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Review

Immune Adaptation to Environmental Influence: The Case of NK Cells and HCMV

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The immune system of an individual human is determined by heritable traits and a continuous process of adaptation to a broad variety of extrinsic, non-heritable factors such as viruses, bacteria, dietary components and more. Cytomegalovirus (CMV) successfully infects the majority of the human population and establishes latency, thereby exerting a life-long influence on the immune system of its host. CMV has been shown to influence the majority of immune parameters in healthy individuals. Here we focus on adaptive changes induced by CMV in subsets of Natural Killer (NK) cells, changes that question our very definition of adaptive and innate immunity by suggesting that adaptations of immune cells to environmental influences occur across the entire human immune system and not restricted to the classical adaptive branch of the immune system.

Introduction

Human immune systems are highly diverse, but the reasons for this diversity have not been fully understood. Recent twin studies indicate that the amount of variation explained by environmental, non-heritable factors is much larger than the contribution of heritable factors [1,2]. Accordingly, the heritable influence on disease risk tends to be low for most immune-mediated disorders [3]. The analysis of healthy human twins also revealed that immune parameters were more similar between younger than older genetically identical twins [2]. Together, these findings suggest that human immune systems are shaped by a combination of heritable and non-heritable influences and that environmental factors exert a cumulative influence that increasingly overshadows the influences of heritable traits with age. Adaptive changes to recognized antigens is traditionally a hallmark of adaptive immunity, but a growing number of studies has challenged this view by describing examples of similar adaptations in innate cell populations.

Possibly the most striking illustration of this new paradigm is our dramatically changing view of NK cells. Our initial understanding of these cells as killer cells, complementing cytotoxic T cells in the context of missing self-recognition has been extended to involve many additional functions. The population of NK cells is now known to be highly diverse [4] and regulated in a quantitative rather than binary fashion [5]. The more recently described 'memory-like' or 'adaptive' features add an additional level of complexity to NK cell biology (Figure 1, Key Figure). The adaptive changes observed in NK cells in response to environmental factors such as viruses are in line with recent evidence suggesting that human immune systems, as a whole, vary more as a consequence of non-heritable than heritable influences [2]. As an example of one such non-heritable influence, human CMV (HCMV) (CMV from here on) was shown to influence nearly 60% of all immune cell frequencies, functional responses, and serum protein concentrations

Trends

Human immune systems vary in healthy individuals as a consequence of non-heritable more than heritable influences.

Cytomegalovirus (CMV) has emerged as one key factor with a broad influence on the human immune system, impacting the majority of cell populations and serum proteins.

Specific populations of natural killer (NK) cells, predominantly expressing the activating receptor NKG2C and the carbohydrate antigen CD57, expand as a consequence of CMV infection and display certain hallmarks of adaptive immune responses (e.g., clonal expansion, functional superiority, long-term persistence).

CMV-adapted NK cells are characterized by decreased expression of multiple signaling molecules and transcription factors as well as broad epigenetic modifications.

Functionally, CMV-adapted NK cells are superior in performing antibody-dependent cellular cytotoxicity (ADCC), rendering them a potential therapeutic target.

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Key Figure

Visualization of Differences and Similarities between Memory Natural Killer (NK) Cells in Mice and Adaptive NK Cells in Humans

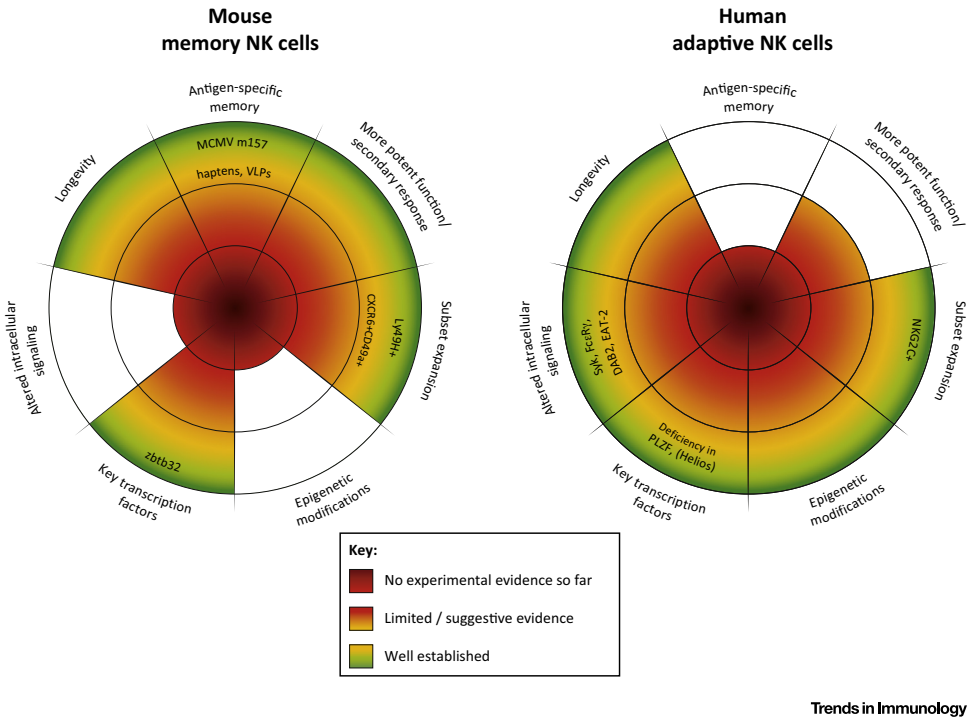

Figure 1. Certain NK cell populations in mice and humans display properties that are usually restricted to cells of the adaptive immune system; for example, longevity, subset expansion, and increased/altered functionality during a secondary response. However, some features have not been observed across species: antigen-specific NK cell memory has until now been demonstrated only in mice (and macaques), whereas broad alterations of intracellular signaling and DNA methylation have so far been reported in adaptive human NK cells.

measured [2]. Strikingly, the discovery and characterization of adaptive NK cells in humans has also been closely linked to this pathogen. In this review, we therefore approach this dynamic field in contemporary immunology by focusing on the illustrative example of adaptive human NK cells in the context of CMV infection (Figures 1 and 2).

NK Cell Adaptation to Environmental Factors in Murine Model Systems

Pioneering studies in mice described highly antigen-specific memory of NK cells in hapten-induced contact hypersensitivity reactions as well as in responses elicited by UV-inactivated vesicular stomatitis virus (VSV) or VLP-based vaccines containing antigens from influenza or HIV-1 [6,7]. The NK cell subpopulation mediating this antigen-specific response was largely liver resident and expressed the chemokine receptor CXCR6 and CD49a [7,8]. Although the precise receptor–ligand interactions that enable the generation of hepatic NK cell memory remain enigmatic, adoptive transfer experiments demonstrated that memory NK cells retained their specificity for at least 4 months in the absence of antigen [7].

A second line of evidence was obtained in mouse CMV (MCMV) infection, arguably the best characterized infection model in murine NK cell biology. In certain mouse strains, an NK cell