In the news

MAPS FOR MALARIA

With more than one million people dying of malaria each year, two new global strategies have been initiated to tackle this deadly disease. At the Global Vaccine Research Forum in Bangkok, the WHO (World Health Organization) announced the launch of the Roadmap — a global effort that promises to accelerate the development of an effective vaccine against malaria (*WHO*, 4 December 2006). This launch coincides with the creation, by researchers in Kenya and Britain, of a real map — the Malaria Atlas Project — that pinpoints locations where malaria is most likely to strike (*BBC News*, 5 December 2006).

The WHO Roadmap calls on scientists, funding organizations and policy experts to work together to develop a malaria vaccine. According to Marie-Paule Kieny, a WHO director, "The Roadmap marks the first concerted global attempt at mapping out a shared plan of action for making a preventive malaria vaccine reality." (*Reuters*, 4 December 2006)

The Roadmap aims to have a first-generation vaccine that is >50% effective and is protective for longer than 1 year by 2015, and a vaccine that is >80% effective and provides protection for longer than 4 years by 2025. To achieve this, the WHO Roadmap recommends standardizing procedures for the assessment of vaccine candidates, broadening the search for a vaccine, improving the capacity for clinical trials in Africa and other malaria-endemic areas, and securing sustainable funding (*ScientificAmerican.com*, 4 December 2006).

As its creators discuss in an article in *PLoS Medicine*, the Malaria Atlas Project will also help in the fight against malaria by enabling individual countries to calculate malaria infection rates, in targeting intervention needs and in measuring progress on a global scale (*PLoS Medicine*, 5 December 2006).

Lucy Bird

IMMUNODEFICIENCY

Beyond expectation

Tyrosine kinase 2 (TYK2) is a member of the Janus kinase (JAK) family and is crucial for relaying intracellular signals from several cytokine receptors. The importance of this tyrosine kinase in innate and adaptive immunity in humans has been highlighted by a recent report describing profound immunological defects in a patient with TYK2 deficiency. The complexity and severity of disease in this patient was unexpected, as mice lacking this kinase have a relatively mild phenotype.

The JAK family proteins, JAK1, JAK2, JAK3 and TYK2, associate with an array of cytokine receptors and become activated after cytokine binding. Activated JAKs phosphorylate the cytokine receptor, which leads to the recruitment and activation of STATs (signal transducers and activators of transcription), followed by nuclear translocation of STATs and gene transcription. TYK2 is activated by several cytokines, including interleukin-6 (IL-6), IL-12, IL-23 and type I interferons (IFNs; that is, IFNα and IFNβ). Surprisingly, however, *Tyk2*$^{-/-}$ mice show only partial defects in signalling in response to type I IFNs and IL-12, and not to the other cytokines, indicating that other JAK family members might compensate for the lack of TYK2 in mouse cells. Until now, it was not clear whether the same was true for JAK proteins in human cells.

The patient investigated in this study had complex immune abnormalities, including hyper-IgE syndrome and susceptibility to infection with many microorganisms. After ruling out several genes known to be associated with primary immunodeficiency, Minegishi *et al.* traced the cause of these defects to a homozygous mutation in *TYK2* that resulted in a premature stop codon and the absence of TYK2 protein. Unlike *Tyk2*$^{-/-}$ mouse T cells, T cells from the patient were completely defective in signalling in response to IFNα and IL-12, as indicated by a failure to induce STAT phosphorylation and to upregulate gene transcription after exposure to each cytokine. Moreover, subsequent experiments showed that the patient's T cells also failed to respond normally to IL-6, IL-10 and IL-23, indicating that, unlike in mouse T cells, TYK2 has an essential and non-redundant role in responding to these cytokines in human T cells.

Because the patient had clinical features that are associated with a T helper 2 (T_H2)-cell response, such as atopic dermatitis and large amounts of IgE in the serum, the authors next assessed the *in vitro* differentiation of the patient's T cells. They showed that even in T_H1-cell-inducing culture conditions, few T cells from the patient differentiated into IFNγ-producing T_H1 cells. By contrast, in T_H2-cell-inducing conditions, differentiation of the patient T cells into IL-4-producing T_H2 cells seemed to be accelerated, compared with T cells from a control donor. This differentiation bias is consistent with the failure of the cells to respond to the T_H1-inducing cytokine IL-12.

Importantly, the defects observed in multiple cytokine signalling pathways that are due to the TYK2 deficiency correlated well with the complex clinical features observed in the patient. First, susceptibility to viral infection could result from the defective type I IFN signalling; second, susceptibility to mycobacterial infection could be due to the defective IL-12 signalling, given its important role in inducing a protective T_H1-cell response; and third, hyper-IgE syndrome could be caused by skewing towards T_H2-cell differentiation. Exactly how the defective IL-6, IL-10 and IL-23 signalling might contribute to the clinical phenotype awaits future study.

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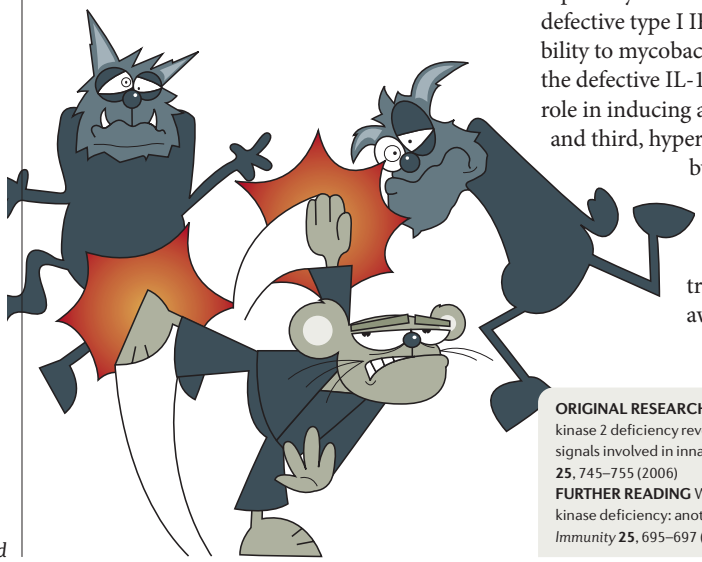

ORIGINAL RESEARCH PAPER Minegishi, Y. *et al.* Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* **25**, 745–755 (2006)
FURTHER READING Watford, W. T. & O'Shea, J. J. Human Tyk2 kinase deficiency: another primary immunodeficiency syndrome. *Immunity* **25**, 695–697 (2006)