Please cite this article in press as: Schmitz et al., Repurposing an Osteoporosis Drug for β Cell Regeneration in Diabetic Patients, Cell Metabolism (2015), http://dx.doi.org/10.1016/j.cmet.2015.05.024

Repurposing an Osteoporosis Drug for β Cell Regeneration in Diabetic Patients

Felizitas Schmitz,[1] Sara Roscioni,[1] and Heiko Lickert[1,2,*]
[1]Institute of Diabetes and Regeneration Research
[2]Institute of Stem Cell Research
Helmholtz Center Munich, Am Parkring 11, 85748 Garching, Germany
*Correspondence: heiko.lickert@helmholtz-muenchen.de
http://dx.doi.org/10.1016/j.cmet.2015.05.024

Replenishing the lost or dysfunctional insulin-producing β cell mass in diabetic patients could slow down or reverse disease progression. Kondegowda et al. (2015) now show that osteoprotegerin and denosumab, inhibitors of the receptor activator of the NF-κB Ligand (RANKL) pathway and osteoclast activation, stimulate human β cell proliferation and therefore possess therapeutic potential.

Type 1 and type 2 diabetes (T1D and T2D) result from autoimmune destruction or loss of functional β cell mass, respectively. Daily insulin injections or current pharmacological treatment do not fully substitute for β cell loss to prevent uncontrolled hyperglycemia and the devastating secondary complications associated with both forms of diabetes. The Joslin Medalist Study demonstrated that even after 50 years of insulin-dependent diabetes, β cells persist and are functional (Keenan et al., 2010). Hence, strategies that trigger endogenous β cell replication or regeneration have great therapeutic value.

Despite the slow turnover of β cells, β cell mass can be expanded upon metabolic demand during pregnancy by the action of lactogenic hormones (Rieck and Kaestner, 2010). Osteoprotegerin (OPG) is upregulated in pregnant mice (Rieck et al., 2009), a finding confirmed in the study of Kondegowda et al. published in *Cell Metabolism*. Additionally, OPG was upregulated in other mouse models associated with increased β cell expansion, pointing at OPG as universal mediator of β cell proliferation (Rieck et al., 2009). OPG acts as soluble decoy receptor and binds to RANKL and TNF-related apoptosis-inducing ligand (TRAIL) receptors RANK and death receptor (DR), respectively, to block their binding (Walsh and Choi, 2014) (Figure 1). The FDA-approved drug and humanized monoclonal antibody denosumab (DMB) binds to human RANKL and inhibits RANK receptor interaction similarly to OPG. Inhibition of RANK receptor blocks osteoclast differentiation and promotes bone formation for osteoporosis therapy (Miller, 2009). Kondegowda et al. show that OPG and DMB stimulate human β cell proliferation, raising the possibility that DMB might be repurposed for β cell regeneration.

Kondegowda et al. showed OPG upregulation in pancreatic islets of transgenic mice overexpressing placental lactogen in β cells compared to normal mice. They successively identified OPG as pivotal mediator of lactogen-driven β cell proliferation. Long-term OPG treatment caused significant increase in β cell proliferation and mass in young mice, and induced β cell proliferation in old mice. OPG injections rescued streptozotocin-induced β cell ablation, resulting in reduced diabetes incidence. OPG also triggered elevated β cell replication in human islet cells without causing dedifferentiation, as measured by PCR analysis of genes relevant to β cell function. Glycogen synthase kinase-3 (GSK3β) and CREB, two factors involved in β cell proliferation (Dalle et al., 2011; Wang et al., 2015), were regulated upon OPG stimulation in rodent and in human islets. A competition assay in human islet cells proved that OPG interferes with RANKL/RANK interaction, thus repressing its downstream signaling. Thus, RANK signaling puts a brake on β cell proliferation, which was confirmed in vitro in islets from the RANK lox animals. Finally, human islets transplanted under the kidney capsule of euglycemic immunodeficient mice exhibited increase β cell proliferation upon a single injection of DMB, indicating that the drug acts as a β cell proliferative trigger in a humanized mouse model.

These pre-clinical results provide important new clues on lactogenic hormone and RANK signaling in human β cell proliferation and hold promise for future clinical use. However, before this can be achieved we need to understand how these signaling pathways mechanistically act together to enhance β cell proliferation. The lactogenic hormones prolactin (PRL) and placental lactogen (PL) are elevated during pregnancy and stimulate proliferation via JAK2, STAT5A/B signaling (Wang et al., 2015) (Figure 1). However, how prolactin receptor signaling transcriptionally activates OPG expression in β cells still remains unclear and deserves further investigation. Another open question concerns the way RANK signaling regulates β cell proliferation. The authors suggest that the CREB and GSK3β mediate the effect of OPG, but the intermediate partners in this signaling cascade are still unknown. It is known that RANK receptor activates several signaling cascades that may phosphorylate and inhibit GSK3β and promote translocation and activation of CREB in other cell types (Walsh and Choi, 2014). How these pathways are modulated in β cells is unclear. Moreover, it is not clear whether GSK3β and CREB act independently to increase OPG-mediated proliferation or interact with each other. And finally, what are the downstream targets of GSK3β and CREB? On one hand, it is known that GSK3β phosphorylation results in activation of β-catenin, which in turn modulates target genes such as cyclins and cyclin-dependent kinases (Figure 1) in β cells (Rulifson et al., 2007). On the other hand, CREB

Please cite this article in press as: Schmitz et al., Repurposing an Osteoporosis Drug for β Cell Regeneration in Diabetic Patients, Cell Metabolism (2015), http://dx.doi.org/10.1016/j.cmet.2015.05.024

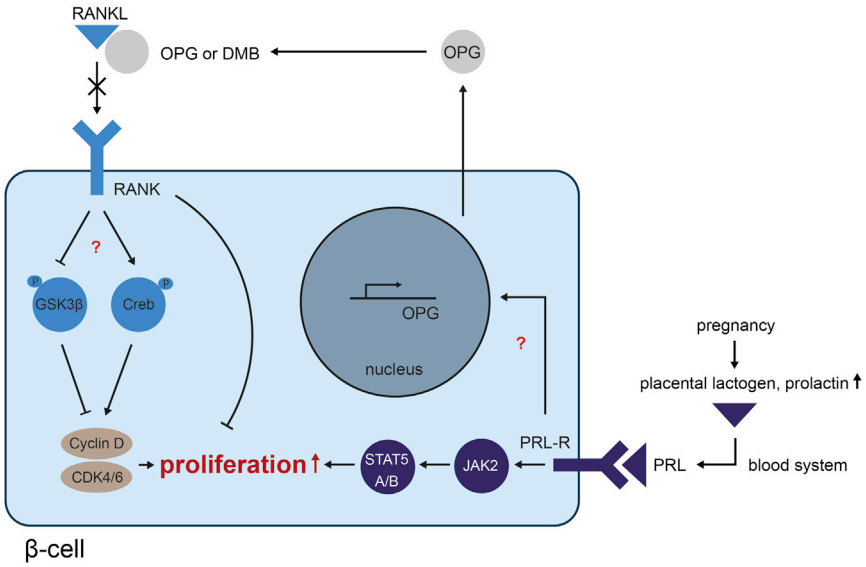

Figure 1. OPG and DMB Induce β Cell Proliferation by Inhibiting RANK/RANKL Pathway and Modulating GSK3β and CREB

β cell proliferation is enhanced during pregnancy by lactogen signaling via JAK2/STAT5A/B. A novel transcriptional target of lactogen signaling in β cells is OPG. OPG and its partial functional equivalent DMB bind RANKL and inhibit RANKL/RANK interaction, thus suppressing downstream signaling. This results in the phosphorylation of GSK3β and CREB, which in turn might trigger proliferation via activation of cyclins and CDKs.

modulates transcription of insulin and cyclins in response to glucose and incretin hormones (Dalle et al., 2011) (Figure 1). Further investigation is warranted to determine whether activation of these specific targets orchestrates the proliferative effects of OPG in β cells.

The importance of the RANK pathway was highlighted in a prospective population-based study that showed that high serum concentration of soluble RANKL was an independent risk predictor for T2D. In addition, circulating OPG emerged with or after T2D and was unrelated to T2D risk. Moreover, OPG treatment of insulin-resistant ob/ob mice caused enhanced insulin sensitivity, suggesting another positive effect of OPG (Kiechl et al., 2013). Given that DMB is an FDA-approved drug with tolerable side effects, it is worth investigating its effect on diabetic patients and the possibility of repurposing the drug. However, some limitations exist. Currently, there are no approved methods to determine β cell mass in humans. Moreover, it will also be necessary to address the question whether the 2- to 3-fold increase in β cell proliferation by OPG is sufficient to compensate for a deregulated glucose homeostasis in diabetic patients; interfering with mitogenic signaling of human β cells is difficult, and treatment of β cells with a GSK3β inhibitor only enhanced β cell proliferation from 0.17% to 0.71% (Wang et al., 2015).

Post hoc analysis from trials investigating the effect of DMB and placebo on postmenopausal women did not find significant differences in glucose homeostasis and diabetes incidence (Schwartz et al., 2013). However, these trials were not designed for this purpose. Long-term randomized placebo-controlled clinical trials with diabetic patients are needed to evaluate the efficacy of OPG or DMB to slow down the progression of diabetes or, even better, to prevent the development of this devastating disease.

The findings by Kondegowda et al. highlight a novel promising approach to stimulate β cell expansion that may pave the way for a more efficacious and less cumbersome therapeutic intervention in diabetes.

REFERENCES

Dalle, S., Quoyer, J., Varin, E., and Costes, S. (2011). Curr. Mol. Pharmacol. *4*, 187–195.

Keenan, H.A., Sun, J.K., Levine, J., Doria, A., Aiello, L.P., Eisenbarth, G., Bonner-Weir, S., and King, G.L. (2010). Diabetes *59*, 2846–2853.

Kiechl, S., Wittmann, J., Giaccari, A., Knoflach, M., Willeit, P., Bozec, A., Moschen, A.R., Muscogiuri, G., Sorice, G.P., Kireva, T., et al. (2013). Nat. Med. *19*, 358–363.

Kondegowda, N.G., Fenutria, R., Pollack, I., Orthofer, M., Garcia-Ocaña, A., Penninger, J., and Vasavada, R.C. (2015). Cell Metabolism *22*. Published online June 18, 2015. http://dx.doi.org/10.1016/j.cmet.2015.05.021.

Miller, P.D. (2009). Curr. Osteoporos. Rep. *7*, 18–22.

Rieck, S., and Kaestner, K.H. (2010). Trends Endocrinol. Metab. *21*, 151–158.

Rieck, S., White, P., Schug, J., Fox, A.J., Smirnova, O., Gao, N., Gupta, R.K., Wang, Z.V., Scherer, P.E., Keller, M.P., et al. (2009). Mol. Endocrinol. *23*, 1702–1712.

Rulifson, I.C., Karnik, S.K., Heiser, P.W., ten Berge, D., Chen, H., Gu, X., Taketo, M.M., Nusse, R., Hebrok, M., and Kim, S.K. (2007). Proc. Natl. Acad. Sci. USA *104*, 6247–6252.

Schwartz, A.V., Schafer, A.L., Grey, A., Vittinghoff, E., Palermo, L., Lui, L.Y., Wallace, R.B., Cummings, S.R., Black, D.M., Bauer, D.C., et al. (2013). J. Bone Miner. Res. *28*, 1348–1354.

Walsh, M.C., and Choi, Y. (2014). Front. Immunol. *5*, 511.

Wang, P., Fiaschi-Taesch, N.M., Vasavada, R.C., Scott, D.K., García-Ocaña, A., and Stewart, A.F. (2015). Nat. Rev. Endocrinol. *11*, 201–212.