ID: MSCA-19-Heimberg03

Discipline: Medicine and Pharmacy

Title: Sexual dimorphism in beta cell function and dysfunction

Abstract: Unraveling the genetic and molecular mechanisms governing normal beta cell biology and beta cell dysfunction is essential to develop novel approaches for the treatment of diabetes. Surprisingly, most beta cell research has primarily focused on male adults, leading to a bias in our knowledge of beta cell biology and possibly ignoring important sex differences with implications for therapy and prevention of diabetes.

Despite the male-bias in research data, available evidence suggests a clear effect of sex on the prevalence of diabetes (7.9% in women and 10.2% in males). Part of this sexual dimorphism can be explained by the differences in beta cell function and susceptibility to beta cell failure in male and female. In studies of both human and rodent islets it was shown that female beta cells have increased insulin secretion in response to glucose load. Glucose-stimulated insulin secretion decreases with age, but remains higher in females compared to males, due to higher mitochondrial biogenesis and function in the female islets. In addition, female beta cells are more resistant to apoptosis induced by pro-inflammatory cytokines, a hallmark of type 1 diabetes (T1D) and a likely reason why T1D is the only auto-immune disease with a male predominance. This phenomenon can be attributed to the protective role of estrogen which acts via estrogen receptor alpha (ERα) on beta cells. Estrogen and estrogen receptor have also been implicated in sexually dimorphic beta cell proliferation in the mouse pancreas. We showed that estrogen signaling via estrogen receptor alpha (ERα) on beta cells is required for increased beta cell proliferation observed in a model of acute pancreatitis and during pancreas development. Moreover, basal beta cell proliferation in normal female pancreas is 2.5-fold higher compared to male beta cell proliferation. These differences in basal proliferation and the role of ERα therein can possibly explain the gender associated differences in compensatory mechanism of beta cells under conditions of increased metabolic demand or stress.

The present project is based on the suggestion that beta cell function may be regulated in a sex-specific manner. Using mice and human cells, we aim to identify sexual dimorphic regulation of beta cells by characterization of (i) sex-specific differences in beta cell gene expression and (ii) the impact of gender-biased genes and signaling pathways on sexually dimorphic responses to anti-diabetic treatments.

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