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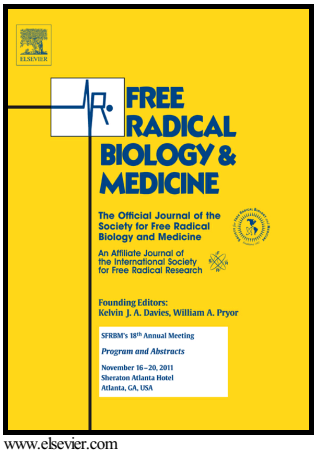

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Cholesterol crystals increase vascular permeability by inactivating SHP2 and disrupting adherens junctions

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ABSTRACT

To understand the adverse effects of cholesterol crystals on vascular homeostasis, we have studied their effects on endothelial barrier function. Cholesterol crystals increased endothelial barrier permeability in a dose and time dependent manner. In addition, cholesterol crystals induced tyrosine phosphorylation of VE-cadherin and α-catenin, disrupting endothelial AJ and its barrier function and these effects required xanthine oxidase-mediated H_2O_2 production, SHP2 inactivation and Frk activation. Similarly, feeding C57BL/6 mice with cholesterol-rich diet increased xanthine oxidase expression, H_2O_2 production, SHP2 inactivation and Frk activation leading to enhanced tyrosine phosphorylation of VE-cadherin and α-catenin, thereby disrupting endothelial AJ and increasing vascular permeability. Resolvin D1, a specialized proresolving mediator, prevented all these adverse effects of cholesterol crystals and cholesterol-rich diet in endothelial cells and mice, respectively. Based on these observations, it is likely that cholesterol crystals via disrupting AJ increase vascular permeability, a critical event of endothelial dysfunction and specialized proresolving mediators such as Resolvin D1 exert protection against these effects.

Graphical abstract