Plenary Lecture Abstract

New Paradigm for Chronic Inflammation Mediated by Glycosphingolipids

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Ganglioside GM3, a sialic acid containing glycosphingolipid, has been known to participate in insulin signaling by regulating the association of the insulin receptor in caveolae microdomains (lipid rafts), which is essential for the execution of the complete insulin metabolic signaling in adipocytes. Macrophage-secreted factors including proinflammatory cytokines, TNF-α and IL1-β, in adipose tissues have been known to limit the local adipogenesis and induce insulin resistance, however, the interplay between adipocytes and macrophages upon regulation of GM3 expression is not clear. GM3 was virtually absent in primary adipocytes differentiated from macrophage-depleted mesenteric stromal vesicular cells, which accompanies enhancement of insulin signaling and adipogenesis. We found that the expression of GM3 is governed by soluble factors including steady-state levels of proinflammatory cytokines secreted from resident macrophages. The direct involvement of GM3 in insulin signaling is demonstrated by the fact that embryonic fibroblasts obtained from GM3 synthase (GM3S) deficient mice have increased insulin signaling, when compared to wild type embryonic fibroblasts, which in turn leads to enhanced adipogeneis. In addition, GM3 expression in primary adipocytes is increased under proinflammatory conditions as well as in adipose tissue of diet-induced obese mice. Moreover, GM3S deficient mice fed high fat diets become obese but are resistant to the development of insulin resistance and chronic low-grade inflammatory states. Thus, GM3 functions as a physiological regulatory factor of the balance between homeostatic and pathological states in adipocytes by modulating insulin signaling in lipid rafts. Furthermore, we have identified the significant increases of GM3 molecular species possessing pro- inflammatory actions through TLR4. Collectively, we propose a novel inflammation amplification loop triggered by GM3 molecular species.