The 2011 Nobel Prize in Physiology or Medicine was awarded to Dr Jules A. Hoffmann and Dr Bruce A. Beutler for their discoveries of the role of Toll-like receptors (TLRs) in innate immunity and to Dr Ralph M. Steinman for his discovery of dendritic cells and their role in adaptive immunity. These discoveries have had a tremendous impact on our field. A recent article by Chutarbanova and Imler in the *Arteriosclerosis, Thrombosis, and Vascular Biology* series “History of Discovery” recounted the discovery of TLRs.\(^1\) Dr Charles Janeway initially postulated the existence of innate immune pattern-recognition receptors that detect molecular structures ubiquitously shared among pathogens that allow bridging between the innate and adaptive immune systems.\(^2\) A role for the *Toll* gene in the innate immune system of the fly *Drosophila melanogaster* was first described in 1996 by the Hoffman laboratory.\(^3\) The first mammalian Toll homolog was reported by the Janeway laboratory a year later.\(^4\) In 1998, the Beutler laboratory identified TLR4 as the elusive mammalian receptor that detects bacterial lipopolysaccharide.\(^5\) In a subsequent study by Akira’s group, knockout mice were generated to confirm that TLR4 recognizes lipopolysaccharide from Gram-negative bacteria, whereas TLR2 recognizes protein components of the Gram-positive bacterial cell wall.\(^6,7\) These studies support Janeway’s original hypothesis of the importance of pattern-recognition receptors in the innate immune response.\(^8\)

Given the known role of innate immunity in the pathogenesis of atherosclerosis and other vascular diseases, it was not surprising that TLRs were shown to affect atherosclerosis. Early studies demonstrated TLR1, TLR2, and TLR4 expression in both murine and human atherosclerotic plaques.\(^9,10\) Subsequent studies showed that TLR1/interleukin-1 receptor, TLR2, TLR3, and TLR4 were involved in atherosclerosis in murine models.\(^11–17\) Interestingly, administration of either exogenous TLR ligands or the pathogens themselves accidentally activate the innate immune system enhancing atherosclerosis. In addition, receptor complexes consisting of different TLRs and scavenger receptors have been identified.\(^19\)

For instance, binding of oxidized lipoproteins to a CD36-TLR4-TLR6 heterotrimERIC complex induces chemokine expression in macrophages and monocytes.\(^20\) Although many advances have been made in characterizing the role of TLRs in atherosclerosis, additional studies are warranted and may lead to the development of novel therapeutics to treat this devastating disease.

The discovery by Steinman and Cohn in 1973 of a new cell type that they called the dendritic cell was immensely important to the field of adaptive immunity.\(^21\) As with innate immunity, adaptive immunity plays a central role in atherosclerosis due to the inflammatory nature of the disease.\(^22\) Indeed, dendritic cells have been shown to be key initiators and regulators of the immune response in atherosclerosis.\(^23\) Studies with mouse models have implicated dendritic or dendritic-like cells in the initiation, progression, and regression of atherosclerosis.\(^24–27\) A sign that Steinman himself was entering the field of atherosclerosis was evidenced by his recent article describing the presence and properties of dendritic cells in the aortic sinus, aortic cells, and cardiac valves of mice.\(^28\) Not having his contributions is a significant loss to our field.

**Disclosures**

None.

**References**


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