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Epigenetic Regulation of Vascular Calcification

Hyun Kook
Chonnam National University, Korea

Calcium deposition to vascular smooth muscle matrix, vascular calcification (VC), makes the vessels rigid, which results in the increase in the morbidity and mortality of the patients with cardiovascular diseases or renal diseases. Previously, we suggested that histone deacetylase (HDAC) 1 prevents VC, whereas its E3 ligase, mouse double minute 2 homolog (MDM2) exaggerates it by inducing the polyubiquitination of HDAC1 (Nat Comm 7: 10491, 2016). In the current presentation, we will discuss the mechanism of two main epigenetic regulators of histone deacetylase and non-coding RNA. Our group further extended the previous results whether MDM2-induced VC is dependent on its ubiquitination activity by utilizing cellular or animal models with genetically engineered mice. We observed that vascular smooth muscle cell-specific conditional knockout of Mdm2 blunted the vitamin D3-induced vascular calcification. We generated both MDM2 Y489A that lacks ubiquitination activity and MDM2 ΔR, a RING domain-deleted truncated mutant. Compared with wild type (WT), the HDAC1-ubiquitination activities of MDM2 of both Y489A and ΔR were significantly reduced. WT potentiated inorganic phosphate (Pi)-induced VC by inducing runt-related transcription factor 2 (Runx2), whereas Y489A and ΔR failed to do so. We generated three different transgenic lines to overexpress WT, Y489A, and ΔR. TgMDM2 WT elicited calcium deposition, while TgMDM2 Y489A or TgMDM2 ΔR failed to do so. As an alternative key epigenetic regulator, non-coding RNAs are under extensive investigation in association with VC. By RNA sequencing, we found some candidate circular and long non-coding RNAs that are expected to affect the VC, which will be dealt in the presentation in detail. Taken together, the epigenetic regulation of both HDAC1 and non-coding RNA participate in the development of VC, which will be novel therapeutic targets of the diseases.