It Takes Two to Tango

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In the study by Jacquemin et al., the authors reported that ligands for NKG2D are upregulated in vitiligo perilesional skin and especially in patients with active disease. The reasons for the elevated expression of NKG2D ligands are unknown. This study, however, provides a framework for understanding vitiligo: Skin resident CD8 T cells recognize and kill melanocytes through NKG2D signaling. This event results in the increased production and release of cytokines and the development of long-lasting CD8 T cells, which in turn causes the recruitment of new T cells, thus perpetuating and disseminating the disease.


Vitiligo is a disease characterized by the destruction of melanocytes, and there are no FDA-approved treatments (Ezzedine et al., 2015). In most individuals, tightly controlled mechanisms facilitate the development of protective responses against foreign pathogens, while avoiding autoimmunity. However, for reasons that remain largely unknown, in autoimmune vitiligo, T cells turn against melanocytes (Engelhorn et al., 2006; Ezzedine et al., 2015; Gregg et al., 2010; Harris, 2016; Mosenson et al., 2013; van den Boorn et al., 2009). In this issue of JID, Jacquemin et al. (2020), provide compelling data that implicates NKG2D in the pathogenesis of autoimmune vitiligo.

NKG2D is an activating receptor that is expressed by many cytotoxic lymphocytes and that can bind to a large number of ligands that are expressed in the context of cell stress (Bauer et al., 1999; Cerwenka et al., 2000). Although its canonical function is to facilitate the recognition and killing of stressed cells, infected cells, or cancer cells (Bauer et al., 1999; Cerwenka et al., 2000), studies have shown an association between CD8 T cells expressing NKG2D and various autoimmune diseases. Such diseases include skin conditions such as alopecia areata (Dai et al., 2016; Petukhova et al., 2010; Xing et al., 2014) and vitiligo (Ezzedine et al., 2015; Yu et al., 2012) and other diseases such as pancreatitis, diabetes, (Markiewicz et al., 2012) and celiac disease (Meresse et al., 2004; Tang et al., 2015). Also, using vaccine mouse models, engagement of NKG2D, but not 2B4 (another activating receptor), results in exacerbation of CD8 T cell–mediated vitiligo (Zloza et al., 2011). Importantly, the study of Jacquemin et al. (2020) shows that NKG2D-expressing CD8 T cells preferentially populate areas of active vitiligo. This finding is in line with the reported proinflammatory functions of NKG2D. For example, the authors show that skin-infiltrating NKG2D effector memory T cells are characterized by a high capacity to produce the Th1-related cytokines IFN-γ and TNF-α. These observations could help explain part of the mechanism by which CD8 T cells cause vitiligo.

It takes two to tango. In order for NKG2D to function, it must be engaged by its ligands. NKG2D is a promiscuous receptor that binds to a variety of stress ligands. These ligands include the members of Rae-1α–ε and H60α–c families (Cerwenka et al., 2001; O’Callaghan et al., 2001) in mice and MICA/B and ULBP1–6 in humans (Cosman et al., 2001). Expression of NKG2D ligands on the cell surface is strictly regulated. In healthy conditions, little or no NKG2D ligands are expressed (Cerwenka et al., 2001; O’Callaghan et al., 2001), but they are induced by transcriptional upregulation under stress-related conditions such as infection and transformation (Cerwenka et al., 2001; O’Callaghan et al., 2001). Other forms of cellular insult (DNA damaging agents, TLR signaling, cell proliferation, or exposure to certain cytokines) can also result in NKG2D ligand surface expression (Cerwenka et al., 2000; Cosman et al., 2001; Diefenbach et al., 2000). In the study by Jacquemin et al., the authors reported that, in addition to NKG2D, its ligands MICA and MICB were also increased in vitiligo perilesional skin and especially in patients with active disease. Although the reasons for the elevated expression of NKG2D ligands in the skin of patients with vitiligo are unknown, these data may provide insights into mechanisms by which CD8 T cells expressing NKG2D get activated and mediate their cytolytic function.

Is NKG2D signaling part of a pathophysiological loop that triggers and perpetuates vitiligo? This is an important question that must be considered. Based on current studies, one could conclude that skin-resident NKG2D CD8 T cells recognize and kill melanocytes. However, what prompts CD8 T cells to survive and continue killing? Studies by our group showed that NKG2D signaling transcriptionally favors CD8 T-cell memory formation through T-bet repression and that this replaces the need for CD4 T-cell help (Zloza et al., 2012). We also demonstrated that NKG2D signaling provides effector CD8 T cells during the killing of target cells with a transcriptional program that enables them to become long-lasting cells (Perez et al., 2019).

We termed this step memory certification. We consider this to be a logical step that is necessary for the formation of memory T cells from effector CD8 T cells.

In aggregate, the studies by Jacquemin et al. and others provide the basis for a working hypothesis for what

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happens in vitiligo (Figure 1). Skin-resident CD8 T cells recognize and kill melanocytes through NKG2D signaling that will also lead to CD8 T cells’ development as long-lasting cells and enhanced production of cytokines and chemo-attractants, which, in a positive feedback loop, enhances CD8 T-cell function and increases NKG2D expression and the recruitment of new T cells, thus perpetuating and disseminating the disease.

CONFLICT OF INTEREST
No funding organization was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; nor the decision to submit the manuscript for publication.

REFERENCES

Figure 1. Graphical representation of NKG2D role in vitiligo. (a) The interaction between the peptide:MHC-I interaction and the self-reactive TCR on CD8 T cells is weak, thus failing to induce melanocyte destruction. (b) Stressed melanocytes express NKG2D ligands (i.e., MICA). Given that NKG2D acts as a TCR costimulatory receptor, the threshold for T-cell activation is reduced, resulting in the recognition and killing of melanocytes. CD8 T cells that receive NKG2D signaling are certified to become long-lasting cells, thus perpetuating the disease. MHC-I, major histocompatibility complex I.

Clinical Relevance
- Vitiligo has no effective treatment.
- Interfering with NKG2D signaling could impact vitiligo onset and perpetuation.
- These results may improve our understanding of other forms of autoimmunity.

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