Insulin Resistance in Adipocyte as a Membrane Microdomain Disorder

Jin-ichi Inokuchi
(Division of Glycopathology, Institute of Molecular Biomembrane and Glycopathology,
Tohoku Pharmaceutical University)

Membrane microdomains (lipid rafts) are now recognized as critical for proper compartmentalization of insulin signaling. We previously demonstrated that in adipocytes in a state of TNFα-induced insulin resistance, the inhibition of insulin metabolic signaling and the elimination of insulin receptors (IR) from the caveolae microdomains were associated with an accumulation of the ganglioside GM3 [1, 2]. To gain insight into molecular mechanisms behind interactions of IR, caveolin-1 (Cav1) and GM3 in adipocytes, we have performed immunoprecipitations, cross-linking studies of IR and GM3, and live cell studies using total internal reflection fluorescence microscopy (TIR-FM) and fluorescence recovery after photobleaching (FRAP) techniques. We found that (*i*) IR form complexes with Cav1 and GM3 independently; (*ii*) in GM3-enriched membranes the mobility of IR is increased by dissociation of the IR-Cav1 interaction; (*iii*) the lysine residue localized just above the transmembrane domain of the IR β-subunit is essential for the interaction of IR with GM3. Since insulin metabolic signal transduction in adipocytes is known to be critically dependent on caveolae, we propose a new pathological feature of insulin resistance in adipocytes caused by dissociation of the IR-Cav1 complex by the interactions of IR with GM3 in microdomains [3].

[1] *J. Biol. Chem.***277**, 3085 (2002)
[2] *Glycobiology* **15**, 21 (2005)
[3] *Proc. Natl. Acad. Sci*. 104. 13678 (2007)