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SIGNALLING

A new master to rival NF-κB?

The activation of nuclear factor-κB (NF-κB) transcription factors is crucial for driving many innate defence mechanisms but the complete set of transcription factors that regulates innate immunity to infection is not well defined. Now, a study by Irazoqui and colleagues suggests that TFEB is an evolutionarily ancient transcription factor that promotes host tolerance of infection.

Inspired by the initial identification of NF-κB in the fruit fly *Drosophila melanogaster*, the authors set out to define the transcription factors that promote innate immunity in the nematode *Caenorhabditis elegans* — an organism that lacks NF-κB. Computational analyses suggested that the MiT-class transcription factor HLH-30 (which is orthologous to mammalian TFEB) may be crucial for regulating the *C. elegans* response to *Staphylococcus aureus* infection. Using an HLH-30 reporter strain of *C. elegans*, the authors found that HLH-30 is expressed in most tissues, and that it distributes equally between the cell nucleus and cytoplasm in resting tissues. However, in response to infection with *S. aureus*, HLH-30 rapidly accumulated in the nucleus, strengthening the idea that it may be involved in the early induction of host defence mechanisms.

Indeed, a comparison of infected wild-type and HLH-30-deficient worms indicated that almost 80% of *S. aureus*-induced genes are upregulated in an HLH-30-dependent manner in *C. elegans.* Moreover, compared with wild-type worms, HLH-30-deficient worms showed decreased survival following infection with *S. aureus* or other strains of pathogenic bacteria. However, both wild-type and HLH-30-deficient worms had similar bacterial loads during infection, which suggests that HLH-30 promotes host tolerance of infection. The authors found that HLH-30 regulates the expression of genes that are important for immune signalling and antimicrobial responses in *C. elegans*, as well as genes that are associated with cellular repair processes and autophagy. Importantly, several of these pathways were found to be essential for promoting host tolerance of bacterial infection in *C. elegans*.

Finally, the authors addressed whether this pathway is relevant to mammalian immunity by assessing TFEB function in mouse macrophages. In mammalian cells, TFEB is retained in the cytoplasm in an inactive phosphorylated state and the dephosphorylation of TFEB drives its relocalization to the nucleus to promote gene transcription. Notably, the authors found that infecting mouse macrophages with *S. aureus* led to the dephosphorylation and translocation of TFEB into the nucleus. Furthermore, mouse macrophages in which TFEB expression was inhibited showed decreased expression of pro-inflammatory genes following *S. aureus* infection.

Additional studies are needed to determine exactly how TFEB regulates mammalian responses to infection. Nevertheless, the authors propose an interesting model suggesting that the last common ancestor of invertebrates and vertebrates may have used both TFEB- and NF-κB-regulated signalling axes to respond to infection, with TFEB regulating cytoprotective genes and NF-κB driving antimicrobial gene expression. They hypothesize that nematode HLH-30 may have evolved to control both of these axes, so that NF-κB became functionally redundant and was lost from the worm genome.

Yvonne Bordon

> “TFEB is an evolutionarily ancient transcription factor that promotes host tolerance of infection”

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ORIGINAL RESEARCH PAPER Visvikis, O. *et al.* Innate host defense requires TFEB-mediated transcription of cytoprotective and antimicrobial genes. *Immunity* http://dx.doi.org/10.1016/j.immuni.2014.05.002 (2014)