Antagonistic effect of magnesium hydroxide nanoparticle on vascular endothelial activation induced by acidic PLGA degradation product

Kyoung-Won Ko, Dong Keun Han
CHA university, Republic of Korea.

Statement of Purpose: Although drug-eluting stent (DES) is mainly coated with biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and poly(D,L-lactic acid) (PDLLA), their acidic degradation products can alter the local microenvironment and affect homeostasis of adjacent tissue. Previously, we developed anti-inflammatory PLGA-based materials including magnesium hydroxide (MH) to relieve the side effects caused by PLGA degradation [1, 2]. However, the underlying molecular mechanism of its protective effects has not yet been clarified. Here, we demonstrated the pathological mechanism of vascular endothelial activation caused by PLGA byproducts.

Methods: To validate the effect of the acidic environment following the degradation of PLGA, the *in vivo* pH change of tissues around the implanted films was measured directly using a pH microelectrode. To verify the pathological mechanism, vascular endothelial activation evaluated by addition of PLGA byproducts to mimic an acidic pH environment, and protective molecular mechanism of MH, using various molecular biological tools *in vitro*.

Results: To mimic the acidification caused by the degradation of PLGA *in vivo*, we first assessed directly the pH changes at two weeks after implantation of PLGA or PLGA/MH films. The tissue surrounding implanted PLGA film was acidified to pH 6.5 or below but was above pH 7 in the PLGA/MH group. The accumulation of PLGA degradation products reduces the pH inside of the PLGA-based materials; local pH values between 1.5 and 4.7 have been reported. However, a variety of buffering systems permit bodily fluids to maintain a narrow pH range *in vivo*. Based on this, we selected the concentration of PLGA byproducts at pH 6.5 for further *in vitro* analysis. The PLGA byproducts accumulated in human coronary artery endothelial cells (HCAECs) through the MCT1, followed by oxidative stress and the activation of the MAPKs/NF-κB signaling pathway. Finally, the PLGA byproducts increased the expression of VCAM-1 as well as the secretion of pro-inflammatory cytokines. On the other hand, the addition of MH nanoparticles significantly diminished the activation of this molecular pathway and the expression of inflammation-related factors induced by acidic PLGA degradation products. Furthermore, Mg^{2+} released from MH nanoparticles restored endothelial function in both intracellular and extracellular space. Taken together, MH nanoparticles prevents the accumulation of PLGA degradation products in HCAECs, thereby repressing the associated vascular endothelial activation.

Conclusions: We provide intriguing clues into the molecular mechanism of endothelial activation induced by acidic PLGA degradation products. PLGA degradation products accumulated in endothelial cells through MCT1, produced abnormal intracellular radical oxygen species (ROS) generation, and activated the MAPKs/NF-κB signaling pathway, which lead to augmented induction of inflammation-related factors. However, the addition of MH particles in PLGA composite effectively prevents PLGA-induced pathological responses.

Our findings propose that hydroxide ions released from MH can attenuate the unidirectional proton-linked transport of degradation products of PLGA across the plasma membrane of HCAECs. Furthermore, Mg^{2+} released from MH directly affects the function of cultured endothelial cells, which play a crucial role in maintaining the functional integrity of the vascular wall in both intracellular and extracellular spaces. Accordingly, our results suggest that the addition of MH to a functional DES coated with PLGA can prevent the cellular stress responses against degradation products of PLGA and improve endothelial function. This concept is expected to be applicable to implants and medical devices using almost all biodegradable polymers.

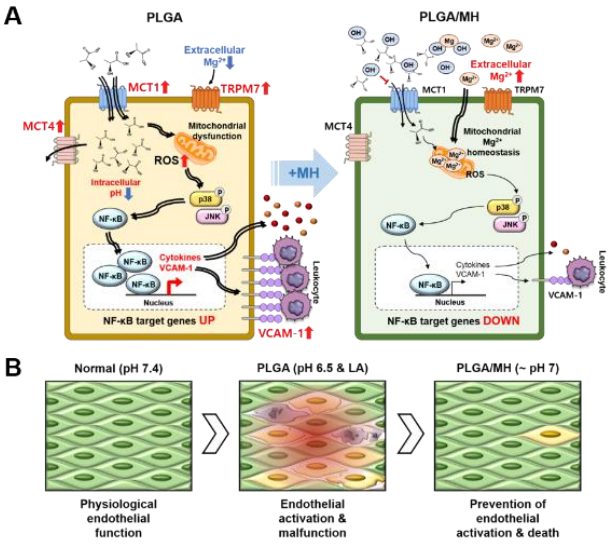

Figure 1. Schematic illustration of the effect of MH on PLGA-induced endothelial activation.

References: [1] E. Lih, ACS nano 2018, 24;12(7):6917-6925. [2] Jeong, D. W., Biomater. Sci. 2019, 7(6): 2499-2510.