Malfunction of Microdomains in the Development of Type2 Diabetes and Insulin Resistance

Jin-ichi Inokuchi (Grad. Sch. Pharm.Ssci. Hokkaido University)

Membrane microdomains (lipid rafts) are now recognized as critical for proper compartmentalization of insulin signaling. We demonstrated previously that in the state of insulin resistance of adipocytes induced by TNF□, the inhibition of insulin metabolic signaling (1) and elimination of insulin receptor (IR) from the caveolae microdomains was caused the accumulation of ganglioside GM3 (2). The selective and significant increase of GM3 in adipose tissues from *ob/ob* mice and Zucker *fa/fa* rats were demonstrated. To insight into the molecular interaction of IR, caveolin-1 and GM3, here we examined the affinity of these molecules by immunoprecipitation and perfomed live cell imaging utilizing FRAP (fluorescence recovery after photobleaching, and found that IR forms complex with caveolin-1 and GM3 independently, and in the GM3 enriched membranes, the mobility of IR was increased by dissociating IR-caveolin interaction. Thus, we propose a new pathological feature of insulin resistance in adipocytes caused by dissociation of IR-caveolin-1 complex by GM3 in microdomains.

(1) Tagami, S. et al., *J. Biol. Chem.* 277, 3085 (2002)
(2) Kabayama. K., et al., *Glycobiology* 15, 21 (2005)