NEWS AND VIEWS

The NK cell: a phagocyte in lymphocyte's clothing?

from Bernard M. Babior and David W. Parkinson

ANIMALS under attack by invading microorganisms are able to kill their attackers by means of a group of exceedingly powerful oxidizing agents which are mobilized in response to the microorganisms' invasion. The earliest evidence for the existence of this oxygen-dependent killing system was reported some 20 years ago by Karnovsky[1] and by Quastel[2]. Since then, this system has been investigated in many laboratories (for reviews see refs 3,4), and it is now understood at least at an elementary level.

The critical step in the mobilization of the lethal oxidizing agents is the activation of a membrane-bound enzyme (or enzyme system) known as the 'NADPH oxidase'. This oxidase is dormant in an unstimulated cell, but comes to life when the cell encounters a microorganism. As its name suggests, the oxidase catalyses the transfer of electrons from NADPH to oxygen. What is unusual about this reaction is that the oxygen is reduced, not by two electrons to form H_2O_2, but by one electron to form the superoxide radical ($O_2^{\cdot-}$).

It is from this innocuous $O_2^{\cdot-}$ radical that all the system's lethal oxidants are formed. These oxidants include hypochlorite (OCl^-), known commercially as a powerful disinfectant, and a group of highly reactive oxidizing radicals, including the hydroxyl radical ($OH^{\cdot}$), one of the most reactive compounds known in chemistry. OCl^- arises through the peroxidase-catalysed oxidation of Cl^- by H_2O_2, which in turn is formed by the dismutation of superoxide ($O_2^{\cdot-} + O_2^{\cdot-} + 2H^+ \rightarrow H_2O_2 + O_2$), a very rapid reaction which consumes most of the $O_2^{\cdot-}$ manufactured by the cell. $OH^{\cdot}$ and the other reactive oxidizing radicals are made from the remaining $O_2^{\cdot-}$; the mechanism of their production is poorly understood apart from the fact that no peroxidase is required, though an iron-catalysed reaction between $O_2^{\cdot-}$ and H_2O_2 ($O_2^{\cdot-} + H_2O_2 \rightarrow OH^{\cdot} + OH^- + O_2$; the famous Haber–Weiss reaction) has been proposed as the source of the hydroxyl radical. It is a striking illustration of the versatility of biological systems that they are able to manufacture and put to use compounds as reactive and dangerous as OCl^- and $OH^{\cdot}$.

Until now, the oxygen-dependent killing system has been thought to be restricted to 'professional phagocytes' (granulocytes and mononuclear phagocytes), the front-line cells whose purpose in life is to engage and destroy invading pathogens. In this issue of *Nature* (p.569), however, Roder and his associates show for the first time that the same system is expressed by a lymphocyte. The lymphocyte that acts like a phagocyte is the natural killer (NK) cell.

The NK cell is a large lymphocyte whose most prominent morphological feature is a single large granule in its cytoplasm[5]. Many biological roles have been proposed for this enigmatic cell, both from experiments testing the effects of partially purified NK cell preparations on various targets[6] and from studies with intact NK-deficient animals and humans[7]. A function in host defense against infection has been postulated on the basis of the NK cell's ability to recognize and kill virus- and parasite-infected target cells. Its capacity to kill certain malignantly transformed cells has led to speculation about its participation in defense against cancer. Finally, it is able to kill certain types of cells in the normal bone marrow and thymus, suggesting that it may serve to control the function of these tissues on a day-to-day basis. The true physiological role of the NK cell, however, is still not fully understood. Even less well understood are the means by which it exerts its diverse effects. In particular, basic questions as to how target cells are recognized and destroyed are largely unanswered.

The work of Roder and his associates now appears to provide a partial answer to at least one of these questions. The ability of the NK cell when exposed to a susceptible target to produce $O_2^{\cdot-}$ (in staggering quantities too; the amount of $O_2^{\cdot-}$ manufactured by these cells can exceed by two orders of magnitude the amounts liberated by fully stimulated neutrophils or monocytes) and to use this $O_2^{\cdot-}$ to kill this target strongly implicates some form of the oxygen-dependent killing system in target cell destruction. This system must comprise more than just $O_2^{\cdot-}$ itself, because NK cells from patients with Chediak–Higashi disease exhibit greatly impaired killing ability despite a normal $O_2^{\cdot-}$-generating response to NK-susceptible targets[8]. The hallmark of Chediak–Higashi disease is the swollen, grotesquely misshapen lysosome that is found in the cells of affected subjects; perhaps the granule of the NK cell is another participant in its oxygen-dependent killing system, and it is the malfunction of this granule that accounts for the defect in NK cell activity in Chediak–Higashi disease. Supporting this notion are recent experiments with metabolic inhibitors which have been interpreted in terms of a 'stimulus–secretion' model of NK cell activity[9], consistent with the morphology of the cell as a large lymphocyte containing a granule which, after all, must be there for a reason.

Like all novel discoveries, the finding that NK cells can kill with oxygen raises more questions than it answers. Is NK cell function impaired in chronic granulomatous disease, the inherited disorder in which phagocytes are unable to manufacture their lethal oxidants[3]? What are the other components of the oxygen-dependent killing system of the NK cell? Does the NK cell possess oxygen-independent killing mechanisms like those described by Elsbach in the rabbit and human neutrophil[10]? What do these findings say about the relationship between the NK cell and other types of lymphocytes, some of which have killer activity of their own? Is the NK cell a true lymphocyte, or is it nothing but a phagocyte in lymphocyte's clothing? □

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