Cell death in the immune system

Cell death in the immune system has a number of functions: in the selection of immune cells, in limiting the size (or down-sizing) the pool of reactive cells, and in the direct defence against microbes. We have been looking at cell death in T cells (T cells clonally expand, and most T cells die at the end of an immune reaction, leaving only memory cells behind) and in the more recent past at neutrophils. Cell death may be more of a regulatory factor in limiting neutrophil activity compared to T cell activity since neutrophils, once activated, probably can keep going for longer without specific stimulus than activated T cells (which may depend on TCR-stimuli). The system we are using (conditional expression of active Hoxb8) further beautifully permits the study of the interrelation of cell death and differentiation of neutrophil precursor stages.

Neutrophil granulocytes (neutrophils)

Neutrophils are intriguing, and in our view without justification neglected, immune cells. In especially infections caused by pyogenic bacteria neutrophils are quick to arrive (this is circular because pyogenic bacteria are basically defined as the ones causing pus, and pus is largely neutrophils. Pyogenic bacteria are the normal, common bacteria in human infections such as *Staphylococci*, *Streptococci* or *E. coli*). Here neutrophils are the first line of defence: they are called into action by tissue resident cells (such as keratinocytes and macrophages) and start eating and killing the bacteria. In many infections not caused by pyogenic bacteria, for instance chlamydial infections, mycobacteria or even viruses and parasites, neutrophils also appear. Here they have no obvious direct anti-pathogen function. However, they very likely instruct the more complex immune reaction.

We mostly work with neutrophils differentiated from mouse committed progenitors *in vitro*. This system is obviously a little artificial but provides great ways of genetically modifying and investigating the cells. We have studied how apoptosis in neutrophil is initiated and implemented (and are still doing this). We are also studying how gene deficiencies that cause a loss of neutrophils in humans (such as deficiency in the enzyme G6PC3) affect neutrophil differentiation and survival. The experimental system permits the investigation of neutrophil differentiation much more easily than other systems, and we are using it to try to understand human disease.

We have fairly good evidence that at least in some cases neutrophils are important for the development even of adaptive immune responses. We are trying to work out what they are doing.

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