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Sommario/riassunto

The main causes of morbidity and mortality in diabetes are macrovasular and microvascular complications, including atherosclerosis, nephropathy, and retinopathy. As the definition of atherosclerosis as a chronic, smoldering, inflammatory disease has gained general acceptance, the attention of researchers has focused on the triggers of chronic vascular inflammation. The oxidation and other forms of modification of lipids and lipoproteins have emerged as a major pathogenic factor in atherosclerosis, with a significant interaction with the immune system. Modified lipoproteins by themselves are proinflammatory through the activation of the innate immune system as a consequence of the interaction with scavenger receptors and/or toll-like receptors expressed by a variety of cell types, including phagocytic cells and dendritic cells. A variety of modified forms of LDL (mLDL), including oxidized, malondialdehyde-modified, and Advanced Glycation End-product-modified LDL induce autoimmune responses in humans. Those modifications seem enhanced in diabetes, and the progression of atherosclerosis is accelerated in diabetic patients. The immune response to all forms of mLDL results in both activation of T cells in the arterial wall and in an autoimmune response characterized by the formation of IgG antibodies. Both arms of the immune response are believed to play a role in vascular inflammation. While the cell response is likely to activate resident macrophages, the humoral immune response results in the production of IgG antibodies that bind

to specific epitopes in modified forms of LDL, generate immune complexes both intra- and extravascularly, and those complexes are able to activate the classical pathway of the complement system as well as phagocytic cells via Fc? receptors. In vitro studies suggest that the pro-inflammatory activity of immune complexes containing mLDL is several-fold higher than that of the modified LDL molecules by themselves. Clinical studies have provided significant support to the pathogenic role of immune complexes containing modified LDL in the development of atherosclerotic complications in patients with both type 1 and type 2 diabetes. At the same time, there is increasing evidence that the formation of immune complexes containing modified forms of LDL may also be involved in the pathogenesis of diabetic nephropathy and retinopathy. These are areas in which more research is needed to fully understand the pathogenic mechanisms activated by those immune complexes. Of interest is the fact that animal models have suggested the possibility of modifying the adaptive humoral immune response in ways that would result in slowing down, and perhaps prevent, the atherosclerotic process. This possibility is sufficiently alluring as to justify increased research efforts, both in animal models (including diabetic animals) and translational clinical studies. The manipulation of the T regulatory population is another area of potential translational impact, which has hardly been explored. Indeed at this point of time, what seems to be a high priority is an increased and open interchange of information among investigators, trying to reach a better general understanding and integration of knowledge generated from a variety of approaches and perspectives. This Research Topic provided an optimal platform for this open interchange of information. We encouraged interested scientists to submit mini-reviews, methods papers, review articles, perspectives and original research articles covering this topic in all its diversity to facilitate the communication of perspectives and new information between scientists interested in understanding the multiple implications of the involvement of the immune system in the pathogenesis of diabetic complications.