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Impaired reverse transendothelial migration capacity governs the enhanced abluminal accumulation of diabetic CD14+ monocytes

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Background: Chronic inflammation drives atherosclerosis. Monocyte recruitment and accumulation in the tissues contributes to chronic inflammation and is an important aspect of the pathobiology of atherosclerosis. Diabetes mellitus (DM) is a leading cardiovascular predisposing to the development of atherosclerosis. Monocytes represent the largest cell-population in the atherosclerotic plaque. However, the mechanisms that drive the accumulation of monocytes in the plaques are not clearly understood.

Purpose: The aim of this study is to understand the hyperglycemia/diabetes-induced changes in the transendothelial and reverse transendothelial migration processes of monocytes under physiological flow conditions and to characterize the underlying mechanisms.

Methods: Monocytes isolated from healthy donors by negative selection were conditioned in hyperglycemic or normoglycemic conditions for 48 hours. These monocytes or monocytes from type 2 diabetes mellitus (T2-DM) patients or from non-diabetic controls were allowed to interact with TNFα -activated HUVEC-monolayer. Experiments were performed under flow conditions found in post-capillary venules. Analysis of migration was performed using Fiji J software. Expression of molecules involved in transmigration and reverse migration was measured using FACS.

Results: Monocytes from T2-DM patients and hyperglycemia-conditioned cells revealed a significantly reduced transendothelial migration capacity. Even though these monocytes adhered to the HUVEC monolayer, only few of them transmigrated. Moreover, the transmigrated cells from diabetic patients and hyperglycemia-conditioned cells accumulated in the ablumen after transendothelial migration. Time in the ablumen was prolonged and there was a significant reduction in the reverse transendothelial migration. Expression levels of chemokine receptors, which had been shown to be essential for transendothelial migration process, were reduced in diabetic monocytes.

Conclusion: Our results revealed for the first time that the enhanced diabetic monocyte accumulation in the albumen is not secondary to the elevated transmigration through the endothelium. Instead, the accumulation of monocytes in the vessel wall is due to the direct consequence of dysfunctional reverse transendothelial migration. These novel findings could explain the underlying reasons leading to the elevated inflammatory monocyte accumulation, chronic inflammation and subsequent atherosclerosis development in T2-DM patients. Our results highlight the importance of restoring the reverse transendothelial migration capacity of monocytes to reduce monocyte accumulation and atherogenesis in the diabetic environment.

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