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Integrins consist of α and β subunits. Each subunit has a large extracellular region, a single transmembrane domain and a short cytoplasmic tail (except for β4 integrin). The *N*-terminal domains of the α and β subunits associate to form the integrin headpiece, which contains extracellular matrix (ECM) binding site, whereas the *C*-terminal segments transverse the plasma membrane and mediate interactions with the cytoskeleton and signaling molecules. The most general feature of integrins is that their interaction with its ligand can activate intracellular signaling pathways and cytoskeletal formation (outside-in signaling). Another important feature of integrins is inside-out signaling, in which intracellular signals received by integrins or other receptors, in turn, activate its extracellular domain and contribute to the assembly of the ECM. The role of integrins in cancer has been somewhat controversial with data suggesting tumor suppressive effects while others are in favor of an aggressive behavior. Why has the controversy occurred? One possibility may be explained by that the majority of researchers mainly focused on the expression levels of integrins only, and neglected effect of a posttranslational modification, N-glycosylation, on the integrin functions. In fact, the integrins are heavily N-glycosylated.

In this grant, we utilized cell model systems under pathological conditions, such as TGF-β-induced epithelial-to-mesenchymal transition (EMT) and overexpression of an oncogenic gene Golgi phosphoprotein 3 (GOLPH3) to examine roles of N-glycosylation on integrin-mediated signaling. We found that, 1) the expression of N-acetylglucosaminyltransferase III influenced EMT-like changes through not only E-cadherin-mediated cell-cell adhesion but also integrin-mediated cell migration (1); 2) GOLPH3 specifically up-regulated sialylation of integrin N-glycans, promotes sialylation-dependent cell migration and PI3K-AKT signaling (2). Now, we focus on effects of N-glycans of integrins on supra-complex formation, and try to clarify the underlying molecular mechanisms in cancers.

1. Roles of *N*-acetylglucosaminyltransferase III in epithelial-to-mesenchymal transition induced by TGF-β1 in epithelial cell lines. Xu, Q., Isaji, T., Lu, Y., Gu, W., Kondo, M., Fukuda, T., Du, Y. and Gu, J. *J Biol Chem.* 287:16563-74, 2012

2. An oncogenic protein Golgi phosphoprotein 3 up-regulates cell migration via sialylation. Isaji, T., Im, S., Gu, W., Wang, Y., Hang, H., Lu, J., Fukuda, T., Hashii, N., Takakura, D., Kawasaki, N., Miyoshi, H. and Gu, J. *J Biol. Chem.* in press, 2014