Regulation of Atherosclerosis by Calpain Proteolytic Systems

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Vascular inflammation in atheroprone vessels propagates throughout the arterial tree in dyslipidemic patients, thereby accelerating atherosclerotic progression. To elucidate the mechanism of vascular inflammation, most previous studies have focused on inflammation-related signals that are sent in response to vasoactive stimuli. However, it is also important to understand how normal blood vessels become defective and start degenerating. Growing evidence suggests that major protein catabolism pathways, including ubiquitin-proteasome and autophagy, are disturbed in atheroprone vessels and contribute to the pathogenesis of atherosclerosis. We previously identified the proatherogenic roles of calpain proteolytic systems. Calpains are stress-inducible intracellular proteases, and regulate variety of cellular functions (eg. cell motility, inflammatory responses) through limited proteolytic cleavage. For instances, overactivation of calpain-2 in vascular endothelial cells leads to proteolytic cleavage of VE-cadherin thereby inducing proatherogenic vascular endothelial hyperpermeability (Miyazaki T *et al.*, Circulation. 2011). Moreover, contribution of non-proteolytic calpain-6 to the conversion of macrophages into atheroprone phenotypes has been recently manifested (Miyazaki T *et al.*, J Clin Invest. 2016). In this presentation, I will discuss the current understanding of how those systems potentiate atherosclerotic diseases.

[Related articles]

- **Miyazaki T**, Miyazaki A. Defective protein catabolism in atherosclerotic vascular inflammation. **Front Cardiovasc Med.** 2017;4:79. [Please visit Frontier's Research topic: New Trends in Vascular Inflammation Research: From Biology to Therapy]
- **Miyazaki T.** *et al.* Calpain-6 confers atherogenicity to macrophages by dysregulating pre-mRNA splicing. **J Clin Invest**. 2016;126:3417-3432.
- **Miyazaki T**. *et al.* m-Calpain induction in vascular endothelial cells on human and mouse atheromas and its roles in VE-cadherin disorganization and atherosclerosis. **Circulation**. 2011;124:2522-2532.