



Title	Mutations in the hepatocyte nuclear factor-1 gene in southern Chinese subjects with early-onset type 2 diabetes
Author(s)	Xu, JY; Chan, VNY; Lam, KSL
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S-E-3

Patocytosis, a Cellular Process by which Macrophages Reverse Aggregated Low-Density Lipoprotein

WY Zhang,¹ I Ishii² and HS Kruth²

¹Dept. of Medicine, The University of Hong Kong, Hong Kong, ²Section of Experimental Atherosclerosis, NHLBI, NIH, Bethesda, MD USA

Background: Aggregation of low-density lipoproteins (LDL) is believed to contribute to their retention in atherosclerotic lesions. Previously, we showed that aggregated LDL (AgLDL) induces and enters surface-connected compartments (SCC) in human monocyte-derived macrophages by a process we have named patocytosis. We now show that patocytosis is also a process by which macrophages reverse AgLDL.

Method: Macrophages were loaded with AgLDL and exposed to 10% lipoprotein deficient serum (LPDS) for 1day. Disaggregation of AgLDL was verified by filtration and by electron microscopy. The factor in serum that mediated AgLDL release and disaggregation was determined using inhibitors of plasmin and plasminogen activators.

Results: Macrophages released and disaggregated AgLDL when exposed to LPDS or plasminogen. The factor in serum that mediated AgLDL release and disaggregation was plasmin generated from plasminogen by macrophage uPA. Disaggregation of AgLDL causes it to fuse forming lipid particles larger than LDL. Similar-sized disaggregated lipid particles have been observed in and isolated from atherosclerotic lesions.

Conclusion: Plasmin-mediated reversal of LDL aggregation can account for the lesion lipid particles that are larger than LDL. Also, reversal of LDL aggregation could facilitate removal of LDL aggregates from atherosclerotic lesions because efflux of lipoproteins from the vessel wall is inversely proportional to their size.

S-E-4

Mutations in the Hepatocyte Nuclear Factor-1 α Gene in Southern Chinese Subjects with Early-Onset Type 2 Diabetes

JY Xu, VNY Chan and KSL Lam

Department of Medicine, The University of Hong Kong, Hong Kong

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes classically characterized by an early age of onset (<25 years) and an autosomal dominant mode of inheritance.^[1] It has been shown that heterozygous mutations in the gene encoding transcription factor hepatocyte nuclear factor (HNF) -1 α are associated with MODY type 3.^[2,3] To investigate the contribution of mutations in the HNF-1 α gene to early-onset type 2 diabetes with a positive family history of diabetes in Southern Chinese, we have collected 102 families with at least 2 closely related members have type 2 diabetes, and at least one was diagnosed at \leq 30 years of age. The 10 exons, flanking introns and promoter region have been amplified by polymerase chain reaction using specific primers [3] and sequenced directly. In the first 29 families studied, 4 (13.8%) mutations have been identified. These included 3 reported mutations (frameshift mutation Pro379fsdelCT, nonsense mutation R171X, and missense mutation G20R) and one novel missense mutation (P112L), which was not detected in 100 unrelated subjects with normal glucose tolerance. All 4 mutations are located in highly conserved regions of the HNF-1 α gene. In conclusion, mutations in the HNF-1 α gene appear to be an important cause of early-onset type 2 diabetes in Southern Chinese.

References

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