T lymphocytes contribute to Tissue Factor activation in promoting Acute Coronary Syndrome


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Introduction: For long time, vessel-wall tissue factor (TF) has been considered a major determinant of thrombosis. Acute thrombus formation on disrupted atherosclerotic plaques plays a key role during the onset of Acute Coronary Syndrome (ACS). Lesion disruption facilitates the interaction between circulating blood and pro-thrombotic stimuli which are present within the atherosclerotic lesion, such as TF. Recent studies identified a hypercoagulable state associated with an increase in circulating TF activity, leading to the concept of ‘vulnerable blood’. Certain pathological conditions, such as hyperlipidemia and diabetes, show a higher incidence of thrombotic complications. These conditions are characterized by the presence of high levels of circulating TF activity. Lately, accumulating evidence showed that activated T Lymphocytes may be involved in plaque rupture and increase TF activity.

Methods and Results: Tlymphocytes were isolated from buffy coats of healthy volunteers (control, n=12) and were stimulated with 1-metoxi-2-propilacetate (PMA)/ionomycin (P/I) and several cytokines in vitro. After stimulation, we found higher expression levels of TF, as detected by FACS, real time PCR and western blotting. Then, Tlymphocytes were treated with increasing concentration (25-50-100 µg/ml) of Low-Density Lipoproteins (LDLs) and Oxidized LDLs (OxLDLs) for 24, 48 and 72 hours. According to literature, OxLDLs induce TF expression in macrophages, endothelial and smooth muscle cells, but no data are available for Tlymphocytes. Thus, TF expression was investigated in Tlymphocytes treated with OxLDLs. TF gene expression changed in a dose-dependent manner, showing a 40 fold-increase vs non-stimulated cells, with a pick at 48 hours. TF protein expression showed the highest raise at 72 hours. Gene expression profiles of OxLDLs treated-Tlymphocytes were generated by microarray. Results were compared with data obtained from LDLs treated- and untreated-Tlymphocytes. Only genes with >2-fold increase or decrease were considered significant. Functional and network analyses of statistically significant genes were performed using Ingenuity Pathways Analysis 8.0 (IPA). IPA analysis showed that the up-regulated genes were mainly associated to inflammation and immune system pathways (IL6-, IL17-, Thrombin-, iNOS-, PKCΘ-, B Cell Activating Factor-, B cell Receptor-, 4-IBB-signalling). The results were validated by real time PCR.

Conclusions: Our data suggest that Tlymphocytes, by contributing to TF activation, may be involved in plaque rupture and the subsequent onset of ACS. In order to understand the pathways involved in ACS, the present study employed a genome-wide microarray approach to detect changes in gene expression of Tlymphocytes treated with OxLDLs. However, inflammation and immune system pathways seems to plays a crucial role in the pathophysiology of ACS and lay the basis for further development of new predictive biological markers for this pathological condition.

