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In Vivo T-Type Ca2+ channel inhibition facilitates maturation of Glucose-Dependent Ca2+ signaling in human iPSC-Derived islets

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T-type Ca2+ channels operate in embryonic stem cells, but conduct relatively small Ca2+ currents in mature human β cells. In certain pathological contexts, e.g., when T-type Ca2+ channels undergo elevated expression, they mediate exaggerated Ca2+ influx to dissipate β cell maturity. This prompted us to hypothesize that altered T-type Ca2+ channel activity in human iPSC-derived islet (hiPSC-islet) cells affect maturation. To test our hypothesis, we transplanted hiPSC-isles into the anterior chamber of the eye (ACE) of immunodeficient mice, intravitreally infused T-type Ca2+ channel blocker NNC55-0396 and performed *in vivo* and ex vivo measurements. *In vivo* stereomicroscopy showed that transplanted hiPSC-islets underwent initial adhesion to, gradual integration with and eventual engraftment as well as survival on the iris. *In vivo* confocal microscopy revealed that intracameral hiPSC-islets were satisfactorily vascularized and displayed intense light scattering signals, reflecting the abundance of zinc-insulin crystals inside insulin secretory granules, within two months post-transplantation. Furthermore, intravitreally-infused NNC55-0396 did not influence the macromorphology, vascularization and light scattering signals. Interestingly, ex vivo [Ca2+]i measurements disclosed that intravitreally-infused NNC55-0396 significantly decreased basal [Ca2+]i levels and increased glucose-stimulated [Ca2+]i responses in intact hiPSC-isles. In conclusion, the present study verifies that the immunodeficient mouse ACE can serve as a unique site for pharmacological manipulation of *in vivo* maturation of hiPSC-islets. These cells can not only be micro-imaged intravitally, noninvasively and longitudinally, but also retrieved without suffering physical and chemical disturbance for more precise ex vivo studies, as exemplified here by [Ca2+]i measurements. Importantly, our data demonstrate that inhibition of T-Type Ca2+ channels facilitates glucose-dependent Ca2+ signaling in hiPSC-islets. These findings are important and support the notion that altered T-type Ca2+ channel activity may serve as a key signal in hiPSC-islet cell maturation.

Biography

Kaixuan Zhao is a PhD candidate in Medical Science at Karolinska Institutet, Sweden. She is studying the role of voltage-gated Ca2+ channels in beta cell maturity. Her efforts have resulted in interesting publications in Proc Natl Acad Sci USA, Cell Mol Life Sci and Cell Transplantat.

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