use of different viruses as backbones for oncolytic vectors.

Conflict-of-interest disclosure: S.H.T. owns equity in Western Oncolytics. ■

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