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HOST-PATHOGEN INTERACTIONS

"Complementing" Toll Signaling

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Studies of signal transduction are often focused on dissecting the cellular response to a single stimulus that activates a single receptor. These types of studies laid the foundation for our current understanding of signaling, as well as the generation of countless arrow-containing models in today's textbooks. Implicit in most models is the suggestion that the arrows emanating from an activated receptor represent the core signaling pathways that are always activated by a given receptor, thus leading to a core cellular response. In nature, however, it is likely that no signaling pathway is activated in isolation. Rather, cells often respond to multiple stimuli simultaneously, and the cellular response may be the result of several signaling pathways. A new study attempts to model such conditions in vitro and reveals that when macrophages encounter bacteria, two signal transduction pathways interact in a way that profoundly alters the cellular response to infection.

When encountering bacteria, macrophages typically respond by activating at least two signaling pathways (*1*). One pathway promotes phagocytosis and killing of the microbe in lysosomes, whereas the other pathway promotes the release of factors that lead to inflammation. The complement system represents the most widely used phagocytosis-promoting receptors in mammals; it consists of soluble factors that survey the extracellular environment for microbes to opsonize (*2*). The Toll-like receptor (TLR) system represents the most widely used inflammation-promoting receptors in mammals; it consists of transmembrane receptors that survey the extracellular environment for microbes (*3*). Upon detection, TLRs activate signaling pathways that result in the production of inflammation-inducing and antimicrobial factors, such as nitric oxide (*4*).

In terms of fighting infection, it is widely assumed that complement and TLRs would be interdependent on one another, but the means by which these pathways interact was thought to be indirect (*1*, *5*, *6*). For example, complement-bound bacteria may more efficiently activate plasma membrane–localized TLRs as a result of tightly binding the plasma membrane during phagocytosis. Alternatively, complement could enhance delivery of microbes to TLRs found in lysosomes. Wang *et al*. have discovered that this view is not the whole story (*7*). Rather than simply helping to deliver microbes to these TLRs, the complement component C5a directly regulates the signaling function of the TLRs themselves.

Using *Porphyromonas gingivalis* as a model pathogen, Wang *et al*. show that signaling by the complement 5a receptor (C5aR) inhibits the antimicrobial activities of TLR2. Whereas *P. gingivalis* stimulated TLR2 to activate nitric oxide production by macrophages, *P. gingivalis* that was coated with C5a did not. The inability of TLR2 to induce nitric oxide production upon simultaneous C5aR engagement led to a decrease in bacterial killing and survival of the pathogen. These data indicate that complement does not simply deliver bacteria to TLR2; rather, signaling by the complement receptor somehow integrates into the signaling by TLR2 to create a functionally different cellular response.

C5aR engagement by *P. gingivalis* led to the cyclic adenosine monophosphate (cAMP)–mediated activation of protein kinase A (PKA) and inhibition of nitric oxide production by TLR2. Notably, C5aR did not inhibit the release of inflammatory cytokines by infected macrophages, only nitric oxide production. Thus, TLR2 signaling is not simply blocked by simultaneous C5aR signaling but is specifically modified to ensure the selective inhibition of antimicrobial actions. Investigating the means by which C5aR could influence TLR2 signaling, Wang *et al*. found that in order to generate this inhibitory cAMP, both TLR2 and the C5aR must be activated (neither receptor was capable of inducing the production of high concentrations of cAMP alone).

At a first approximation, this study would suggest that the C5aR should be considered a bona fide anti-inflammatory receptor that functions to interfere with TLR2 signaling. However, grouping C5aR with other established anti-inflammatory receptors such as the interleukin-10 receptor (IL-10R) and transforming growth factor–β (TGF-β) receptor is not appropriate. In the case of the latter two receptors, IL-10 and TGF-β function to degrade critical TLR signaling proteins such as MyD88 (myeloid differentiation primary response gene 88) and IRAK (interleukin-1 receptor-associated kinase 1) family members (*8*, *9*), thus leading to a general inhibition of TLR-mediated signal transduction. Moreover, IL-10 and TGF-β exert their inhibitory functions without simultaneous administration of TLR ligands. The fact that C5aR can inhibit some TLR2-dependent responses (such as nitric oxide production) but not others (such as IL-6 production) suggests a different mechanism of inhibition by this complement receptor. It is unlikely that the C5aR-induced cAMP functions to degrade MyD88; rather, it may function to alter some downstream MyD88-dependent response to TLR2 signaling (Fig. 1). On the basis of their different mechanisms of action, we suggest that IL-10R and the TGF-β receptor be considered "TLR inhibitory receptors," whereas the C5aR represents a "TLR modulatory receptor." The functional difference between these two categories is that the inhibitory receptors block most or all TLR-induced signaling responses, whereas the modulatory receptors alter a subset of such responses. How many other TLR modulatory receptors exist (and their physiological relevance) is unknown.

Although the precise mechanism by which simultaneous C5R and TLR2 signaling results in increases in cAMP production and PKA activity is unclear, the Wang *et al*. study reveals the exciting possibility that there is no such thing as a generic signaling pathway in vivo. Rather, mammalian cells may respond to diverse signals in different ways, and the cellular outputs are the result of crosstalk that simply cannot be predicted by studying each receptor in isolation. A fundamental challenge we now face is how to experimentally dissect a given signaling pathway in vivo in the face of myriad unrelated stimuli.

As with all exciting studies, several questions arise from this work. For exam-

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ple, are the results obtained with *P. gingivalis* and C5aR representative of all interactions between TLR2 ligands and this complement receptor? Of the TLRs, TLR2 binds to the largest number of ligands, ranging from bacterial lipoproteins and porins to parasitic lipoproteins (*10*). Whether all TLR2 ligands display the same behavior as a whole *P. gingivalis* bacterium is unknown. Also, it stands to reason that other bacteria-sensing TLRs would follow the same rules as TLR2 in terms of functional interactions with the C5aR. An interesting comparison would have been with the lipopolysaccharide (LPS) receptor TLR4. C5aR is known to antagonize TLR4 signaling (*11*), but this is thought to occur at the level of mitogen-activated protein kinase activation and results in decreases in cytokine production. Does this receptor also exhibit antagonistic crosstalk with C5aR in terms of nitric oxide production and if not, which mechanism of inhibition (TLR2 or TLR4) is the exception and which is the rule? Lastly, the question of why both TLR2 and C5aR must be activated simultaneously in order to observe the increases in cAMP is unanswered. The experimental approach taken by Wang *et al*. is suited to address these questions, and we eagerly await the next discovery of how complement can "complement" TLR responses.

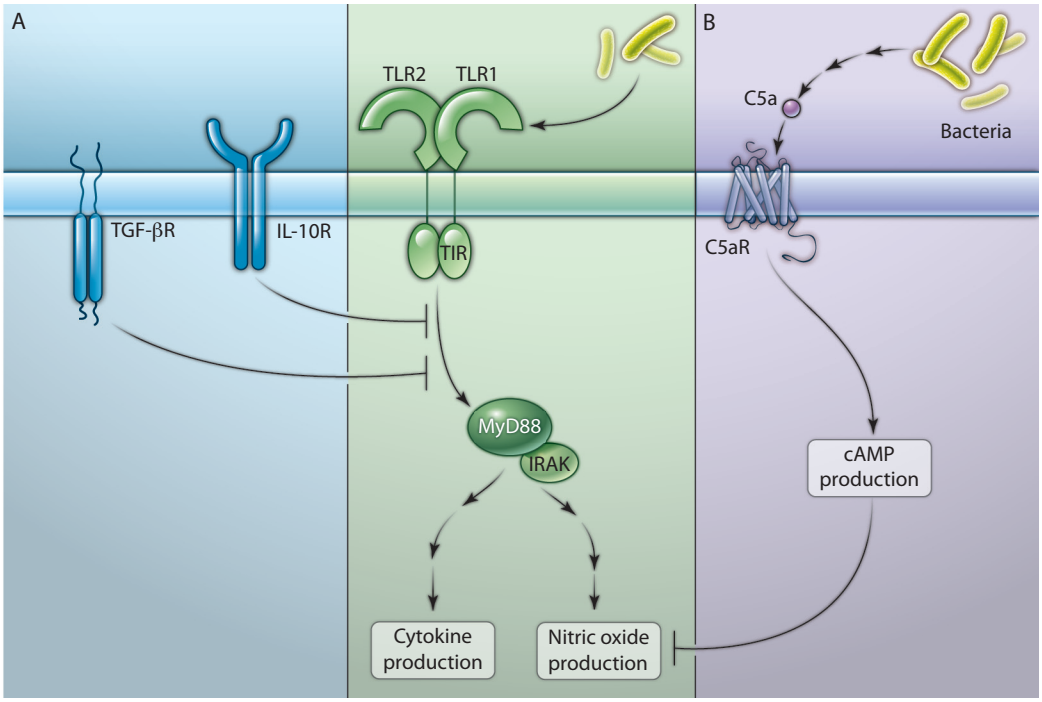

Fig. 1. Two categories of receptors may exist to alter the signaling pathways induced by TLRs. (**A**) The TLR inhibitory receptors function to inactivate TLR signaling and prevent most if not all inflammatory responses. (**B**) The TLR modulatory receptors function to alter a subset of signaling events and consequently alter a subset of cellular inflammatory responses. The C5aR represents one such TLR modulatory receptor, which acts with TLR2 to induce production of high concentrations of cAMP, which then functions to interfere with TLR-induced nitric oxide production and bacterial killing. TIR, Toll–interleukin-1 receptor-like domain.

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