domain 8 and is therefore protected from hydrolysis (and thereby inactivation). In addition, the orientation of the TED of C3, which is in part maintained by the anaphylatoxin domain, prevents a histidine residue in the TED from interacting with the thioester and forming a reactive intermediate. Cleavage of the anaphylatoxin domain of C3 to produce C3b induces a conformational change that disrupts both of these protective mechanisms and exposes the reactive thioester.

These structures should provide further clues about the function and origin of the complement system and create new avenues for treating diseases that are associated with defects in complement.

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References and links

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SIGNALLING

Achieving stimulus-specific gene expression

Nuclear factor-κB (NF-κB) is a transcription factor that is commonly active in various immune and inflammatory responses downstream of many cell-surface receptors. So, how can these different receptors induce different patterns of gene expression if they all have the same signalling end-point in terms of inhibitor-of-NF-κB kinase (IKK)-mediated NF-κB activity? Two studies reported in *Science* have used a combination of computer models and *in vitro* experiments to explain the stimulus specificity of the NF-κB pathway, using tumour-necrosis factor (TNF)-mediated signalling through TNF receptor 1 (TNFR1) and lipopolysaccharide (LPS)-mediated signalling through Toll-like receptor 4 (TLR4) as examples.

Both groups noted that TNF and LPS induce different profiles of IKK activity: TNF-dependent activation of IKK reached its peak between 5 and 15 minutes and then showed oscillatory behaviour if the stimulus continued, whereas LPS-mediated signalling resulted in a slower biphasic IKK response, which consisted of a small initial increase in IKK activity followed by a larger increase and a slowly attenuating later phase. Using a computational simulation of the IKK–NF-κB pathway, which was then confirmed by *in vitro* measurements, Hoffmann and colleagues showed that these differences in IKK profile correlate with distinct NF-κB-activity profiles. The oscillating response to TNF is thought to be the result of a negative-feedback mechanism by which NF-κB activation results in the synthesis of inhibitor of NF-κB (IκB) protein, so why does LPS not induce a similar pattern?

Baltimore and colleagues analysed the MyD88-dependent and MyD88-independent (TRIF-dependent) pathways of TLR4 signalling separately, using mouse embryonic fibroblasts that were deficient in MyD88 or TRIF. They showed that stimulation with LPS in the presence of either of the TLR4-signalling pathways alone resulted in oscillatory NF-κB activation. Using a computer model to simulate the two TLR4-signalling pathways, they predicted that the MyD88-independent pathway requires a time delay before it is activated, which might occur if protein synthesis is required for this pathway. Indeed, in LPS-stimulated, MyD88-deficient cells treated with the protein-synthesis inhibitor cycloheximide, NF-κB activation was prevented. Hoffmann and colleagues also reported that the second phase of IKK activity in response to LPS was inhibited by cycloheximide. Both groups showed that stimulation with LPS induced expression of TNF and that the second phase of IKK activity in response to LPS depends on TNF-mediated signalling. Hoffmann and colleagues showed that this second phase of TNF-induced IKK activity is essential for LPS-specific gene expression.

Therefore, the authors of both studies propose that the biphasic IKK response to LPS is the result of a positive-feedback mechanism in which early NF-κB activity through the MyD88-dependent pathway is accompanied by TNF production induced by the MyD88-independent pathway, which results in late NF-κB activity through TNF-mediated signalling. According to Baltimore and colleagues, each of these pathways individually has oscillatory behaviour, due to negative feedback, but their combination out of phase results in a more stable response. Therefore, the stimulus-specific expression of genes mediated by the same transcription-factor pathway can be controlled by positive- and negative-feedback mechanisms that determine the timing of transcription-factor activity.

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