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Inhibition of neuraminidase-1 sialidase activity by interfering peptides impairs insulin receptor activity in vitro and glucose homeostasis in vivo

Neuraminidases also named sialidases are glycosidases which catalyze the removal of terminal sialic acid residues from glycoproteins, glycolipids and oligosaccharides. Mammalian Neuraminidase-1 (NEU-1) is involved in regulation of cell surface receptors such as insulin receptor (IR), epithelial growth factor receptor, low density lipoprotein receptor and toll like receptor 4. At the cell membrane, NEU-1 can be associated with the elastin-binding protein and the carboxypeptidase protective protein/cathepsin A to constitute the elastin receptor complex. In this complex, NEU-1 plays a key role in elastogenesis, signal transduction through this receptor and in biological effects of the elastin-derived peptides on atherosclerosis, thrombosis, insulin resistance, non-alcoholic steatohepatitis and cancers. Thus, several research teams are developing inhibitors targeting this sialidase. In a previous study, we developed interfering peptides to inhibit the dimerization and the activation of NEU-1. We then investigated the effects of these peptides on IR activation in vitro and in vivo. Using cellular overexpression and endogenous expression models of NEU-1 and IR, we have shown that interfering peptides inhibit NEU-1 dimerization and sialidase activity which results in a reduction of IR phosphorylation. These results demonstrated that NEU-1 positively regulates IR phosphorylation and activation in our experimental conditions. In vivo, biodistribution study showed that interfering peptides are well distributed in mice. Treatment of C57Bl/6 mice during eight weeks with interfering peptides induces a hyperglycemic effect in our conditions. Altogether, our results indicate that inhibition of NEU-1 sialidase activity by interfering peptides decreases IR activity in vitro and glucose homeostasis in vivo.

Keywords: Extracellular matrix, Neuraminidase-1, Insulin receptor, Interfering peptides, Receptor activation.

Biography

Prof. Amar Bennasroune is teacher-researcher in cell biology at Université de Reims Champagne-Ardenne (France) since 2015. He leads a research group within the laboratory called « Matrice extracellulaire et dynamique cellulaire » (UMR CNRS URCA 7369). His research focuses on the development of inhibitors of neuraminidase 1, a sialidase involved in various pathophysiological contexts such as atherosclerosis and insulin resistance, using several strategies as interfering peptides or natural bioactive molecules extracted from plants.

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