2.The role of the LncRNA-FA2H-2-MLKL pathway in atherosclerosis by regulation of autophagy flux and inflammation through mTOR-dependent signaling

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文章简介

动脉粥样硬化是一种慢性炎症反应性疾病。王前教授团队为揭示 lncRNA 与动脉粥样硬化的相关性，采用基因芯片检测 ox-LDL 刺激前后 THP-1 细胞差异表达 lncRNA，发现 lncRNA-FA2H-2 在 ox-LDL 刺激组中表达水平降低，生物信息学分析提示混合连接激酶结构域样蛋白（MLKL）可能受 lncRNA-FA2H-2 调控。体外实验沉默了 lncRNA-FA2H-2 及过表达 MLKL 可以促进炎症反应，抑制自噬流；而同时沉默 lncRNA-FA2H-2 及过表达 MLKL 可以增强 ox-LDL 诱导的炎症反应；另外，3-甲基腺嘌呤（PI3K 抑制剂）及自噬基因 Atg7 沉默后可以增强沉默 lncRNA-FA2H-2 及过表达 MLKL 所引起的炎症反应；结果证实 MLKL 可能通过靶向 mTOR 依赖的信号通路影响自噬过程。此外，通过 apoE 基因敲除的小鼠动脉粥样硬化模型证实 lncRNA-FA2H-2 敲除后可降低微管相关蛋白 1 轻链 3II 及溶酶体相关膜蛋白 1 的表达，但是可增加斑块中选择性自噬接头蛋白 p62、MLKL、血管细胞粘附分子 1、单核细胞趋化蛋白 1 及白介素 6 的表达。这些结果提示 lncRNA-FA2H-2-MLKL 通路在自噬及炎症反应中起着关键作用，lncRNA-FA2H-2 及 MLKL 可能为动脉粥样硬化疾病的治疗靶点。

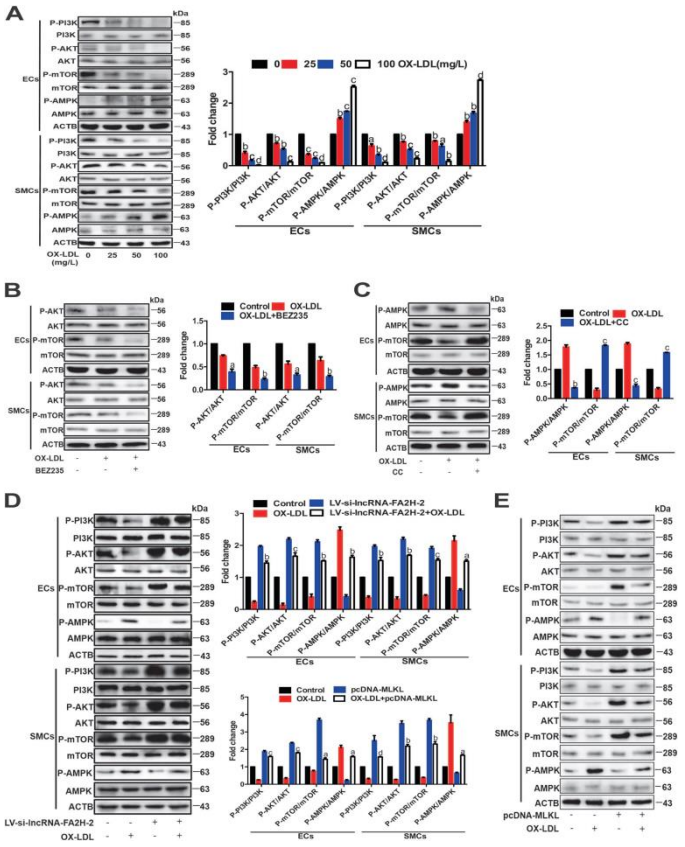

Fig. The lncRNA-FA2H-2-MLKL was associated with the mTOR dependent signaling pathway upon OX-LDL exposure. a ECs and SMCs were treated with OX-LDL (0, 25, 50, and 100mg/L) for 24h. Total and phosphorylation levels of PI3K, AKT, mTOR, and AMPK were determined by western blotting. aP<0.05, bP<0.01, cP<0.001, and dP<0.0001 versus the 0mg/L group. b ECs and SMCs were pretreated with PI3K inhibitor (1 μm BEZ235) for 72h before OX-LDL (50mg/L) for 24h. Total and phosphorylated levels of AKT and mTOR were measured by western blotting. aP<0.05, bP<0.01 versus treatment with OX-LDL alone. c ECs and SMCs were pretreated with AMPK inhibitor (5μm Compound C) for 1h before OXLDL (50mg/L) for 24h. Total and phosphorylation levels of AMPK and mTOR were measured by western blotting. bP<0.01, cP<0.001 versus treatment with OX-LDL alone. d ECs and SMCs were pretreated with LV-si-lncRNA-FA2H-2 before OX-LDL (50mg/L) for 24h. Total and phosphorylated levels of PI3K, AKT, AMPK, and mTOR were detected by western blotting. aP<0.05, bP<0.01, and cP<0.001 versus treatment with OX-LDL alone. e ECs and SMCs were treated with pcDNA-MLKL before OX-LDL (50mg/L) for 24h. Total and phosphorylation levels of PI3K, AKT, mTOR, and AMPK were determined by western blotting. aP<0.05, bP<0.01, cP<0.001, and dP<0.0001 versus treatment with OX-LDL alone. All values are expressed as mean±SD (n=3).