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Sommario/riassunto

Recognition and killing of aberrant, infected or tumor targets by Natural Killer (NK) cells is mediated by positive signals transduced by activating receptors upon engagement of ligands on target surface. These stimulatory pathways are counterbalanced by inhibitory receptors that raise NK cell activation threshold through negative antagonist signals. While regulatory effects are necessary for physiologic control of autoimmune aggression, they may restrain the ability of NK cells to activate against disease. Overcoming this barrier to immune surveillance, multiple approaches to enhance NK-mediated responses are being investigated since two decades. Propelled by considerable advances in the understanding of NK cell biology, these studies are critical for effective translation of NK-based immunotherapy principles into the clinic. In humans, dominant inhibitory signals are transduced by Killer Immunoglobulin Like Receptors (KIR) recognizing cognate HLA class I on target cells. Conversely, KIR recognition of "missing self-HLA" - due to HLA loss or HLA/ KIR mismatch - triggers NK-mediated tumor rejection. Initially observed in murine transplant models, these antitumor effects were later found to have important implications for the clinical outcome of haplotype-mismatched stemcell transplantation. Here, donor NK subsets protect against acute myeloid leukemia (AML) relapse through missing self recognition of donor HLA-C allele groups (C1 or C2) and/or Bw4 epitope. These studies were subsequently extended by trials investigating the antileukemia effects

of adoptively transferred haplotype-mismatched NK cells in non-transplant settings. Other mechanisms have been found to induce clinically relevant NK cell alloreactivity in transplantation, e.g., post-reconstitution functional reversal of anergic NK cells. More recently, activating KIR came into the spotlight for their potential ability to directly activate donor NK cells through in vivo recognition of HLA or other ligands. Novel therapeutic monoclonal antibodies (mAb) may optimize NK-mediated effects. Examples include obinutuzumab (GA101), a glyco-engineered anti-CD20 mAb with increased affinity for the FcRIIIA receptor, enhancing antibody-dependent cellular cytotoxicity; lirilumab (IPH2102), a first-in-class NK-specific checkpoint inhibitor, blocking the interaction between the major KIR and cognate HLA-C antigens; and elotuzumab (HuLuc63), a humanized monoclonal antibody specific for SLAMF7, whose anti-myeloma therapeutic effects are partly due to direct activation of SLAMF7-expressing NK cells. In addition to conventional antibodies, NK cell-targeted bispecific (BiKEs) and trispecific (TriKEs) killer engagers have also been developed. These proteins elicit potent effector functions by binding target ligands (e.g., CD19, CD22, CD30, CD133, HLA class II, EGFR) on one arm and NK receptors on the other. An additional innovative approach to direct NK cell activity is genetic reprogramming with chimeric antigen receptors (CAR). To date, primary NK cells and the NK92 cell line have been engineered with CAR specific for antigens expressed on multiple tumors. Encouraging preclinical results warrant further development of this approach. This Research Topic welcomes contributions addressing mechanisms of NK-mediated activation in response to disease as well as past and contemporary strategies to enhance NK mediated reactivity through control of the interactions between NK receptors and their ligands.