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TLR-mediated innate immune recognition

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Immune recognition has always been one of the main points of interest in immunology. It is well appreciated that there are several distinct strategies of immune recognition that operate in the mammalian immune system. These are traditionally grouped as innate and adaptive, based on the use of either germline-encoded or somatically-generated receptors, respectively. Beyond the genetic nature of the receptors involved, however, the distinction between the two types of immune recognition is not always clear-cut. For example, complement receptors, TLRs, and presumably other types of non-clonal “innate” immune receptors can cooperate with B cell receptors in pathogen recognition, and this involves, at least in some cases, co-recognition by the two types of receptors. In addition, the architecture of antigen receptor complexes bears a striking resemblance to a class of innate immune receptor complexes that signal through ITAM-containing adaptor proteins, such as DAP12. In both cases multi-protein receptor complexes are assembled through ionic interactions between charged residues in the transmembrane regions and signal through similar pathways involving ITAM dependent activation of Syk-72 and ZAP-70.

Although the classification of immune recognition into innate and adaptive is useful in many ways, it may obscure the heterogeneity of receptors and mechanisms of innate immune recognition. Indeed, the mammalian innate immune system uses several different classes of receptors, including TLRs, NODs, and NALPS, Dectins, RIG-I and MDA-5 and others [1,2]. Some of the receptors are transmembrane proteins (e.g., TLRs and Dectins), some are secreted (e.g., penthaxins and collectins), and some are intracellular cytoplasmic receptors (e.g., RIG-I/MDA-5, NODs). All these receptors detect conserved microbial structures and function as pattern recognition receptors.

However signaling pathways initiated by different classes of receptors are very distinct, as are the immune responses induced by these receptors. Furthermore, in some cases different classes of receptors can be “co-engaged” by a given pathogen, for example, TLR2 and Dectin-1 in fungal recognition, and TLRs and NODs in bacterial recognition. In these cases, recognition and signaling mechanisms may have become coupled in some ways to allow coordinated functioning of different receptor classes. However, other combinations of receptors, for example, Dectin-1 and RIG-I, presumably never co-engage and thus would not be expected to be functionally coupled. Currently our knowledge of the functional and mechanistic links between different pattern recognition receptors is incomplete and would have to be improved in order to understand the full complexity of innate immune recognition.

While other classes of pattern recognition receptors continue to be characterized, TLRs enjoyed most of the research attention in the past few years. This issue of *Seminars in*

Immunology contains reviews that summarize the current state of the TLR field. The purpose of this overview, aside from serving as a formal introduction, is to highlight some of the key aspects of TLR biology with the emphasis on some major unresolved questions.

TLR-mediated immune recognition

One of the most challenging aspects of TLR biology is the molecular characterization of TLR-mediated recognition of microbial ligands. This, and related issues are summarized and discussed by Miyake [3]. Several fundamental questions currently remain almost completely unaddressed: Do TLRs directly recognize microbial structures? Although there is sufficient evidence to suggest that TLRs at least contribute to direct ligand recognition, the extent of this contribution and the exact molecular details remain completely unknown. One puzzling feature of TLR-mediated recognition is the ability to detect (by some TLRs) a variety of microbial ligands that have nothing in common in terms of their structure. This is most obvious in the case of TLR2, but may also be the case with other TLRs. The role of various accessory proteins in TLR-mediated recognition is also incompletely understood. Although the functional significance of CD14 and MD2 is well appreciated, it is likely that many more (yet to be characterized) accessory proteins are involved in ligand sensing and TLR activation. However, even in the case of the best characterized accessory protein, CD14, it is still poorly understood how it aids TLR4-and TLR2-mediated recognition.

A highly contentious issue is the question of endogenous TLR ligands. Do they exist? They certainly do, as far as nucleic acid ligands are concerned. In fact, triggering of TLR7 and TLR9 by endogenous RNA and DNA complexes plays an essential role in the antibody-dependent systemic autoimmune disease, lupus, as discussed by Shlomchik and colleagues [4]. However, in the case of TLRs 7 and 9, the ligands are essentially the same whether they are microbial or self in origin, and their recognition is presumably unintentional. The question is, are there endogenous ligands that evolved to activate TLRs? This type of endogenous ligand probably does exist, at least for some TLRs. The problem is that most of the published observations reporting such ligands are likely to be due to contaminating microbial ligands, particularly LPS and lipopeptides. Accordingly, all of the reported “endogenous ligands” were found to activate TLR2 and TLR4. The reason for an assumed contamination is the use of recombinant proteins produced in bacteria. A simple way to avoid contamination and to ensure the authenticity of the presumed ligands is to use proteins produced in mammalian cells (when the putative ligands are proteins), or to use alternative approaches that avoid the risk of contamination. This was successfully done with hyaluronic acids [5] and should be possible in other cases.

TLR-mediated signaling pathways

Signaling pathways activated by TLRs have been characterized through genetic and biochemical approaches leading to identification of most signaling components, their order in signaling pathways, and their interactions. This subject is reviewed by Akira and colleagues [6]. The major issues to be addressed in this area include elucidation of the mechanisms of signal transduction, their regulation, and their integration with other signaling pathways, including the pathways activated by other pattern recognition receptors. It is still completely unknown exactly how TLRs activate their signaling pathways, how they recruit TLR-containing signaling adaptors, and what determines specificity in adaptor recruitment and function. Now that the race to identify novel signaling components is over, it is a good time to start characterizing their mechanisms of function.

TLR-mediated antimicrobial defense

The critical role of TLRs to bacterial and viral recognition is well appreciated (reviewed by Barton [7] and Zychlinsky and colleagues [8]). It is also increasingly clear that the relative contribution of TLRs or other classes of pattern recognition receptors may vary depending on the pathogen. Indeed, in the case of RNA viruses, RIG-I and MDA-5 may play a more prominent role, and Dectin-1 has important function in fungal recognition. Furthermore, TLRs do not appear to have any role in recognition and immunity against helminthes and their role in protozoan recognition, although well documented in some cases, may not be universal. Thus a major challenge remains to characterize the full spectrum of functioning of TLRs together with other types of pattern recognition receptors, in host defense from infections.

TLR-mediated control of adaptive immunity

Self/non-self discrimination and control of adaptive immunity has been a subject of intense interest and debate for many years. Characterization of the role of TLRs in these processes clarified many issues of this complex problem. Availability of TLR ligands and TLR-deficient mice allowed for detailed analyses of the mechanisms and pathways involved in the initiation of adaptive immune responses. Not surprisingly, dendritic cells and their regulation by TLRs attracted most of the attention. The progress in this area is discussed by Iwasaki and colleagues [9]. There are certainly many important mechanistic questions that remain to be addressed, but one additional issue of major interest is whether TLR-induced adaptive immune responses are qualitatively different from the ones induced by other classes of receptors, for example, by Dectins or RIG-I/MDA-5.

In summary, the TLR field has significantly matured in the past few years, but the progress has been very uneven, with some areas enjoying most of the developments (characterization of TLR ligands and signaling components), while other areas lagging far behind (e.g., molecular mechanisms of ligand recognition). Hopefully this compendium of expert reviews will provide not only authoritative update of the field, but also inspire further studies of this fascinating receptors.

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