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INNATE IMMUNITY

Linking hypoxia and NF-κB

The hypoxic response is crucial for tissue homeostasis and cell survival in low oxygen environments, and is essential for the normal function of innate immune cells in oxygen-deprived tissues. It has been established that innate immunity and the hypoxic response are linked at the molecular level, but the exact nature of this link was not previously known. Now, Karin and colleagues have clarified the connection between nuclear factor-κB (NF-κB), a mediator of innate immune responses, and hypoxia-inducible transcription factor 1 (HIF1), an important regulator of hypoxic adaptation, to directly link these two evolutionarily ancient stress responses.

The α subunit of HIF1 accumulates in cells under conditions of low ambient oxygen and activates genes that promote survival and energy production, such as *Glut1* (glucose transporter type 1), and genes that promote restoration of blood supply, such as *Vegf* (vascular endothelial growth factor). HIF1α is also activated following infection and inflammation. Previously, nuclear accumulation of HIF1α was thought to occur in hypoxic cells due to the inability of oxygen-dependent prolyl hydrolases (PHDs) to degrade HIF1α in these conditions.

NF-κB is also modestly activated under hypoxic conditions, in part owing to the release of IKKs (inhibitor for NF-κB kinases) — kinases that initiate the pathway that leads to NF-κB activation — from their PHD-mediated inhibition. Activation of NF-κB results in the induction of a different subset of pro-inflammatory and pro-survival genes than HIF1α encoding cytokines, antimicrobial peptides and proteins involved in energy metabolism.

Examination of IKKβ-deficient macrophages (which have impaired NF-κB activation) showed that the basal levels of *Hif1a* mRNA were markedly reduced in these cells compared with wild-type macrophages, and that the induction of HIF1α-dependent genes, such as *Glut1* and *Vegf*, in response to bacterial infection was dependent on IKKβ. Together with molecular analysis showing that the RelA (also known as p65) subunit of NF-κB interacts with the *Hif1a* promoter, these data indicate that NF-κB positively regulates *Hif1a* expression in macrophages under resting and activating conditions. Furthermore, IKKβ was required for the optimal accumulation of HIF1α protein in macrophages in response to hypoxic conditions, which indicates that the hypoxia-induced increase in intranuclear HIF1α is not solely due to inhibition of PHDs but also to NF-κB-mediated transcriptional control. Analysis of tissues isolated from mice that had been exposed to low ambient oxygen revealed that IKKβ is also necessary for HIF1α-dependent hypoxic responses in the liver and brain.

So, this work identifies NF-κB as an important regulator of the hypoxic response and clarifies the mechanism of HIF1α activation following bacterial infection. These findings expand our understanding of the physiological stress responses that occur in ischaemic, infected and inflamed tissues.

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ORIGINAL RESEARCH PAPER Rius, J. *et al.* NF-κB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1α. *Nature* 23 April 2008 (doi:10.1038/nature06905)