HERV-W expression in immature dendritic cells and macrophages from type 2 diabetes mellitus

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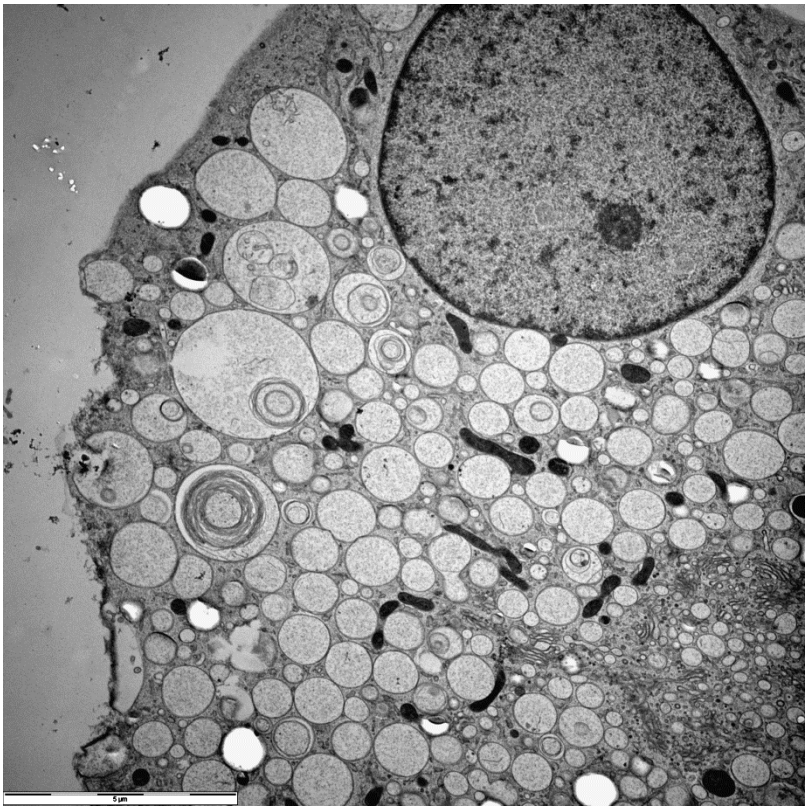
Purpose. Macrophages constitute major effectors in various inflammatory conditions. This cell type is difficult to enrich from tissues but may be recruited and studied from precursors in peripheral blood. We here asked whether immune phenotypes of cultured macrophages and immature dendritic cells isolated from patients with diabetes mellitus type 2 may give us a hint for the inducing stimulus. Human Endogenous retrovirus Type W (HERV-W) has now consistently been associated with Multiple Sclerosis through MSRV-Env expression, but may also play a role in other diseases. HERV-W env gene encodes a protein associated with systemic inflammation and neurotoxicity. Methods: Flow cytometry of whole blood was performed to characterize leukocyte subpopulations including monocytes and dendritic cells. In addition, inflammatory antigen presenting cells were enriched by in vitro culture and tested for lineage specificity, phagocytosis, and the expression of the P2X7 ion channel as well as HERV-W env. Staining was further tested by standard immune fluorescence. Summary of results: Signatures of cultured antigen presenting cells were compatible with M1 phenotypes, or a CD14-negative immature dendritic cell type, both with prominent P2X7 expression. A new subclassification of M1 phenotypes was identified on the basis of plasma membrane expression of the potassium channel Kv1.3, the complement C5a receptor (CD88), and high affinity TNF-RI (CD120a). Cultured M1 type macrophages with the highest P2X7 expression and function, as determined by ATP-inducible ion flux appear to have the strongest expression and microparticle-release of HERV-W env. Another subclassification based on the co-expression of CD14 and CD16, is often applied in freshly isolated non-cultured monocytes. These CD14/CD16 expressing monocytes, named non-classically activated monocytes are a characteristic of T2DM disease states and correspond to the immune complex-activated M2b type macrophage, which also secretes IL-1β. Cultured M2b macrophages were also positive for HERV-W env. By contrast, HERV-W env negatie cultured macrophages expressing CD163, characteristic for the M2c subtype with prominent anti-inflammatory properties and a tissue repair phenotype, were isolated from control sepsis patients. Summary: In vivo-activated antigen presenting cells mature during in vitro culture and give rise to a characteristic, patient-specific phenotype. Activation of subtypes of M1 macrophages distinguished by CD88, P2X7 and Kv1.3 as well as M2b macrophages coexpressing CD14 and CD16 were characteristic for T2DM patients with sepsis and expressed highest levels of HERV-W env, as well as HERV-W-positive microparticles. P2X7 activation appears to be crucial for microparticle release.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