Review of: "Determinants of IGF-II influencing stability, receptor binding and activation"

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Over the past 3-4 years, great progress has been made in studying the structural biology of the insulin receptor family, which consists of three receptors: insulin receptor (IR), insulin-like growth factor 1 receptor (IGF-IR) and insulin receptor-related receptor (IRR). There are several structures of the the complexes of the insulin receptor with insulin, the insulin-like growth factor receptor with insulin, Insulin like growth factor I (IGF-I), and Insulin like growth factor II (IGF-II). Also, the first structural data on the IRR receptor have been obtained recently.

The authors of this article focused on elucidating the molecular details of the interaction of IGF-II with the IR and IGF-IR. IGF-II and insulin are highly homologous, and it is well known that IGF-II is involved in regulation of development and embryonic growth. Moreover, IGF-II is overexpressed in many types of cancer. Therefore, elucidation of the details of its interaction with receptors is, of course, an important task for the development of inhibitors or antagonists of IGF-II action. The authors of this publication have demonstrated using mutagenesis the role of the residue Q18 in IGF-2 for binding to receptors, as well as for the ability to activate intracellular signaling proteins and DNA synthesis in cells. To understand the roles of IGF-II residue Q18 three IGF-II mutants were produced: Q18I IGF-II, Q18M IGF-II and Q18Y IGF-II. Mutant Q18Y of IGF-II potentially can mimic insulin since tyrosine is located at position Q18 in insulin. All three of these substitutions have little effect on binding to the IGF-IR receptor. However, mutant Q18Y of IGF-II snows noticeable increase in binding to forms of the insulin receptor IR-A and IR-B. Whereas other mutations almost do not influence binding to IR-A and IR-B forms. Thus, the authors have showen that Q18 is involved in selectivity of IGF-1R/IR binding. Further, by treating L6 rat skeletal myoblasts cells overexpressing the human IR-A with various concentrations of these mutants, it is shown that, despite differences in binding to receptors, cellular effects, namely, activation AKT and ERK signaling and DNA synthesis, are at the level of wild-type IGF-2.

These results look a little surprising and, in our opinion, the authors of this article used an incorrect cell line to determine the effect of various IGF-II mutants on intracellular signaling. It is known that L6 cells mainly express the IGF-IR receptor and authors used these cells with overexpression the IR-A for signaling experiments. IGF-II and IGF-II mutants have higher affinity to IGF-IR receptor. In this case, the absence of any significant difference in the activation of intracellular proteins is apparently explained by the fact that this effect is mainly due to the activation of the IGF-IR receptor in these cells. The authors should first obtain a L6 cell line with a knockout of the IGF-IR receptor and only then express the insulin receptor in these cells. In this case, probably, the effect of the action of IGF-II mutants would be much more noticeable.