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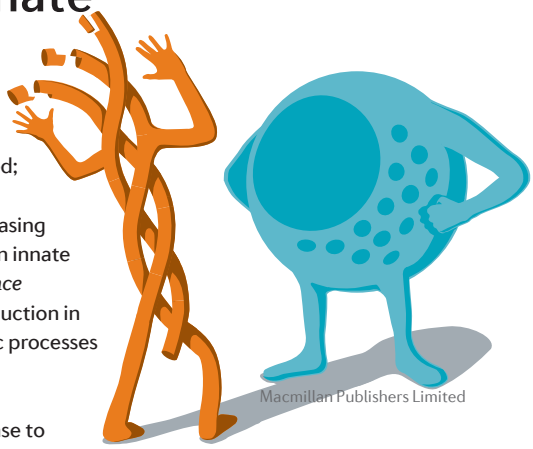
INNATE IMMUNITY

Fibrinolytic and innate systems collide



The roles of the nuclear factor of activated T cells (NFAT) transcription factors in the adaptive immune system are well characterized; for example, these proteins regulate T cell activation, differentiation and tolerance. Increasing evidence has shown that NFAT also has a role in innate immunity, and new research published in *Science Immunology* reveals that it regulates IFNγ production in natural killer (NK) cells and controls fibrinolytic processes required to clear skin infections in mice.

Using a mouse model deficient in NFAT cytoplasmic 2 (NFATc2) to examine the response to *Candida albicans* fungal infection, Granucci, Zanoni *et al.* showed two distinct phases of the immune response. First, an abscess forms to contain the pathogen; then, ulceration in the skin occurs, which facilitates the expulsion of the pathogen from the tissue. Abscess formation was reliant on transforming growth factor-β (TGFβ), a pro-fibrotic signal. Although both wild-type and NFATc2-deficient mice were able to initiate abscess formation, the mutant mice produced abscesses with considerably thicker collagenous walls, a feature attributed to higher TGFβ levels. Importantly, the second ulceration phase did not occur in NFATc2-deficient animals, suggesting that the 'switch' between phases might rely on attenuating TGFβ activity.

To better understand the dysregulation of TGFβ, the researchers examined the role of its negative regulator IFNγ. Compared with wild-type mice, the mice deficient in NFATc2 showed attenuated IFNγ levels after infection. Furthermore, the non-ulcerative phenotype could be recapitulated in wild-type animals treated with IFNγ antagonists. On probing, the researchers were able to show that ulceration relied on plasminogen to plasmin conversion, a process that promoted abscess collagen breakdown. Plasmin levels are regulated by the opposing activities of tissue plasminogen-activating factor (tPA) and plasminogen activator inhibitor 1 (PAI1); here, IFNγ (which is not widely recognized to have a role in the fibrinolytic pathway) was shown to regulate tPA production.

Next, the authors turned their attention to determining the source of IFNγ. Although depleting NK cells with anti-asialo GM strongly decreased the IFNγ levels in the wild-type mice, and also diminished ulceration in infected animals, expression of NFATc2 in NK cells was not required for IFNγ production. Instead, dendritic cells were shown to express NFATc2; this expression was required for IL-2 secretion that, in turn, promoted IFNγ production by NK cells.

These findings together culminate in a model whereby, in response to infection, dendritic cells release IL-2, prompting the production of IFNγ by NK cells. IFNγ then regulates the TGFβ-mediated pro-fibrotic containment of the pathogen (abscess formation) and regulates the fibrinolytic ulcerative programme that leads to abscess clearance.

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