## Review

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# Microbial manipulation of receptor crosstalk in innate immunity

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### Summary

Many successful pathogens manipulate signalling crosstalk interactions between innate immune receptors as a way to modify the host immune response and promote their adaptive fitness.

These diverse 'crosstalk manipulation' tactics can be grouped into common themes. Pathogens can co-opt host inhibitory receptors; instigate signalling crosstalk pathways to synergistically induce immunosuppressive mediators; stimulate inside-out signalling to transactivate safe uptake pathways; selectively inhibit T helper 1 ($T_H1$) cell -mediated immunity using complement–Toll-like receptor (TLR) regulatory crosstalk; exploit TLR–TLR cross-inhibition; and disrupt functional receptor interactions that are necessary for cooperative protective signalling.

In co-opting inhibitory receptor crosstalk, pathogens mainly target receptors that signal through immunoreceptor tyrosine-based inhibitory motifs (ITIMs). These receptors recruit phosphatases, such as SH2 domain-containing protein tyrosine phosphatase 1 (SHP1), that in turn attenuate signalling induced by juxtaposed activating receptors (such as TLRs).

Effective mechanisms by which pathogens can take control of host receptors include the use of microbial structures that mimic host ligands or counter-receptors and virulence enzymes that convert host molecules (such as C5 and adenosine monophosphate) into active agonists.

Several pathogens can exploit TLRs or other receptors to transactivate their 'safe' uptake by complement receptor 3, which is normally involved in the phagocytosis of apoptotic cells and is thus not linked to vigorous pro-inflammatory or microbicidal pathways (such as those activated by Fcγ receptor-mediated phagocytosis).

Understanding the mechanisms by which pathogens manipulate signalling crosstalk between receptors of innate immunity is essential for developing interventional approaches to redirect the host response towards protective immunity.

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