THERAPY

# An unhelpful hand

Increased signalling through the insulin-like growth factor (IGF) pathway has been implicated in the progression of several types of human cancer. The IGF2 ligand is frequently overexpressed in colon and breast cancers, and inhibitors of one its receptors, IGF1 receptor (IGF1R), are in clinical trials. However, Ulanet *et al.* now demonstrate that IGF2 signalling through a second receptor — insulin receptor (INSR) — can contribute to tumorigenesis and intrinsic resistance to anti-IGF1R therapy.

In the RIP1-Tag2 transgenic mouse, the rat insulin promoter (RIP) directs expression of the simian virus 40 (SV40) large T-antigen (Tag) in pancreatic β-cells, resulting in pancreatic neuroendocrine tumours (PNETs). Both IGF2 and IGF1R have key roles in PNET development, making the RIP1-Tag2 model a prototype for IGF2-driven carcinogenesis. Hanahan and colleagues therefore assessed the potential therapeutic efficacy of the IGF1R-specific monoclonal antibody A12 in these mice. Surprisingly, A12 had no significant impact on PNET growth or invasiveness despite successfully reducing IGF1R levels.

Could the observed intrinsic resistance to anti-IGF1R therapy result from IGF2 signalling through INSR? Quantitative real-time PCR showed that both INSR isoforms, *Insra* and *Insrb*, as well as *Igf1r*, are expressed during PNET development. Moreover, western blotting revealed IGF1R and INSR to be post-transcriptionally upregulated, and IGF2 stimulation of tumour-derived β-cells resulted in the activation of both receptors. Targeted deletion of *Insr* in β-cells (β-IRKO) of RIP1-Tag2 mice led to decreased tumour burden and increased apoptosis. With such results suggesting that INSR functionally contributes to PNET tumorigenesis, the authors assessed the therapeutic efficacy of A12. Remarkably, A12-treated RIP1-Tag2; β-IRKO mice showed significant inhibition of tumour growth, indicating that loss of INSR can sensitize these tumours to anti-IGF1R therapy. Extending their findings from the PNET mouse model to human cancer, the authors found that INSR loss may similarly sensitize breast cancer cells to the inhibitory effects of A12. Cell lines with a high INSR/IGF1R ratio, such as MDA-MB-231, were insensitive to inhibition of IGF signalling by A12, in contrast to cell lines with a low ratio, such as MCF-7. Knocking down INSR expression by small interfering RNA sensitized both MCF-7 and the previously resistant MDA-MB-231 cells to A12 inhibition. Furthermore, A12 inhibited the *in vitro* growth of both cell lines on stable knock down of INSR expression.


The results of Ulanet *et al.* suggest a functional role for INSR in tumour progression, and implicate increased INSR signalling in intrinsic resistance to anti-IGF1R therapy in an IGF2-driven PNET model. The role of INSR in glucose homeostasis raises concerns that co-targeting IGF1R and INSR may result in unacceptable toxicity. However, toxicity might be minimized by specifically targeting the INSRA isoform.

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**ORIGINAL RESEARCH PAPER** Ulanet, D. B. *et al.* Insulin receptor functionally enhances multistage tumour progression and conveys intrinsic resistance to IGF-1R targeted therapy. *Proc. Natl Acad. Sci. USA* 10 May 2010 (doi:10.1073/pnas.0914076107)