Comment on Foley et al, page 435

How killers kill

Jeffrey S. Miller  University of Minnesota

Previously, it was assumed that functional signaling by KIRs required only that they encounter their ligands. Now, new work by Foley and colleagues presented in this issue of Blood suggests that the rules of NK–cell alloreactivity may be more complicated than initially thought.

Several families of inhibitory and activating receptors regulate natural killer (NK)–cell function. In hematopoietic-cell transplantation (HCT), NK-cell activity has been correlated with less relapse and superior overall survival in myeloid malignancies.\(^1\) This was based on finding an increased frequency of alloreactive NK cells in patients receiving transplants from donors possessing an inhibitory killer immunoglobulin-like receptor (KIR) ligand absent in the recipient. This KIR-ligand incompatibility model has been applied to several clinical cohorts with mixed results,\(^2\) perhaps due to differences between the transplantation platforms. For example, Ruggeri et al use haploidentical donors and potent T-cell depletion by CD34 selection. Our own group has shown that the presence or absence of T cells in the graft affects the frequency of KIR expression after HCT.\(^3\) However, other biologic mechanisms may determine NK-cell alloreactivity besides those predicted by the frequency of KIR-bearing NK cells.

Some inhibitory KIRs (KIR2DL1, KIR2DL2/L3, and KIR3DL1) interact with public epitopes of class I HLA molecules, which are defined by precise amino acid sequences for HLA-C2, C1, and Bw4 group alleles. Inhibitory signals through these receptors disrupt the cytolytic pathway, preventing target-cell lysis. The article by Foley et al focuses on the interaction between KIR3DL1 and its ligand, Bw4. Initially, it was believed that Bw4 was only expressed by NK cells. Recently, several HLA-A alleles possessing the Bw4 motif were identified by sequencing (HLA-A*2301, *2402, *2501, and *3201). However, the strength of their interactions with KIR3DL1 remained unclear. Adding further complexity to the issue is the discovery that the allelic polymorphisms of KIR3DL1 affect receptor surface density,\(^4\) although the impact this has on function is unclear.

Foley et al studied the interactions between polymorphisms of KIR3DL1 and Bw4 by evaluating KIR3DL1\(^+\) NK cells against several different Bw4-ligand–expressing lymphoblastoid targets. Using functional readouts, they found that some Bw4 alleles, such as HLA-A*1301 and *1302, provided poor protection against lysis. In contrast to reports by others, there was no difference in the potency of inhibiton between Bw4 alleles defined by an isolectric versus threonine at position 80. HLA-A*2402 and *3201 delivered potent inhibitory signals through KIR3DL1, whereas HLA-A*2501 and *2301 were weak ligands. The relative expression of KIR3DL1 expression on NK cells correlated with the potency of their killing of Bw4\(^+\) targets. KIR3DL1\(^+\) bright cells were more cytolytically active than KIR3DL1\(^-\) dim cells, and the surface density of KIR3DL1 was predicted by specific alleles. In summary, NK-cell alloreactivity was affected by KIR3DL1 density, and not all Bw4 epitopes induced potent inhibitory signals—findings that suggest important structure/function interactions.

One of the most interesting questions in NK–cell biology today is to understand how NK cells are educated. Several models have been proposed to explain the interaction of inhibitory KIR expression with the acquisition of effector function. Disarming refers to the suppression of effector function in maturing NK cells that receive stimulatory signals opposed by inhibitory signals via self-HLA receptors, analogous to the development of T-cell anergy.\(^5\) Licensing describes a terminal differentiation step by which NK cells acquire mature function only when they receive appropriate signals via an inhibitory receptor ligating with self-HLA.\(^6\) Although the exact mechanism is not well defined, there is consensus that NK cells expressing class I–recognizing receptors have more potent cytotoxic function than those not expressing inhibitory receptors.\(^7,8\) Foley and colleagues demonstrate that interactions between KIR3DL1 and Bw4 epitopes in vitro can influence the frequency of KIR3DL1–expressing NK clones, suggesting that these interactions play a role in NK–cell KIR repertoire formation. The physiologic relevance of this finding to HCT warrants further study.

Twenty years ago, NK cells were considered to be homogenous unrestricted killers. We now know that their precise function is determined by a number of class I–recognizing inhibitory receptors. The work of Foley and colleagues demonstrates that a receptor encountering its ligand does not necessarily confer a homogenous inhibitory signal. Rather, polymorphisms at either the receptor or the ligand can further modulate the signal. This current study helps to define some of the specific interactions between KIR3DL1 and Bw4–containing epitopes. Further studies of other inhibitory and activating KIRs and their impact on function may allow us to better exploit NK cells for therapeutic purposes.

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

REFERENCES

How killers kill

Jeffrey S. Miller