Toll-like Receptor Polymorphisms and Carotid Artery Intima-Media Thickness

To the Editor:

Chronic inflammation represents a hallmark of atherosclerosis. Thus, there is growing interest in the role of innate immune defense mechanisms in arterial plaque formation, and several studies directly implicate signaling by toll-like receptors (TLRs) in the pathogenesis of atherosclerosis. However, these links are not completely understood, and further studies determining the clinical relevance of TLRs in atherosclerosis are clearly needed.

We thus read with interest the article of Labrum et al. In a large prospective setting they studied 2 single nucleotide polymorphisms in TLR-2 (Arg753Gln) and TLR-4 (Asp299Gly) and their association with the progression of intima-media thickness. The study did not confirm previous smaller studies demonstrating that these polymorphisms may not be associated with development and course of atherosclerosis, we prefer a more functional explanation that may also clarify to some extent the heterogeneous results obtained so far.

It has been reported that two cosegregating variants of TLR4 attenuate LPS signaling and are accompanied by LPS hyporesponsiveness. However, further studies revealed other genes and receptors to be clearly involved in modulating the response to lipopolysaccharides. Moreover, recent studies reported that heterozygous polymorphisms of TLR-2 (Arg753Gln) and TLR-4 (Asp299Gly) do not suffice to alter the response of monocytes exposed to lipoteichoic acid and lipopolysaccharides, respectively. In the study of von Aulock et al, even an individual who was homozygous for a TLR-4 polymorphism showed no difference in responses to lipopolysaccharides as compared with wild-type individuals. Finally, it has been claimed that these TLR polymorphisms represent functional knockouts of lipoteichoic acid and lipopolysaccharide signaling. Hence, growing evidence suggests that alternative LPS-recognizing molecules may compensate TLR signaling in the case of TLR-2 (Arg753Gln) and TLR-4 (Asp299Gly). Apart from the functional relevance, the overall low incidence of individuals with homozygous polymorphisms (<1%) makes these polymorphisms a risk factor of lesser demographic importance.

In summary, recent research has clearly demonstrated the important role of innate immunity in the development of atherosclerosis. However, with respect to the aforementioned arguments, we believe that comparing TLR-2 and TLR-4 polymorphisms with a macroscopic surrogate marker like intima-media thickness may be beyond the possibilities of these single features. Further studies are needed to define the role of intact TLR signaling in the initiation and progression of atherosclerosis.

Disclosures

None.

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