In a thoughtful and balanced review in this issue of *Growth Hormone & IGF Research*, Kim and Accili address the complex question of what mechanisms determine the specificity of intracellular signaling by the insulin receptor (IR) and insulin-like growth factor-I (IGF-I) receptor (IGF-IR) tyrosine kinases.1 Despite extensive structural homology in both the ligands and the receptors, and largely overlapping intracellular signaling networks, the two receptors appear in vivo to mediate distinct and only partially overlapping patterns of physiological responses, as evidenced by the markedly different phenotypes of homozygous knock-out mice. The genetics suggests that IGF-IR is primarily a growth promoter and the IR a metabolic regulator.

However, in vitro experiments have shown that, in a given cellular context, the IR can mediate mitogenic responses and the IGF-IR metabolic responses. The IR for one thing mediates growth in response to IGF-II during a period of embryonic development.1 The IR is a growth promoter in a T-cell lymphoma line devoid of IGF-IRs and unresponsive to the IGFs.2 The truncated intracellular domain of the IR, like that of the IGF-IR, fused to an avian sarcoma virus, had a strong transforming and tumorigenic activity in chick embryo fibroblasts.3,4 Conversely, the IGF-IR was shown to mediate IGF-I and insulin's metabolic effects on glucose transport and glycogen synthase in fibroblasts5 and myoblasts6 from IR knockout mice, although studies in hepatocytes from the same mice have suggested that different pathways may mediate the metabolic responses to insulin and IGF-I.1 These and other data reviewed by Kim and Accili suggest that the two receptors do have an intrinsic ability to mediate at least some of the other’s functions. Comparison of the signaling specificities of the intracellular domains of the IR and IGF-IR using chimeric constructs have suggested that the differences are quantitative rather than qualitative (See references 41–431).

It is clear, as the authors point out, that some factors “extrinsic” to the nature of the signaling cascades may affect signaling specificity, such as kinetics of insulin and IGF-I secretion, IGF binding proteins, level of receptor expression, spatial localization6 and kinetics/duration of intracellular signals,7 as well as developmental regulation. The role of the time factor (transient vs sustained signaling) has been well documented regarding the specificity of MAP kinase signaling8 or the metabolic vs mitogenic properties of insulin analogues.7

Among “intrinsic” elements that may confer signaling specificity, the authors mention differences in the catalytic activities of the two kinase domains or structural/sequence differences in the receptor C-terminal domains, differential interactions with IRS (Insulin Receptor Substrate) molecules and recruitment of different signaling molecules (such as CEACAM-2/pp120 and MAD2 for IR and 14-3-3, Grb10, IIP-1 and c-Crk for IGF-IR). As far as Grb10 is concerned, however, a recent study shows that its BPS domain inhibits the catalytic activity of both receptor kinases.9 As the authors point out, we know very little about the potential specificity of mechanisms of signal termination. Scaffold proteins (e.g. those that bind
together selected partners among the multiple iso-
mers of the MAP kinase cascade) may also play an
important role in facilitating signal transduction by pre-
forming multimeric complexes that can be rapidly
activated by incoming signal, thus regulating the speci-
ficity, efficiency and amplitude of signal propagation. Other elements of specificity are discussed in another
recent review.

It is clear that the currently available methodologies
comparing the patterns of gene expression induced
among others proteomics. Genomics may also prove
overexpression.

and therefore still carry the potential disadvantage of
actions; however, they still require cell transfection
elements of spatial localization and kinetics of inter-
fer the advantages over current approaches of allow-
ung proteins fused to spectral variants of the green
fluorescent protein (GFP)12 or bioluminescence res-
onance energy transfer using for example Renilla
luciferase as donor and GFP as acceptor. These of-fer the advantages over current approaches of allow-
ning real-time imaging in living cells, providing the key
elements of spatial localization and kinetics of inter-
actions; however, they still require cell transfection
and therefore still carry the potential disadvantage of
overexpression.

Among alternative approaches, the authors mention
among others proteomics. Genomics may also prove
useful. A recent study using microarray analysis for
comparing the patterns of gene expression induced
by insulin and IGF-I in NIH-3T3 cells has generated
promising results.13 Thirty genes (27 of which were
not previously known to be IGF-I responsive) were
upregulated by IGF-I but not by insulin. Nine genes,
one of which was previously known to be insulin
responsive, were upregulated by insulin but not by
IGF-I. Interestingly, more than half the genes upreg-
ulated by IGF-I (but none of those specifically up-
regulated by insulin) are associated with mitogene-
sis and differentiation. This finding is important, but
does not answer the question of at which point in the
upstream signaling cascade do the divergences occur
that cause this differential gene expression. This re-
sult contrasts with another microarray study15 study-
ing the gene expression pattern induced by the platelet-
derived growth factor-β and FGF receptors, which
found that the same set of 66 immediate early genes
was induced, while a subset of the same genes was
induced by epidermal growth factor (which shares the
same signaling pathways). Thus, for those growth fac-
tors, little specificity was found even at the gene expres-
sion level that could explain their different biological
actions.

Finally, as strongly suggested by the authors, the time
may be ripe to go back to an in vivo genetic approach to
physiology by ’knocking in’ hypomorphic (i.e. with de-
creased function or expression rather than total inacti-
vation) mutated or chimeric alleles of receptors and/or
signaling molecules in mice, as several recent successful
examples encourage us to try.

I also believe that in order to understand better the
complexity and multidimensionality of what is in-
creasingly called ’combinatorial signaling’,16 it will be
necessary to develop new theoretical–mathematical
approaches to the modelling of integrated networks,
including for example applications of logical switching
theory and queuing theory.

REFERENCES

1. Kim JJ, Accili D. signaling through IGF-I and insulin receptors: where is the specificity? Growth Horm IGF Res 2001; 12:
2. Ish-Shalom D, Christoffersen CT, Vorwerk P, et al. Mitogenic properties of insulin and insulin analogues mediated by the
sequence of the human insulinlike growth factor-I receptor on its transforming and tumorigenic potential. J Virol 1993; 67:
9–16.
5. Lamothé B, Baudry A, Christoffersen CT, et al. Insulin
receptor-deficient cells as a new tool for dissecting complex
Significance of Pulsatile Hormone Secretion. Novartis
Foundation Symposium 227. New York: Wiley. 2000:
46–60.
9. Stem EG, Gustafson TA, Hubbard S. The BPS domain of Grb10
inhibits the catalytic activity of the insulin and IGF1 receptors.
10. Levchenko A, Bruck J, Sternberg PW. Scaffold proteins may
biaffectively alter the levels of mitogen-activated protein
11. Dupont J, Leech D. Insulin and insulin-like growth factor-I
receptors: similarities and differences in signal transduction.
12. Penaszky A, Day KN. Visualizing protein interactions in living
cells using digitized GFP imaging and FRET microscopy.

