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Pillars of Immunology

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The last decade of the 20th century witnessed a dramatic expansion in the field of immunology, including major discoveries that markedly increased our understanding of innate immunity. This rapid growth in knowledge was fueled by the development of comprehensive gene libraries and advances in computational analysis. These new tools led to productive cross-fertilization between insect and plant genetics and mammalian immunology, as well as the rapid identification and analyses of immune receptors and their signaling pathways. Examples of these discoveries include the identification of mammalian TLRs and Nod-like receptors in the late 1990s (1–4). The two papers that are the focus of this installment of the *Pillars of Immunology* series were published in 1997 and are good examples of seminal discoveries in the area of innate immunity signaling. Both papers relate to the identification of MyD88 as an essential adaptor protein in the IL-1R1 signaling pathway (5, 6). MyD88 was first identified as a myeloid differentiation primary response gene in 1990 (7). Subsequently, Dan Hultmark was the first to notice amino acid homology between MyD88 and the cytoplasmic domains of *Drosophila* Toll and mammalian IL-1 receptors, leading him to suggest that "MyD88 may define a family of signal transduction molecules with an ancestral function in the activation of the immune system" (8). In the *Immunity* paper "MyD88: an adapter that recruits IRAK to the IL-1 receptor complex," Wesche et al. (6) performed biochemical analysis of the activated IL-1R1 protein complex and identified MyD88. In contrast, in the *Science* paper "IRAK (Pelle) family member IRAK-2 and MyD88 as proximal mediators of IL-1 signaling," Muzio et al. (5) theorized that MyD88 was a proximal adaptor of the IL-1R signaling pathway based on the presence of amino acid homology between MyD88 and the cytoplasmic domain of the IL-1R accessory protein (IL-1RAP). Using dominant negative constructs that expressed the COOH-terminal domain of MyD88, both Wesche et al. (6) and Muzio et al. (5) showed that MyD88 was required for NF-κB activation in response to IL-1R1 signaling. Another significant contribution of the aforementioned studies was the molecular ordering of IRAK, MyD88, and TRAF6 in the IL-1R1 signaling pathway. MyD88 has a modular structure with a death domain at its NH2 terminus and a Toll/IL-1R (TIR) domain at its COOH terminus. Using coimmunoprecipitation experiments, Wesche et al. (6) and Muzio et al. (5) showed that the TIR domain of MyD88 interacts with the TIR domains of IL-1R1 and IL-1RAP. Furthermore, they showed that MyD88 binds the serine-threonine kinases IRAK1 and IRAK2, mammalian homologs of *Drosophila* Pelle in the Toll pathway, via a heterotypic death domain–mediated interaction (5, 6). Thus, MyD88 functions as a pure adaptor linking the IL-1R1 to downstream IRAK kinases. The role of MyD88 is similar to that of Tube, a *Drosophila* MyD88 homolog, in the activation of Pelle as revealed by genetic studies of dorsoventral patterning via the Toll receptor signaling pathway (9–11).

Although the studies by Wesche et al. and Muzio et al. were innovative, their significance was limited by the fact that their conclusions were based largely on the use of dominant interfering forms of MyD88 in overexpression systems. The confirmation of the role of MyD88 in IL-1R1 signaling came a year later with the analysis of mice with targeted deletion of the *MyD88* gene. In elegant studies, Adachi et al. (12) showed that MyD88 was required for the induction of T cell proliferation and production of acute phase proteins and cytokines in response to IL-1β in vivo. Around the same time, IL-18, a cytokine structurally related to IL-1β (13), was shown to activate NF-κB signaling via IRAK (14). The relation of IL-18 to IL-1β was further revealed when the IL-18R was cloned and found to be homologous to IL-1R1 and IL-1RAP (15, 16). Similar to *Drosophila* Toll and mammalian IL-1R1/IL-1RAP, the cytoplasmic portion of IL-18R contains a TIR domain that mediates the interaction with the TIR domain of MyD88 (17). In agreement with these findings, Adachi et al. (12) also found that MyD88 was essential for the induction of NF-κB and MAPK signaling in response to IL-18. The impact of insect genetics and bioinformatics tools on our understanding of mammalian immunology was also reflected in the discovery of several other IL-1R family members, such as IL-1RL1 (18, 19). Shortly afterward, by using overexpression studies, Medzhitov et al. (3) showed that MyD88 is critical for TLR signaling. This was confirmed in vivo by the Akira laboratory using MyD88-deficient mice (20). Collectively, these studies defined MyD88 as a critical adaptor for signaling induced by the IL-1/IL-18/Toll receptor superfamily.

The significance of the early studies by Wesche et al. and Muzio et al. goes beyond the link of MyD88 to the IL-1R1. Both groups performed biochemical and functional studies to define the molecular ordering of MyD88, IRAKs, and TRAF6

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Abbreviations used in this article: IL-1RAP, IL-1R accessory protein; TIR, Toll/IL-1R.

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in the IL-1R1 signaling pathway. Prior to the aforementioned work, it was known that IL-1β stimulation induced a complex of IL-1R1 and IL-1RAP, leading to recruitment and phosphorylation of the IRAK kinase to the complex (21, 22). The work by Wesche et al. and Muzio et al. showed that MyD88 was the link between IL-1R1 and IRAK to induce NF-κB activation. Because these molecules, or their family members, are involved in many receptor pathways, these initial studies provided a working framework to understand the cascade of events that operate in the IL-1R/TLR family and related signaling pathways. Genetic proof of the role of IRAK1 and IRAK2 as well as IRAK4 and TRAF6 in IL-1R1/IL-18R and TLR signaling was reported shortly after by several groups (23–27). Subsequent studies revealed that IRAK2 was activated downstream of IRAK4, and IRAK1 and IRAK2 acted sequentially in TLR signaling (28).

In summary, these two papers provided the first experimental evidence that MyD88 functioned as a critical adaptor molecule bridging IL-1R1 to the IRAK complex and are therefore deserving of special recognition as *Pillars of Immunology*. The role of MyD88 in innate immunity is now widely accepted and documented by papers too numerous to cite in this type of review. Since these early reports, structural studies and mutational analyses have confirmed the molecular details of the MyD88-mediated interactions described in these two original papers. Strategies by which both bacterial and viral proteins such as vaccinia virus protein A46R and hepatitis C virus nonstructural protein NS5A target MyD88 signaling to evade immune detection have been described (29). Clinically, rare MyD88 mutations are associated with immunodeficiencies that predispose patients to recurrent life-threatening bacterial infections analogous to MyD88 deficiency in mice that leads to susceptibility to various pathogens (30). Finally, roles for MyD88 signaling in the regulation of inflammation during cancer progression of the intestine (31), liver (32), pancreas (33), and skin (34) are beginning to emerge. Clearly, the MyD88 adaptor protein mediates numerous biologically important signal transduction pathways in innate immunity.

Disclosures

The authors have no financial conflicts of interest.

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Corrections

Warner, N., and G. Núñez. 2013. MyD88: A critical adaptor protein in innate immunity signal transduction. *J. Immunol.* 190: 3–4.

On page 3, the reference cited in the sentence "Shortly afterward, by using overexpression studies, Medzhitov et al. (3) showed that MyD88 is critical for TLR signaling" was incorrect. The correct reference is:

Medzhitov, R., P. Preston-Hurlburt, E. Kopp, A. Stadlen, C. Chen, S. Ghosh, and C. A. Janeway, Jr. 1998. MyD88 is an adaptor protein in the hToll/IL-1 receptor family signaling pathways. *Mol. Cell.* 2: 253–258.

In addition, there was another article with the same conclusion published around the same time that we inadvertently failed to cite:

Muzio, M., G. Natoli, S. Saccani, M. Levrero, and A. Mantovani. 1998. The human toll signaling pathway: Divergence of nuclear factor κB and JNK/SAPK activation upstream of tumor necrosis factor receptor–associated factor 6 (TRAF6). *J. Exp. Med.* 187: 2097–2101.

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