Diabetic conditions act as matchmaker for monocytes and vascular smooth muscle cells

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LIFESTYLE FACTORS, together with genetic predisposition, contribute to the current rapid growth in number of patients with diabetes mellitus. This has resulted in a dramatic increase in patients with cardiovascular disease, given that diabetes is a major risk factor for the development of atherosclerosis (1). Understanding the molecular and cellular mechanisms that lead to the development of atherosclerosis is critical for the identification of strategies to limit the progression of this disease before it has clinical consequences. Published studies have revealed that many different cell types, including monocytes/macrophages, lymphocytes, endothelial cells (ECs), and vascular smooth muscle cells (VSMCs), are involved in atherogenesis (12, 13, 16, 18).

Monocytes/macrophages play key roles at all stages of atherosclerosis (12, 18). In response to atherogenic stimuli, monocytes located within the circulation adhere to, and migrate across, the endothelium. These initial processes may be reversible, whereas the subsequent prolonged intimal retention of monocytes/macrophages and formation of foam cells represent a central pathogenic process in atherogenesis (12, 18). Atherosclerotic lesions in patients with diabetes are characterized by excessive macrophage/fibrous/cell infiltration (compared with those from nondiabetic individuals), suggesting that the recruitment of monocytes to the vessel wall may be augmented under diabetic conditions (15). However, the precise mechanisms by which monocytes/macrophages are retained within the vessel wall, survive, and differentiate into foam cells are not well documented as far as diabetic conditions are concerned.

VSMC migration and proliferation and inflammatory gene expression are also well-documented events in atherosclerosis (6), and diabetic conditions have been shown to enhance these processes (16). Although ECs are thought to be the major cell type responsible for interacting with macrophages, increasing evidence suggests that adhesive interactions between migrated monocytes and VSMCs may contribute to monocyte-macrophage retention within the vasculature (6). The potential of VSMCs to interact with monocytes is indicated by the finding that VSMCs express adhesion molecules within atherosclerotic lesions but not in normal vessels (2). Indeed, direct contact between VSMCs and macrophages has been detected within human atherosclerotic plaques by electron microscopic and immunohistochemical analyses (20). However, the mechanisms by which the subendothelial retention of monocytes occurs under diabetic conditions, and the role played by VSMCs in this process, remain unclear.

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, a study performed in Natarajan’s laboratory [Meng et al. (14)] is reported in which that group addressed the effects of diabetic conditions on the binding of monocytes to VSMC, and their subsequent differentiation, using in vitro, ex vivo, and in vivo methods. Hyperglycemia and the subsequent formation of advanced glycation end products (AGEs) are recognized as essential mediators in the pathogenesis of diabetic vasculopathy (4). Diabetogenic conditions such as high glucose (HG) and activation of AGES/RAGE (receptor for AGES) enhance inflammatory gene expression and proatherogenic responses in VSMCs (9, 16). In one set of experiments, these authors (14) found that human aortic VSMCs (HVSMS) treated with diabetic stimuli such as HG or S100B, a ligand of RAGE (19), exhibited enhanced binding of human THP-1 monocytes. Moreover, these diabetic stimuli increased the expression of the chemokine fractalkaline (FKN) in HVSMS. Previously, it was recognized that FKN and monocyte chemoattractant protein (MCP-1) are important chemokines, since they serve as mediators of the interaction between monocytes and ECs or VSMCs, and also that they play distinct roles in the development of atherosclerosis (3). Natarajan’s group (14) have now demonstrated that pretreatment of HVSMS with neutralizing antibodies to FKN or MCP-1 significantly inhibited monocyte/VSMC binding, whereas monocytes treated with FKN exhibited enhanced binding to VSMC. Against the above background, these new findings strongly suggest that in diabetic conditions, there is enhanced monocyte-VSMC binding and that this enhancement is related to the presence of increased levels of certain chemokines (i.e., FKN and MCP-1). This is supported by reports showing that AGESs (1) and S100B can increase MCP-1 expression in cultured VSMCs (9, 17) and 2) that HG conditions induce upregulations of FKN and MCP-1 in VSMCs (7).

Meng et al. (14) further investigated whether monocyte binding might be enhanced in mouse VSMCs (MVSMS) isolated from db/db mice, a well-established model of type 2 diabetes. In a previous report by Natarajan’s group (11), short-term ex vivo cultures of MVSMS isolated from db/db mice displayed enhanced proinflammatory responses, including MCP-1 expression and monocyte binding. In the new study (14), MVSMS isolated from diabetic db/db mice (vs. nondiabetic control db/+ mice) were found to exhibit enhanced monocyte binding and increased FKN expression. Furthermore, pretreatment of db/db MVSMS with neutralizing antibodies to MCP-1 or FKN attenuated the enhanced monocyte/MVSMC binding. For a better indication of the possible in vivo significance, Meng et al. (14) investigated the interaction between monocytes and VSMCs using endothelium-denuded aortas, with an exposed VSMC layer, isolated from...
type 2 diabetic db/db mice or type 1 diabetic streptozotocin-induced mice. In each of these diabetic models, increased monocyte adhesion to endothelium-denuded aortas (viz. to the VSMC layer) was seen, and aortic FKN expression was significantly increased compared with controls. These findings are consistent with a previous report that in patients with atherosclerosis or diabetes, FKN expression is upregulated and concentrated in the medial layer of the vessel wall (21). Thus Meng et al. (14) have provided convincing evidence that an enhancement of monocyte-VSMC interaction results from the existence of a diabetic condition (which can be either type 1 or type 2) and that this enhancement is due to increased FKN and MCP-1 levels.

The pathophysiological consequences of monocyte-VSMC interaction events remain poorly characterized. Direct cell-to-cell interactions between monocytes and VSMCs are known to enhance monocyte procoagulant activity and to increase the production, within both cell types, of atherosclerosis-related factors such as metalloproteinase-1 (22). It would therefore appear that VSMC and monocytes/macrophages are not merely innocent coexisting neighbors within the vessel but that monocyte-VSMC interactions provide additional regulatory signals in the pathogenesis of atherosclerosis. Actually, almost 15 years ago, one research group noted that very few apoptotic monocytes were to be found in early atherosclerotic lesions, when VSMCs are abundant, leading them to propose that local interactions between these two cell types may protect the monocytes (10). Moreover, a previous study by Natarajan’s group (5) established that monocyte-VSMC binding served to inhibit serum deprivation-induced monocyte apoptosis, whereas both the expression in monocytes of CD36 [which correlates with the uptake of oxidized low-density lipoprotein (ox-LDL) and with foam-cell formation (8)] and the uptake of ox-LDL by monocytes were increased under these conditions. This suggests that interactions between monocytes and VSMCs may 1) contribute to monocyte survival (antiapoptotic phenomenon) and represent part of the mechanism responsible for monocyte accumulation in early atherosclerosis after their migration to the subendothelial layer and 2) contribute to their subsequent differentiation to the macrophage phenotype and to foam-cell formation (5, 6).

Although it seems clear that monocyte-VSMC interaction is enhanced in diabetic conditions, the functional importance of this phenomenon remains uncertain. The final experiments described by Meng et al. (14) addressed this point. The differentiation of monocytes into macrophages and their subsequent transformation to lipid-laden foam cells constitute major events in the development of atherosclerotic lesions (8). Meng et al. (14) found that the monocyte expression of CD36 was increased following coincubation with VSMCs under diabetic conditions and that the expression of CD36 in mouse monocyte cells was increased by binding to MVSVMCs obtained from diabetic db/db mice (vs. those from db/+ mice). Collectively, the above findings strongly suggest that monocyte-VSMC interactions play important roles in the promotion of monocyte retention, in foam-cell formation, and in atherogenesis and that these events are greatly enhanced under diabetic conditions.

Since diabetes is associated with significantly accelerated rates of atherosclerosis, a proper understanding of the regulation of the binding of monocytes to VSMCs, and their subsequent differentiation, may eventually furnish new therapeutic targets for diabetes-associated atherosclerosis.

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No conflicts of interest are declared by the author(s).

REFERENCES

