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Molecular characterization and design of a key new hormone, irisin

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Exercise has well-recognized beneficial effects on system metabolism. Irisin was recentlyidentified as an exercise-induced peptide hormone secreted by skeletal muscle in mice andhumans. The hormone is thought to bind to so far unidentified surface receptor on white fat cellsand induces "browning" effects that improve the tissue metabolic profile and increase wholebodyenergy expenditure. As a potential new anti-obesity and anti-diabetes target, this peptidehormone is however poorly characterized. We have successfully manufactured recombinant irisin, which provides a key reagent for detailed biochemical, biophysical, and pharmacologicalcharacterizations. Wild type irisin exists in the form of dimer in solution. Through structurebasedcomputational modelling and systematic surface mutagenesis, we have mapped out the detailed dimeric interface and engineered monomeric irisin variants. Successful manufacture of astable, monomeric, active irisin provides a novel biological for the treatment of obesity and type2 diabetes. Furthermore, we discovered a novel biological function of irisin towards pancreatic β-cells, an effect has not been reported so far. Putative membrane receptor for this hormone waslocalized to the cell surface membrane of both β-cells and adipocytes. Using a novelphotoaffinity crossing approach, we are actively pursuing to identify the cell surface membranereceptor through which the hormone functions. Our work provided an excellent example of theutility of structure-based and computer aided design for novel protein therapeutic targets.

Biography

Bin Xu received his PhD from Case Western Reserve University in 2004, followed by postdoctoral studies at Fred Hutchinson Cancer Research Center. Since 2011, he has been atenure-track Assistant Professor in the Department of Biochemistry and Center for Drug Discovery at Virginia Tech. His research interests concern cell surface receptor-ligand binding, signalling, novel receptor discovery, and translational structure-based and computer-aided liganddesign with applications to novel peptide hormone-receptor recognition, nutrient-sensing GPCRs, and immunoreceptors - viral ligands host-pathogen interactions relevant to diabetes, obesity, and infectious diseases. He has published more than two dozen publications in premierinternational peer-reviewed journals.

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