Signal transduction by Toll-like receptors (TLRs) is initiated by the recruitment of the adapter protein MyD88, leading to a signalling pathway which culminates in the activation of NF-κB. Using MyD88-deficient mice, MyD88 has been shown to be critical for the induction of such NF-κB-dependent genes as TNF by all TLRs. For TLR-4 and TLR-3 signalling however, NF-κB activation is still evident in these mice and a ‘MyD88-independent pathway’ is still active, which culminates in activation of IRF-3 and induction of interferon-β. A second adapter, Mal (also known as TIRAP) was implicated in signalling by TLR-4 but not TLR-9 or IL-1RI, pointing to specificity. Studies from Mal-deficient mice indicate however that it is not involved in the ‘MyD88-independent pathway’ but seems to be functionally similar to MyD88 with regard to TLR-4 signalling to NF-κB. Interestingly, it is also required for TLR-2 signalling. Structural models predict differences between Mal and MyD88 and suggest that Mal is more likely to bind TLR-4 directly than TLR-2 although this remains to be experimentally tested. Mal also appears to be a phosphoprotein in resting cells, unlike MyD88, and most interestingly, Mal undergoes de-phosphorylation followed by recruitment to TLR-4 in LPS-treated cells. Other MyD88-like adapters are being found in the human genome, the most recent being TRIF, which appears to be required for TLR-3 signalling to NF-κB and IRF-3. These findings point to further complexity in TLR signalling and are revealing intricacies in the molecular basis to innate immunity previously unsuspected.