



### ***Natural killer (NK) cells migrate to inflamed lymph nodes and provide IFN- $\gamma$ for Th<sub>1</sub> priming***

The cells of the “innate” immune system respond to pathogens within hours upon infection while the “adaptive” immune response, ensured by the participation of dendritic cells and T and B lymphocytes, takes days to develop. Traditionally, cells of the innate and the adaptive arms have been considered to play their functions independently from each other. NK cells recognize and kill stressed, transformed and infected cells and, therefore, have been long considered as part of the innate immune system. Recent *in vitro* evidence suggests, however, that NK cells may also participate in adaptive immune responses by modulating dendritic cell function and by producing the cytokine IFN- $\gamma$ . Normally NK cells mature in the bone marrow, circulate in blood and spleen, but are otherwise largely excluded from the lymphatic system. In December 2004 Alfonso Martín-Fontecha in the group led by Federica Sallusto at the IRB described in *Nature Immunology* (*Nat. Immunol.*, 2004; 1260-1265) that NK cells are rapidly recruited to inflamed lymph nodes, which are activated by dendritic cells and by certain adjuvants. The molecular requirements for the recruitment of NK cells from blood to lymph nodes was addressed by the selective depletion of endogenous NK cells and the adoptive transfer of NK cells which were lacking particular chemokine receptors. These experiments, performed in collaboration with the Max Delbrück Center in Berlin and the Harvard Medical School in Boston, revealed that, in contrast to naïve T cells, NK cell entry into stimulated lymph nodes was mediated by the chemokine receptor CXCR3 rather than CCR7. Further it was shown that upon entry to stimulated lymph nodes, NK cells produce IFN- $\gamma$ , a critical factor for the differentiation of CD4 T helper (Th1) cells. The study demonstrates that the final outcome of the adaptive immune response may depend on the interaction of multiple cell types, including those considered to belong to the innate arm of the immune system.

### ***New strategies to combat Alzheimer's disease***

Alzheimer's disease (AD), a neurodegenerative disorder, currently affects about 18 million people worldwide - a number that is predicted to double by 2025 due to an aging population. Patients with AD show a progressive decline in brain functions, including memory, language, and comprehension. Most researchers in the field agree that the main problem in AD is the body's inability to get rid of the A $\beta$  peptide that gets chopped out of the APP protein to form toxic aggregates in the brain. The most obvious route to prevent A $\beta$  deposition would be to block the enzymes that cleave APP, called  $\beta$ - and  $\gamma$ -secretases. However, the  $\gamma$ -secretase is known to do its cleaving work on other proteins that are essential for normal functioning of the body and its inactivation has grievous side effects, whilst the architecture of the  $\beta$ -secretase active site requires an effective inhibitor to be a very large molecule, thus difficult to transport across the blood-brain barrier.

The group of Dr. Maurizio Molinari at the IRB took a step back and reasoned that a more selective way to prevent A $\beta$  formation was to prevent the cleavage of APP by shielding with a specific antibody the  $\beta$ -secretase cleavage site. In this way, the  $\beta$ -secretase could cleave all other cellular substrates, but APP. But antibodies usually only operate on the outside of cells. By engineering the genes for two of the antibody chains into a single gene, it was possible to put the new gene into cells and get them to make a single-chain antibody, also called an intrabody that associated with human APP as soon as it was synthesized in the endoplasmic reticulum thereby efficiently inhibiting the  $\beta$ -secretase operated cleavage and the generation of the toxic A $\beta$  peptide.

While the results are dramatic, they are tempered by the fact that all of the experiments were performed on human cells grown in a lab dish. Here, it is easy to introduce the intrabody gene to the cells. In the human brain, however, this would require some fancy gene therapy techniques that have not yet been designed or tested. But although this method could not be used directly in patients, it does show the team's novel idea is valuable for intervening in a disease process. Published in *The Journal of Cell Biology* 168, 863-868; 2005 (Paganetti *et al.*)