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ESC Basic Research Council First contact Initiative Grant Report

In cardiovascular field monocytes/macrophages are well appreciated to be the central cellular components in atherosclerosis[1]. They appear in the atherosclerotic lesions at the very initial stages and contribute to their further development through to the occlusive complications[2]. The monocyte/macrophage accumulation is being triggered at the very initial stage of atherogenesis by atherogenic lipoproteins, especially chemically modified ones, accumulating subintimally at vulnerable arterial sites[3].

Monocytes are major cellular player in the accelerated atherogenesis in diabetic individuals. This occurs due to the activated (pro-inflammatory) status of monocytes in diabetes mellitus (DM). DM is a complex metabolic state with hyperglycemia considered to be a key event in the development of diabetic vascular complications by causing divergent cellular dysfunction. Hyperglycemia occurs as a result of impaired glucose utilization by tissues due to either whole-body insulin resistance in DM type 2 (relative insufficiency) or lack of sufficient availability of insulin in DM type 1 (absolute insufficiency)[4]. Generally, lack of physiological effects of insulin on the cells and related hyperglycemia-induced cellular biochemical alterations are two major factors resulting in cellular dysfunction in DM. Fruitful discussions during the visit of Dr. Vadim Tchaikovski to the Haemostasis Thrombosis & Vascular Biology Unit at University of Birmingham made possible by ESC First Contact Initiative Grant led to summarizing major biochemical pathways through which lack of proper insulin signalling and resulting elevated glucose levels can lead to monocyte/macrophage dysfunction:1) insulin resistance-related aberrations in monocyte/macrophage function; 2) increased glucose utilization via polyol/AR and hexosamine pathways; 3) increased AGE formation and signalling via the receptor for AGE (RAGE); 4) mitochondrial oxidative stress;

5) activation of PKC. Prepared review (initial draft is being circulated among co-authors) focuses on the mechanisms of DM-dependent alterations in monocyte/macrophage biology and their consequences for accelerated atherosclerosis in DM.

HbA1c is a well-established marker for assessing the metabolic control in diabetic patients. In the DCCT/EDIC study, HbA1c could, however, explain a small fraction of the increased risk of complications in DM[5]. These results highlight the dramatic and long-lasting effects that short-term hyperglycemic spikes can have and suggest that transient spikes of hyperglycemia may be an HbA1c-independent risk factor for diabetic complications. Indeed, transient hyperglycemia induces long-lasting activating epigenetic changes in the promoter of the nuclear factor NF-kB subunit, which cause increased p65 gene expression[6]. Hyperglycemia-associated biochemical alterations affect the lipid metabolism in plaque macrophages. In diabetic atherosclerotic lesions macrophages are characterized by AGE/RAGE-, ROS-, and PKC-dependent increased expression of CD36 and SR-A[7],[8],[9]. Macrophages with characteristic insulin resistance also show significant up-regulation of CD36 and SR-A with subsequent increased uptake of modified LDL[10],[11], the effect being also the consequence of hyperglycemia-related alterations[12]. Increased signalling through these so-called pattern recognition receptors (CD36 and SRA) may play an additive effect to by lipid overload-induced endoplasmic reticulum (ER) stress[10] and, therefore, amplify the macrophage apoptosis in atherosclerotic lesions in DM.

CD36 is a critical molecule regulating cholesterol uptake and thereby contributing to atherogenesis. Its up-regulation by hyperglycemia is documented. The host group led by Prof. G. Lip has recently described morphological monocyte diversity[13]. The functional consequences of it largely remain to be elucidated. During visit to the Haemostasis Thrombosis & Vascular Biology Unit at University of Birmingham we aimed to investigate whether acute hyperglycemia affects monocyte subset numbers and CD36 expression in otherwise healthy individuals. Acute hyperglycemia has been modelled by oral glucose

tolerance test. Acute hyperglycemia led to particular changes in monocyte subsets and total monocyte count as well as CD36 expression at particular time points following glucose load. The preliminary data has been summarized and the abstract has been submitted to AHA Annual Meeting 2011.

In the last decade a concept of ER stress has been developed[10]. The phenomenon is based on the continuous ER exposure to such stressors as (modified or not) free cholesterol, fatty acids and constituents of lipoproteins[14]. The processes of their oxidative and glycolitic modifications are accelerated in diabetic atherosclerotic lesions and up-take of free and modified cholesterol and lipoproteins are facilitated by DM-associated up-regulation of respective scavenger receptors, such as CD36. This subjects macrophages to chronic lipid overload and ER[15]. There are limited but convincing data that indicate how ER stress–induced macrophage apoptosis may affect the formation of lesional necrotic cores and thus clinically unstable plaques in DM. Several signalling pathways may be involved in apoptosis as a result of ER stress. ER stress-mediated Ca^{2+} influx into cytoplasm has been recently aligned with CD36 signalling[16].

This visit made possible by ESC First Contact Initiative Grant to Dr. Vadim Tchaikovski has triggered collaboration between Department of Cardiology, Angiology and Pulmonology (University of Magdeburg) and University of Birmingham Centre for Cardiovascular Sciences in the area of disease-oriented monocyte biology. The future work will be focused to further elucidate the mechanisms of monocyte/macrophage-mediated accelerated atherosclerosis in DM.

References

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