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MEMORY RESPONSES

Fitter, faster, better innate immune cells

> IFNγ produced by memory T cells coordinates innate immune responses during infection in vaccinated hosts

Innate immune cells are essential for sensing infection and initiating immune responses against microbial pathogens. Now, Soudja *et al.* report that successful memory responses in vaccinated hosts depend on interferon-γ (IFNγ) that is secreted by memory T cells, which directs the recruitment, activation and effector function of innate myeloid and lymphoid cells.

The authors immunized wild-type mice with either phosphate buffered saline or *Listeria monocytogenes* and then challenged them with *L. monocytogenes* 5–6 weeks later. In vaccinated mice, LY6C$^+$ monocytes had already differentiated into effector cells 8 hours after challenge infection. Faster activation of neutrophils, tissue macrophages, dendritic cells (DCs), natural killer (NK) cells and NKT cells was also observed in vaccinated mice compared with naive mice.

Next, the authors analysed spleen tissue sections and showed that the activation of innate cells was associated with enhanced recruitment of these cells from the blood to the infected spleen in vaccinated mice. Clusters of cells (including CD11b$^+$ cells and CC-chemokine receptor 2 (CCR2)-expressing monocytes, as well as memory T cells and NK cells) were detected in the red pulp in the spleens of vaccinated mice 8 hours after infection but this was delayed in naive mice.

To determine whether these differences in naive versus vaccinated mice also altered the activation of pathogen-specific naive T cells, the authors transferred ovalbumin (OVA)-specific CD8$^+$ T cells (OT-I cells) into naive or vaccinated mice. The mice were challenged with OVA-expressing attenuated *L. monocytogenes*. After 7 days, OT-I cells had differentiated into effector cells in naive mice, whereas OT-I cells that were transferred into *L. monocytogenes*-vaccinated mice developed a memory phenotype.

So, are memory T cells crucial for the changes that are observed in innate immune cells in vaccinated mice? The depletion of both CD4$^+$ and CD8$^+$ T cells before challenge infection prevented the early activation of innate cells (8 hours after infection) in vaccinated mice.

To determine whether IFNγ-induced signalling in innate cells is important during memory responses, the authors generated chimeric mice lacking the IFNγ receptor (IFNγR) or the type I IFN receptor (IFNAR1). When these mice were immunized and challenged with *L. monocytogenes*, the differentiation of both LY6C$^+$ monocytes and neutrophils that lacked the IFNγ receptor — but not those that lacked the IFNAR1 — was impaired in the spleen and other infected organs 8 hours after challenge infection. Interestingly, the differentiation of NK cells in IFNγR-deficient mice was delayed but not prevented, which suggests that indirect IFNγ-dependent signals enhance NK cell activation. The recruitment of innate cells into infected tissues was not affected. IFNγ signalling activated monocytes through an IFN-regulatory factor 1 (IRF1)-independent mechanism and synergized with microbial sensing pathways to potentiate innate cell recruitment and activation. Gene expression analysis of LY6C$^+$ monocytes showed specific responses to IFNγ in vaccinated mice (including the expression of guanylate-binding proteins that are implicated in defence against intracellular bacteria) compared with a more general inflammatory response in naive mice.

Finally, the selective depletion of specific cell types in vaccinated chimeric mice lacking the IFNγR showed that monocytes, DCs and macrophages are important for protective recall responses to *L. monocytogenes* infection.

Taken together, these results reveal that IFNγ produced by memory T cells coordinates innate immune responses during infection in vaccinated hosts.

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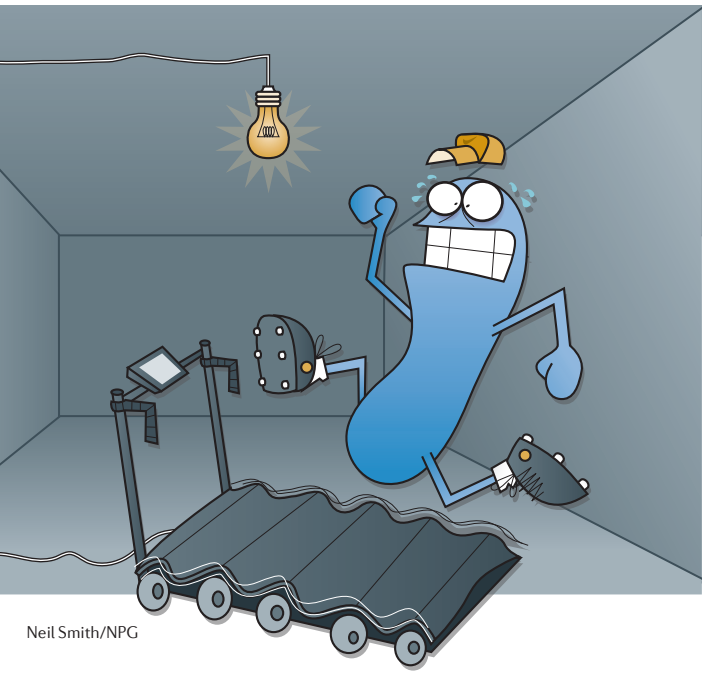

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ORIGINAL RESEARCH PAPER Soudja, S. M. *et al.* Memory-T-cell-derived interferon-γ instructs potent innate cell activation for protective immunity. *Immunity* **40**, 974–988 (2014)