NATURAL KILLER CELLS

A primitive immune system

Charles A. Janeway

THE first great controversy in immunology pitted Metchnikov and the cellularists against Robert Koch and the humoralists[1]. One consequence of the subsequent humoralist victory was the focus of immunology on the chemistry of antibodies and the abandonment of inquiry into the cells that mediate host defence. Interest in some of these cells was revived by Burnet's clonal selection theory of antibody formation[2] and by Gowans's discovery that lymphocytes mediate all specific immune responses[3]. These milestones in immunology directed attention toward the specificity of antigen recognition, and away from Metchnikov's original interest in primitive host cellular responses to infection.

As our understanding of specific antigen recognition has exploded, culminating in the discovery of seven families of rearranging genes encoding T- and B-lymphocyte receptors[4], one can start to ask a more metchnikovian question: did immunological effector mechanisms evolve after the sophisticated recognition systems that now trigger them, or are the recognition systems recent additions to pre-existing, non-clonal systems of host defence[5]? Natural killer (NK) cells — lymphocytes (non-T, non-B) that can kill certain tumour cells[6,7] — may constitute such a system. In demonstrating the presence of the invariant ζ-chain component of the T-cell receptor in NK cells, the paper of Anderson *et al.* on page 159 of this issue[8], may help to answer the question.

Host defence against infection occurs in three phases in mammals: innate resistance that is not inducible; an early, inducible phase that is largely antigen-non-specific; and a late, T-cell dependent phase that is highly antigen specific and generates immunological memory[9]. NK cells participate in the innate[10] and early, interferon-inducible[11,12] phases of the immune response to viral infection (see table below).

Viruses parasitize host cells, where they replicate and produce new virions that spread the infection. The immune response blocks viral spread by making specific neutralizing antibodies and specific (class I MHC-restricted) cytolytic T cells that kill virus-infected cells. Although NK cells are identified by their ability to kill certain tumour cells without prior immunization[6,7], recent evidence has suggested a more important role of NK cells in host defence against viral infection[13]. This is supported by the discovery of an individual whose only demonstrable immunological defect was the absence of NK cells[10]. The early phases of herpes virus infections were markedly exaggerated in this patient and would have been fatal without anti-viral and supportive therapy, although she ultimately made antibody and cytolytic T-cell responses that cleared the infections.

How does an NK cell that lacks a clonally distributed receptor know which target cell to attack? The answer to this question remains shrouded in mystery; indeed, it may be the wrong question. Rather, a single NK cell may have multiple recognitive mechanisms. Thus, NK cells may function as a back-up defence mechanism for cytolytic T cells by destroying cells that lack class I MHC molecules[14]; they have Fc receptors that allow them to kill antibody-coated target cells[15]; they clearly kill certain virus-infected cells[10,13]; they appear to regulate haemopoiesis (through recognition of structures mapping between H-2S and H-2D in the MHC of mice)[16]; and they can directly kill certain bacteria[17].

That NK cells and cytolytic T cells share cytolytic effector mechanisms suggests that the NK cell is an evolutionary forerunner of the cytolytic T cell, just as the 'alternative' pathway of complement activation is likely to be a forerunner of the 'classical' pathway triggered by specific antibody (note the bias in the naming of the 'classical' pathway by humoralists). It seems likely that the host defence systems of primitive organisms consisted of effector cells like the NK cell with multiple non-clonally distributed recognitive mechanisms. Primitive immune systems would be expected to have had few cells, so the effector cells must have been multi-specific. The acquisition by an NK cell of a clonally distributed receptor capable of fine discrimination between self and non-self might have been sufficient to make it a cytolytic T cell. Clonally distributed receptors allow an immune system to recognize infection by any virus and the development of immunological memory through clonal selection.

But the T-cell receptor is not just an antigen-binding molecule. It is also the ligand-binding domain of a signal-transducing molecular complex that includes the CD3 proteins[18] and a polypeptide known as the ζ-chain[19], which is required for effective signal transduction by the T-cell receptor[20]. Homologous chains are also associated with the signal-transducing Fc_ϵ receptor of the mast cell[21]. Thus ζ-like chains may be a common component of signal transduction mechanisms in cells of haemopoietic origin.

The identification by Anderson *et al.*[8] of NK cell ζ-chains, associated with larger structures that may participate in ligand recognition, supports the idea that cytolytic T cells arose from NK-like cells by acquiring a clonally distributed T-cell receptor. Further support for this notion comes from finding NK-like cytotoxic activity in long-term cultured T-cell lines[22]. Such discoveries should help in understanding the evolution of host defence mechanisms. They could spur a reunification of the metchnikovian interest in innate immunity with the mainstream of specific recognition first championed by the humoralists. It is interesting to wonder whether progress has been speeded by the triumph of the humoralists that led to the solution of the antibody problem more than it has been impeded by the early abandonment of metchnikovian thinking. □

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The three phases of host defence against viral infection

Phase	Characteristics	Mechanism
Immediate (< 4 h)	Nonspecific, innate, no memory, no specific T cells	Natural killer cells
Early (4–96 h)	Nonspecific and specific, inducible, no memory, no specific T cells	Interferons α and β Interferon-activated natural killer cells
Late (> 96 h)	Specific, inducible, memory, specific T cells	Cytolytic T cells Interferon Specific antibody

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