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Editorial Comment

Targeting the IGF-1 receptor: from rags to riches

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The existence of the type 1 insulin-like growth factor receptor (IGF-IR) had been surmised for a number of years, before it was cloned in 1986 by Ullrich *et al.* [1]. At that time, the IGF-IR was considered a poor relative of the insulin receptor (IR), with which it has a 70% homology [1], a sort of redundant receptor that the cells used when the IR was defective. The past 15 years have established the IGF-IR as an independent receptor, with overlapping, but different, functions from the IR and playing important roles in apoptosis, cancer, differentiation and even longevity. In this commentary, I will focus on the role of the IGF-IR in cancer, with special emphasis on its use as a possible target for therapeutic purposes.

The role of the IGF-IR in cancer therapy rests on three fundamental observations (with subsequent variations) from the laboratories of Argyris Efstratiadis and ours. In 1993, Efstratiadis and co-workers [2] reported that the targeted disruption of the IGF-IR genes resulted in mice that, at birth, weighed 50% of the weight of wild-type littermates (see review in [3]). If the IGF-II genes were also deleted or inactivated (IGF-II is the only IGF growth factor in mouse embryos), the newborn mice were 30% in size. This finding was of the utmost importance because it established that: (1) The IGF-IR was (and still is) the only growth factor receptor whose deletion gives a growth phenotype in mouse embryos (other growth factor receptors, deleted, may give a lethal phenotype, but not a growth phenotype). (2) It indicated that the IGF-IR is responsible, in a non-redundant way, for 50% of the mouse embryo normal growth. (3) It also showed that 50% of normal growth is outside the jurisdiction of the IGF-IR and can be replaced by other growth factors. In other words, the IGF-IR is not an absolute requirement for growth, it is only required for 100% growth.

The 50% rule has been widely confirmed, not only with the IGF-IR, but also with its downstream effectors (reviewed in [4]). Deletion of the insulin receptor substrate-1 (IRS-1), or Akt, or S6K1, all downstream effectors of the IGF-I and insulin receptors, results in flies (Drosophila) or mice that are alive, but 50% in size. Since deletion of the IR genes results in mouse embryos that are of the same size as wild-type littermates [5], one has to conclude that, at least in mice, it is the IGF axis that controls cell and body size (Drosophila has only one receptor that partakes of both receptors).

The next two steps in the climb of the IGF-IR to recognition deal directly with its role in cancer. The first of these two steps was the observation by Sell *et al.* [6] that mouse embryo fibroblasts (MEFs) with a targeted disruption of the IGF-IR genes (generated from Efstratiadis' embryos) could not be transformed by the Simian Virus 40 (SV40) T-antigen. This was remarkable, as MEFs have a notorious tendency to transform spontaneously, and here was a cell line that could not be transformed by a well known oncogene for mouse cells. It was subsequently shown that R-cells (as the MEFs without IGF-IR were unimaginatively called) cannot be transformed by a variety of viral and cellular oncogenes. R-cells are not totally resistant to transformation. They can be transformed, for instance, by v-src, but they are certainly reluctant to be transformed, either by oncogenes or spontaneously. R-cells can be easily transformed, like other MEFs, if the IGF-IR DNA is re-introduced by transfection. The resistance of R-cells to transformation has been confirmed in several other laboratories (reviewed in [7]).

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When this observation was first made, it invited the corollary that, if cells without the IGF-IR cannot be transformed, then downregulation of the receptor in tumour cells should reverse the transformed phenotype. When this hypothesis was tested, the result went beyond expectations as downregulation of the IGF-IR in tumour cells actually caused massive apoptosis [7]. But the most interesting finding (the 3rd of the three fundamental observations mentioned at the beginning) was that downregulation of the IGF-IR in tumour cells growing in a monolayer only produced a mild inhibition. It was only when the tumour cells were tested in anchorage independence (colony formation in soft agar or xenografts in mice) that the downregulation of the IGF-IR was lethal. For instance, melanoma cells treated with antisense oligodeoxynucleotides (ODN) to the IGF-IR showed only 5–10% inhibition of growth when grown in monolayer cultures. However, when the same cells were seeded in soft agar, treatment with the antisense ODN caused more than 95% inhibition [7]. This observation fits with Efstratiadis' finding that the IGF-IR is NOT an absolute requirement for normal growth, only for 50% of it (growth in a monolayer can be considered "normal", just as growth in soft agar is generally accepted as a signature of transformed cells).

The corollary of these findings is that targeting the IGF-IR in mouse xenografts should cause inhibition or regression of tumours, with little toxicity. This is indeed what one observes. Several reports have appeared showing that targeting of the IGF-IR in tumour cells in animals causes apoptosis of tumour cells and strong inhibition, if not total suppression of growth. Some of these reports have been listed in a recent review by Baserga *et al*. [7]. As an illustration, we shall take the treatment of xenografts of human prostatic cancer cells in mice with antisense ODN to the IGF-IR. A "cure" was observed in at least 3 out of 5 mice, with the other two showing small subcutaneous nodules, with very few cancer cells seen microscopically [7]. The "cures" were probably real cures, because the experiment was designed so that the mice with tumours were treated for 3 weeks, then allowed to live out for another 10 weeks after discontinuing the treatment. Presumably, the tumours did not recur because most of the tumour cells had undergone apoptosis at the beginning of treatment. No toxicity from use of the antisense ODN was observed in these experiments.

The different strategies for targeting the IGF-IR in cancer therapy have been summarised and discussed by Surmacz [8]. Among these strategies is the use of antibodies to the IGF-IR, usually the α subunit that is extra-cellular. A few reports have appeared in which antibodies to the IGF-IR were used to inhibit tumour xenografts in mice [9,10]. The results were encouraging, and again, very little toxicity was observed, at least from what one can gather from the body weights. A variant of the antisense ODN is the use of the corresponding siRNA, which has been proposed successfully by Bohula *et al*. [11]. Another approach is the use of dominant-negative mutants of the IGF-IR [12–14]. Both siRNA and dominant negatives have, however, the problem, common to all plasmids, of an efficient delivery into animals. Min *et al*. [13] used an adenovirus as a vector, which constitutes an improvement, but not a solution. More promising is the search for small molecules that may inhibit the tyrosine kinase activity of the IGF-IR (discussed in [8]). The problem here is the very high homology between the tyrosine kinase domains of the IGF-IR and the IR, more than 94%. However, a seemingly very successful small molecule, selectively inhibiting the IGF-IR tyrosine kinase and inhibiting tumour growth in animals by oral administration, has been reported by Garcia-Echeverria *et al*. [15].

In general, successful mouse experiments have indicated that, for the best results, one has to induce downregulation of the receptor [16]. Unless the receptor is downregulated, apoptosis does not occur [7]. Even so, because of the anti-apoptotic effect of the IGF-IR on many cell types [17], its inhibition could enhance the sensitivity of tumour cells to ionising radiation or chemotherapeutic agents, a supposition that has in fact been demonstrated to be correct [18,19]. It also makes sense that targeting of the IGF-IR may be more effective on metastases, which, at least in theory, can be considered a model of anchorage independence, as they usually arise from single cells or small clusters of metastatic cells. This theoretical assumption has been borne out in several reports indicating that metastases are especially sensitive to downregulation of the IGF-IR [14,20,21].

The transfer of tumour cures in mice to humans has traditionally been disappointing. But at least in the case of the IGF-IR targeting, the theory and the experiment are concordant in indicating that it has very little toxicity. If human tumours (especially metastases and local recurrences) are ever in a state of anchorage independence, then targeting of the IGF-IR has a fighting chance to be useful in humans. This would be a fitting conclusion for a receptor that only a few years ago was deemed a redundant receptor with not much of a future.

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