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Electronegative LDL and Beta-Amyloid Synergistically Induce Platelet Activation that Can Be Inhibited by Novel MicroRNA-145 and NF- κ B Decoys

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Abstract:

Background: In addition to its role in Alzheimer's disease, β -amyloid ($A\beta$) stimulates platelet aggregation by activating NF- κ B. L5, a highly electronegative atherogenic subfraction of low-density lipoprotein (LDL), also induces platelet activation. Our preliminary experiments showed that $A\beta$ and L5 function synergistically; thus, we examined the underlying mechanisms and tested a novel therapeutic approach using oligodeoxynucleotide (ODN) decoys.

Methods and Results: Human plasma LDL was separated into 5 subfractions, L1-L5, with increasing electronegativity. L5, but not L1-L4, induced human platelets to release $A\beta$ from α -granules. By phosphorylating I κ B kinase β (IKK β), both L5 and $A\beta$ induced degradation of kappa B inhibitor (I κ B α) to activate NF- κ B. This led to, by way of c-Jun N-terminal kinase (JNK), the activation of platelet receptor GPIIb/IIIa and platelet aggregation. L5- and $A\beta$ -induced I κ B α degradation was inhibited by ubiquitin-specific peptidase 31 through deubiquitination, which was in turn inhibited by microRNA (miR)-145. However, a specific miR-145 decoy ODN prevented I κ B α degradation by inhibiting miR-145 (Figure), whereas scramble ODN had no effect. Furthermore, a specific NF- κ B decoy prevented NF- κ B-mediated GPIIb/IIIa activation (Figure). Compared to L1, L5 injected into C57/BL6 mice (5 mg/kg of each twice a week for 6 weeks) shortened tail-bleeding time by 38% ($n=6$; $P<0.05$), which was prevented by NF- κ B decoy but not scramble ODN.

Conclusions: Atherogenic L5 LDL potentiates $A\beta$ -mediated platelet activation and aggregation. Novel miR-145 and NF- κ B decoys effectively blocked the synergistic effect of L5 and $A\beta$ and may reduce the risk for thrombotic stroke.

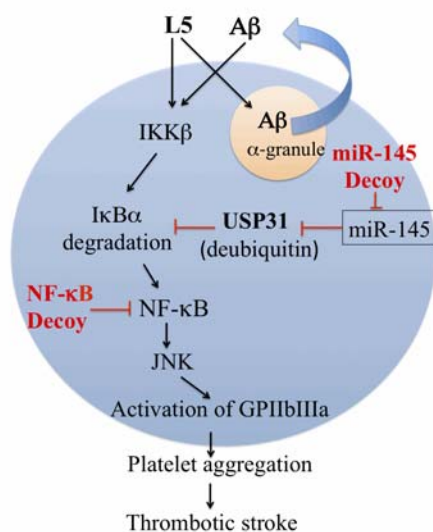


Figure. A working model for L5-potentiated platelet activation induced by $A\beta$. Black arrow, stimulation; red line with end bar, inhibition; blue arrow, direction. $A\beta$, beta-amyloid; miR-145, microRNA-145; JNK, c-Jun N-terminal kinase; USP31, ubiquitin-specific peptidase 31.

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