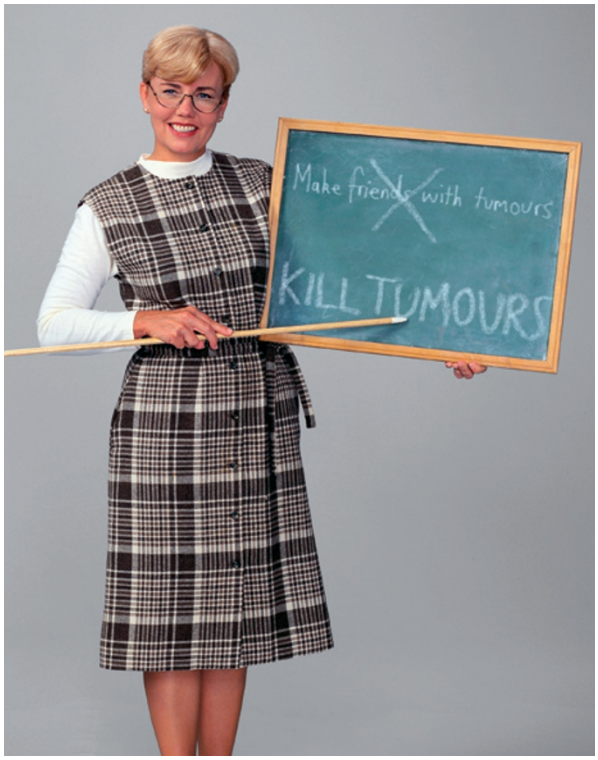
Nature Reviews Immunology | AOP, published online 20 June 2008; doi:10.1038/nri2365

MACROPHAGES

Re-educating macrophages

A new strategy to 're-educate' immune cells and boost their protective activity in cancer and infection has been suggested in recent findings published by *The Journal of Experimental Medicine*.

Cytokines and chemokines in the tumour microenvironment, or released during infection, recruit vast numbers of macrophages, which, when classically activated by microbial products or interferon-γ, can produce pro-inflammatory cytokines that could potentially destroy the tumour or kill the invading organism. However, despite their numbers and intrinsic cytotoxic potential, these cells can fail to combat tumours and infections. This is because the tumour microenvironment and certain pathogens promote a switch in macrophages from a 'classically' to an 'alternatively' activated phenotype that is characterized by the production of the anti-inflammatory molecules interleukin-10 (IL-10) and tumour-necrosis factor (TNF), and a decrease in the production of IL-12, thereby promoting tumour growth and reducing innate immunity. So, an approach that could promote the classical phenotype as opposed to the alternative phenotype of macrophages would have potential therapeutic benefit in infection and cancer.



With this goal and the recent studies implicating nuclear factor-κB (NF-κB) signalling in driving cancer-associated inflammation in mind, the studies by Hagemann *et al.* and Fong *et al.* concentrated on inhibitor of NF-κB kinase β (IKKβ), the master switch for NF-κB activation. Using distinct approaches to specifically inhibit IKKβ in macrophages, the two research groups found that tumour-cell apoptosis and antimicrobial activity were increased when IKKβ was inhibited in macrophages. This, they showed, was because the inactivation of NF-κB by inhibition of IKKβ decreased IL-10 and TNF production by macrophages, whereas it increased their production of the protective cytokine IL-12. IKKβ inhibition was also associated with a decrease in arginase-1 expression, increased expression of nitric-oxide synthase 2 and elevated levels of nitric oxide. Together these results indicate that the inhibition of NF-κB reverted the macrophage phenotype to the classically activated phenotype that has tumoricidal and antimicrobial properties.

Hagemann *et al.* confirmed these results *in vivo* by showing that IKKβ-inhibited macrophages that were transferred into tumour-bearing mice did not polarize into tumour-promoting cells, and the presence of these cells led to a significant decrease in tumour burden compared with mice that received control macrophages. However, despite a sustained effect on tumour growth, the increase in nitric-oxide production by IKKβ-inhibited macrophages was only transient, suggesting an alternative mechanism for the long-term control of tumour growth. Indeed, they showed that it was an IL-12-mediated increase in natural-killer-cell recruitment that contributed to the tumoricidal effect of IKKβ-inhibited tumour-associated macrophages. The parallel study by Fong *et al.* showed that mice with a targeted deletion of IKKβ in macrophages were resistant to bacterial and fungal infection, and this resistance was also associated with increased IL-12 production.

So, these data show that inhibiting IKKβ activity can re-educate immunosuppressed tumour-associated macrophages to kill tumour cells directly through the production of nitric oxide or indirectly through the production of IL-12, which promotes natural-killer-cell-mediated antitumour immunity. Targeting IKKβ in macrophages can also boost immunity to infection by increasing innate immunity. These findings could have important implications for future tumour therapy and strategies to enhance immunity.

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ORIGINAL RESEARCH PAPERS Hagemann, T. *et al.* "Re-educating" tumor-associated macrophages by targeting NF-κB. *J. Exp. Med.* **205**, 1261–1268 (2008) | Fong, C. H. Y. *et al.* An antiinflammatory role for IKKβ through inhibition of "classical" macrophage activation. *J. Exp. Med.* **205**, 1269–1276 (2008)