The role of insulin receptor isoforms in selective insulin signaling in pancreatic beta cell physiology/pathology

**Supervisor:** Ingo Leibiger

**Department:** Dept. of Molecular Medicine and Surgery

**Background:** The development of type 2 diabetes mellitus (T2DM) has reached pandemic proportions and, to be successfully stopped requires new approaches of treatment. The following novel insights from research over the last decade have to be considered. Firstly, GWAS revealed more than 40 candidate genes, most of them potentially linked with pancreatic islet/beta cell function, thus pinpointing the importance of an intact integrated signal-transduction for proper function and survival of the beta cell. Secondly, research initiated by us (1) and since then performed in many laboratories provides clear evidence that besides liver, muscle and fat, the pancreatic beta cell itself is a target for insulin at the level of gene expression, glucose metabolism, insulin secretion, cell survival and proliferation (2). Consequently, insulin resistance at the level of the beta cell will cause/contribute to beta cell dysfunction. Thirdly, the biological relevance of the two insulin receptor (IR) isoforms IR-A and IR-B in selective insulin signaling remained elusive until 2001 when we showed that the insulin gene is activated by signaling via IR-A while the glucokinase gene is activated via IR-B (3). Our research over the last ten years shows that several insulin signaling cascades that originate from the two IR isoforms co-exist in the pancreatic beta cell and are activated simultaneously, thus implying the novel concept of IR cascade-selective insulin resistance. Our data showed that provoking insulin resistance in one, metabolic signaling branch led to re-routing of the insulin signal and activation of a mitogenic branch promoting beta cell proliferation (4). Fourthly, an increasing body of evidence is suggesting a direct correlation between insulin treatment/hyperinsulinemia and cancer progression. Noteworthy, most cancer cells express exclusively IR-A, while the classical insulin target tissues liver, muscle and fat show a high degree of IR-B. Consequently, the development of IR-B-selective insulin mimetics is a potential way to improve treatment in diabetes. Lastly, direct monitoring of beta cell mass and function is complicated by the anatomy of the endocrine pancreas which consists of thousands to a million discrete micro-organs, i.e. islets of Langerhans, which are scattered throughout the pancreas. We have developed an imaging approach that allows monitoring pancreatic islet function and survival non-invasively, longitudinally at single-cell resolution in the living animal (5). We transplant isolated islets into the anterior chamber of the mouse eye (ACE), were they engraft on the iris and become innervated and vascularized. By using the cornea as a natural body-window these islets are readily available for functional microscopic imaging. Our data showed that islets engrafted in the ACE serve as reporters for in situ endogenous islets in the same animal (6-8). The below outlined two sub-projects address these exciting developments. The two major **objectives** of this project are: 1) To investigate the molecular mechanisms and dynamics of beta cell insulin resistance. 2) To identify aptamers that activate and inhibit signaling in an IR isoform-selective manner.
Methodology and work plan. Sub-project 1. Molecular mechanisms and dynamics of beta cell insulin resistance we will study by using a novel by us developed technique that allows in vivo monitoring of beta cell insulin resistance in parallel to whole body and liver insulin resistance (8). We will address i) under what pre-diabetic conditions beta cell insulin resistance is responsible for the development and/or progression of beta cell dysfunction and to what extent dysregulation in beta cell Ca^{2+}-handling contributes to beta cell insulin resistance, ii) whether beta cell insulin resistance is occurring in parallel or as a consequence of insulin resistance in peripheral tissues (liver, muscle, fat); iii) address the role of IR isoforms and proteins involved in insulin signaling in the development of beta cell insulin resistance. Using this approach of online monitoring of the development and progression of beta cell insulin resistance will allow the identification of critical time points in the development of pancreatic beta cell failure, such as onset of dysfunction, progression of failure and exhaustion of beta cell function (de-differentiation, trans-differentiation, beta cell death). Obtaining beta cells at these critical time points and subjecting them to transcriptomic, epigenetic, proteomic analysis and kinase/phosphatase activity profiling using bioinformatics will allow the identification of novel targets for treatment as well as the design of novel treatment strategies in T2DM. Sub-project 2. Aptamers that activate and inhibit signaling in an IR isoform-selective manner. We will identify aptamers that i) can be used as tools to study the biological significance of the two insulin receptor isoforms, and that ii) can serve as lead-compounds for the development of IR-B-selective insulin mimetics that will not allow cancer progression in the treatment of diabetes. This in combination with the by us developed ACE in vivo imaging platform will lay ground for establishing an in vivo screening/validation platform for novel drugs and treatment strategies in T2DM to be used by academia and pharma-industry.

References:

Contact details:
Ingo Leibiger, MD/PhD, Associate Professor
The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet,
Department of Molecular Medicine and Surgery
Email: ingo.leibiger@ki.se
Phone: +46 8 5177 5725
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