Globotriaosylceramide Induces Endothelial Dysfunction in Fabry Disease

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The endothelium critically regulates the contractile status of the vascular smooth muscle cells.\(^{1}\) Dysfunction of endothelial cells (ECs) induces the increased expression of adhesion molecules for inflammatory cells.\(^{2}\) Inflammatory cell migration and vascular inflammation generate an oxidizing environment. The accumulating inflammatory cells produce abundant reactive oxygen species (ROS) and secrete inflammatory cytokines/chemokines and growth factors that contribute to EC dysfunction and vascular smooth muscle cell proliferation.\(^{3}\) Therefore, oxidants were once principally considered agents of vascular injury and disease, and numerous studies have corroborated this role for ROS. However, this has become an outdated theory considering recent evidence suggesting that hydrogen peroxide (H\(_2\)O\(_2\)) also serves as an important signaling molecule in the vascular system when found at low concentrations.\(^{4}\) At low concentrations, H\(_2\)O\(_2\) can act as a second messenger, transducing the oxidative signal into a biological response through post-translational protein modification. These structural changes ultimately lead to altered cellular function.

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Oxygen derivatives, including superoxide (O\(_2^-\)), H\(_2\)O\(_2\), and hydroxyl radical (OH), are called ROS. Strictly controlled ROS formation mediates the physiological functions of the vasculature. Therefore, ROS contribute to vascular protection as well as vascular diseases. Vascular ECs themselves produce small amounts of O\(_2^-\) and H\(_2\)O\(_2\), which play a crucial role in EC protection under physiological conditions.\(^{5,6}\) EC-dependent relaxation is mediated primarily by prostacyclin, nitric oxide (NO), and endothelium-derived hyperpolarizing factors (EDHFs). We and others have demonstrated that H\(_2\)O\(_2\) acts as an EDHF that contributes as a signaling molecule in the vasculature and protects EC function.\(^{5,7}\) Furthermore, the authors demonstrated that H\(_2\)O\(_2\) is a signaling molecule in the vasculature and protects EC function.

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by Rab5C knockdown leads to the recovery of Gb3-induced endothelial dysfunction. Thus, the authors demonstrated that Gb3-induced KCa3.1 degradation played a crucial role in endothelial dysfunction in a mouse model of Fabry disease and in Fabry disease in humans. Because of these findings, the authors proposed a novel mechanism underlying Gb3-mediated EC dysfunction, which is associated with the suppression of EDHF.

**Clinical Perspectives**

Physiological ROS levels are important in the regulation of EC function. The involvement of EC dysfunction in all stages of vascular diseases is generally accepted. Importantly, Choi et al. demonstrated that Gb3 significantly attenuates the activities of endothelial KCa3.1. However, several issues remain regarding the interpretation of this study. First, in the present study, among major glycosphingolipids, only Gb3 was confirmed to attenuate KCa3.1 activity in EC. Second, although the authors derived results by using primary cultured mouse aortic ECs and human umbilical vein ECs, the endothelial response varies according to blood vessel type. Therefore, the EC responses in smaller arteries are of interest because the contribution of EDHF is prominent, especially in microvessels rather than in large vessels.

Third, the authors did not measure the effects of Gb3 on vascular smooth muscle cell. Further studies aimed at elucidating the mechanism of Gb3-mediated vascular dysfunction will provide an important clue to the treatment of Fabry disease.

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**Disclosures**

None.

**References**


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