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Pillars of Immunology

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NKG2D–MICA Interaction: A Paradigm Shift in Innate Recognition

Mathieu Bléry* and Eric Vivier*,†,‡

The way in which immune cells recognize their targets has long been a subject of intense research in the immunological community. The discovery of Abs and identification of the TCR attest to the excitement surrounding this subject. However, the unique and beautiful nature of the mechanisms underlying the generation of these Ag-specific receptors expressed by B and T cells led to the establishment of a dogma according to which T and B cell immunity is highly specific, whereas innate immunity is nonspecific. It is difficult to imagine a nonspecific biological interaction at the molecular level, and studies in the 1990s identified receptors conferring specific recognition capacity on innate immunocytes. In accordance with the vision put forward by Charlie Janeway (1), which was previously featured as one of the *Pillars of Immunology* (2), the identification of a broad panel of receptors recognizing microbial products has radically changed our understanding of immunity (1–3). However, the mechanisms by which innate cells recognize internal challenges, such as tumors or metabolic modifications, remained unclear. In this context, the article by Bauer et al. (4) described a seminal discovery in the field of innate immunity, as it revealed a new mode of immune recognition via the activating cell surface receptor NKG2D.

NK cells, $CD8^+$ T cells, and γδ T cells rapidly and efficiently kill autologous cells, provided that the target cell is adequately and specifically recognized. This specific recognition must be tightly controlled by a combination of activating and inhibitory receptors. At the time this *Pillars of Immunology* article was written by Bauer et al., cytotoxic T cell activation was known to involve Ag recognition. Mechanisms for inhibiting NK cell activation had been clearly described. Inhibitory receptors, such as those of the killer Ig-like receptor family and NKG2A in humans, interacting with classical and nonclassical MHC class I molecules, had been described and the concept of missing self-recognition (i.e., the potential of NK cells to be activated by the lack of an MHC class I molecule) had been widely accepted (5). As the mechanisms for inhibiting NK cells gradually became clear, NK cells came to be seen as constantly activated cells that could kill any other cell not protected by MHC class I molecules, a property described as "natural cytotoxicity." However, this model could not account for the failure of autologous NK cells to kill normal cells lacking MHC class I expression in their immediate vicinity, as observed for RBCs, which are found in constant close proximity to NK cells in both the bloodstream and the spleen. This observation led to the emergence of the concept that NK cells are specifically activated when they come into contact with a virus-infected or tumor cell. Some activating NK cell receptors were already known, with the first to be identified being members of the killer Ig-like receptor family with a short cytoplasmic domain potentially able to bind to MHC class I molecules. The second group of activating receptors to be discovered was the natural cytotoxicity receptors NKp30, NKp44, and NKp46, as well as DNAM-1. However, the ligands for these receptors were unknown at the time.

In this context, Bauer et al. provided the first description of a receptor–ligand pair that could account for the natural cytotoxicity properties of NK cells. The molecules recognized by and activating the NK cells were MHC class I–related protein (MIC)A and MICB in humans. These membrane-bound proteins had previously been described by Thomas Spies and colleagues (6) as stress-induced molecules on epithelial cells, particularly in the gut. Bauer et al. first demonstrated that soluble MICA inhibited the cytotoxicity by γδ T cell clones and NKL cells, a human NK cell line, of target cells expressing MICA, indicating a MICA-dependent mode of killing. The NKL cell line was used to generate Abs, which were screened for the specific inhibition of MICA-dependent killing. The resulting 5C6 and 1D11 Abs stained peripheral blood NK cells, γδ T cells, $CD8^+$ T cells, and a minor subset of $CD4^+$ T cells. Representational difference analysis involving several rounds of hybridization subtraction and amplification from the cDNAs of $CD4^+$ T cell clones positive or negative for staining with 1D11 or 5C6 yielded a differential cDNA product matching the sequence of NKG2D. The NKG2D cDNA had long been known to belong to a family of related cDNA clones encoding type II integral membrane proteins expressed on NK cells and conserved in mammals (7). However, its function remained unclear, as its ligands had not been identified. Bauer et al. demonstrated that the anti-NKG2D Abs 1D11 and 5C6 blocked the MICA-dependent killing of various target cells and could also be used to trigger redirected killing.

*Innate Pharma, 13276 Marseille, France; †Centre d'Immunologie de Marseille–Luminy, Aix-Marseille Université, INSERM, CNRS, 13288 Marseille, France; and ‡Immunologie, Hôpital de la Timone, Assistance Publique–Hôpitaux de Marseille, 13385 Marseille, France

ORCID: 0000-0001-7022-8287 (E.V.).

Address correspondence and reprint requests to Dr. Mathieu Bléry, Innate Pharma, 117 Avenue de Luminy, 13276 Marseille, France. E-mail address: mathieu.blery@innate-pharma.fr

Abbreviation used in this article: MIC, MHC class I–related protein.

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In summary, this article reported that the NKG2D expressed by NK and γδ T cells could bind to MIC proteins and activate cytotoxicity. Thus, innate immune cells such as NK cells can be specifically activated by stressed cells via an activating receptor that recognizes markers of cells in distress. NK cell activation cannot, therefore, be considered to be either constitutive or nonspecific. Several stress-induced ligands for NKG2D have since been described in both humans (MICA, MICB, and ULBP-1 to ULBP-6) and mice (Rae1 family, H60, and MULT-1) (8, 9). Several mechanisms tightly regulating the cell surface expression of NKG2D ligands have also been described, including the regulation of gene expression, stabilization of the mRNA and of the protein at the cell surface, and protein shedding from the cell surface (9).

NKG2D is now recognized as a major component of NK cell activation, and this molecule has been implicated in immunosurveillance. NKG2D-deficient mice have a higher frequency of spontaneous tumors in some genetic backgrounds, such as the Eμ-myc and TRAMP models (10). Interestingly, the NKG2D/NKG2D ligand system appears to have coevolved with certain viruses. Indeed, the human CMV genome encodes the immunoevasin proteins UL-16, UL-142, US-18, and US-20, as well as miR-UL112, all of which interfere with the expression of NKG2D ligands at the surface of infected cells, potentially preventing their recognition by cytotoxic cells (11, 12). Remarkably, MICA*008, the most prevalent form of MICA in the human population, has a truncated intracellular domain, preventing its targeting by human CMV immunoevasins. The ligands of NKG2D are induced by various immune challenges, and the article by Bauer et al. thus revealed a novel mode of immune recognition complementary to Ag-specific recognition by T and B cells. Unlike the TCR and BCR, the NKG2D receptor recognizes the consequences of immune challenges, rather than the challenge itself.

Disclosures

M.B. and E.V. are current employees of Innate Pharma.

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