

A Tale of Two Receptors: Insulin and Insulin-Like Growth Factor Signaling in Cancer

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Inhibition of the type I IGF receptor (IGF1R) has been the focus of numerous clinical trials. Two reports in this issue describe the results of phase I trials of an IGF1R tyrosine kinase inhibitor OSI-906. This commentary will describe the complex

endocrine changes induced by these types of agents. *Clin Cancer Res*; 21(4); 667–9. ©2014 AACR.

See related articles by Jones et al., p. 693, and Puzanov et al., p. 701

In this issue of *Clinical Cancer Research*, two phase I studies of the type I insulin-like growth factor receptor (IGF1R) and insulin receptor inhibitor OSI-906 are presented (1, 2). In *A Tale of Two Cities*, Charles Dickens wrote, "we had everything before us, we had nothing before us." This phrase describes the past several years in the development of the IGF1R inhibitors. Fueled by abundant preclinical and population data implicating IGF1R in cancer biology, strategies to target this transmembrane tyrosine kinase inhibitor (TKI) were developed. A burst of clinical trials involving at least five mAbs and three TKIs directed against IGF1R were planned and completed.

To date, the development of the IGF1R mAbs has largely ended. Although there was some evidence of single-agent activity, the majority of combination therapy trials were failures (reviewed in ref. 3). Initially, the most promising published phase II report of IGF1R combination therapy in non-small cell lung cancer was retracted due to errors in determining response. The recently reported phase III trials showed a trend toward harm for patients receiving chemotherapy and the IGF1R mAb figitumumab (4).

Was IGF1R the right target? As the name suggests, "insulin-like" growth factors are highly related to insulin (Fig. 1A). Both the ligands and receptors have significant homology, yet we have tended to think of the two ligand and receptor systems as having separate physiologic roles. Insulin's role in glucose homeostasis is well understood. IGF-I regulates growth; it is produced at the time of puberty in response to pituitary release of growth hormone (GH). Thus, these two highly regulated endocrine systems have been linked to metabolism (insulin) and growth (IGF-I), but it is clear the two systems overlap in their physiologic functions. IGF-I clearly has metabolic functions and has been used to treat type 2 diabetes (5). Insulin enhances tumor growth in animal models of type 2 diabetes (6). In the development of the IGF1R mAbs, there was an intentional effort to avoid cross-reactivity with the insulin receptor to maintain glucose homeostasis.

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It was well understood in the early development of IGF1R mAbs that insulin and glucose homeostasis was also disrupted with this class of drugs. Phase I trials with figitumumab demonstrated increased levels of GH, IGF-I, insulin, and glucose (7). Figure 1B shows how this occurs. IGF1R mAbs block the endocrine feedback system regulating the production of IGF-I. When patients receive IGF1R mAbs, GH levels increase because the antibodies disrupt the brain's ability to sense the levels of IGF-I. This disruption of a pituitary endocrine system is exactly analogous to premenopausal women receiving tamoxifen. When estrogen receptor- α (ER) is inhibited by tamoxifen, blood levels of estradiol increase because of the disruption of the feedback system (8). However, tamoxifen is still effective in premenopausal women with functioning ovaries because the estradiol/ER interaction is effectively inhibited despite the elevation of blood estradiol.

This is not the case in IGF1R mAb therapy. First, supraphysiologic levels of IGF-I induced by the antibody might be able to stimulate the insulin receptor. Indeed, insulin receptor can be stimulated by IGF ligands. The IGFs exist in two isoforms; IGF-I is structurally related to IGF-I and interacts with insulin receptor with high affinity. Supraphysiologic concentrations of IGF-I may also stimulate insulin receptor. Second, elevated levels of GH result in insulin resistance and elevated levels of insulin (9). IGF-II, a homologous ligand to IGF-I, is also found in adult human blood and has high affinity for the insulin receptor (3). Thus, IGF1R mAbs could result in harm via the elevation of ligands stimulating the insulin receptor while leaving the insulin receptor uninhibited. Indeed, we have shown that sole inhibition of IGF1R results in enhanced signaling through the insulin receptor (10). These data support the argument that disruption of both receptors would be necessary for tumor growth inhibition.

Fortunately, the TKIs are biochemical inhibitors of both receptors' kinase function. Given the high degree of homology of the two receptors, an "IGF1R"-specific TKI has not been possible to develop; existing drugs inhibit both receptors equally. In this issue, the results of two phase I studies of the IGF1R TKI OSI-906 are reported. The first of these reports studied an intermittent dosing regimen; 3 or 7 daily doses out of a 14-day cycle. There are potentially several reasons for the benefit of intermittent dosing, including a reduction in toxicity. In addition, preclinical data suggest that continuous suppression of IGF1R signaling might not be the best strategy to combine with chemotherapy (11, 12). The other study used continuous daily dosing. Both studies reported

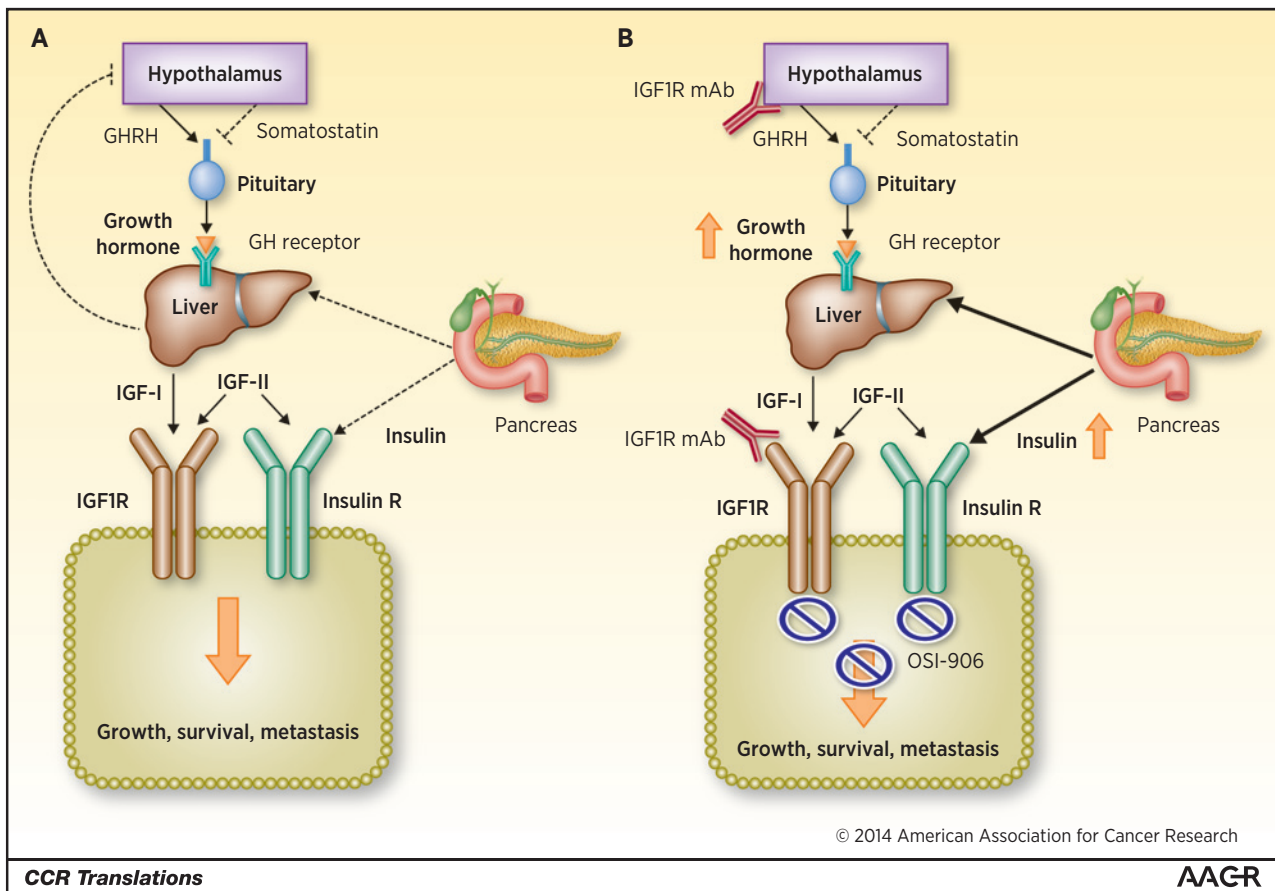


Figure 1. Coordination of IGF-I and insulin signaling. A, in normal conditions, the hypothalamus produces growth hormone releasing hormone (GHRH) and somatostatin to regulate GH production by the pituitary. GH interacts with GH receptor in the liver, resulting in increased serum levels of IGF-I. IGF-I stimulates growth in normal cells by stimulating IGF1R, but also regulates cancer cell growth, survival, and metastasis. Insulin produced by the pancreas interacts with several tissues to maintain glucose homeostasis including the liver. Although most cancer cells also express insulin receptor, under normal physiologic conditions, insulin levels are low (dotted lines) except in response to a meal. IGF-II is produced from many different tissues and binds both receptors. B, when IGF1R signaling is disrupted by a mAb (red symbol), negative endocrine GH feedback is disrupted as the brain does not sense IGF-I levels. Elevated GH (orange arrow) levels result in insulin resistance (partially due to increased free fatty acid efflux from the liver) in peripheral tissues, resulting in enhanced insulin production by the pancreas (thick lines, orange arrow). These elevated insulin levels may stimulate tumor growth. OSI-906 is not specific for insulin or IGF signaling and may be a more effective than IGF1R mAbs in blocking IGF-I, IGF-II, and insulin signaling.

hyperglycemia, but there was a slightly lower incidence in the intermittent dosing schedules. Conversely, nausea was slightly higher when the treatment was given intermittently.

The continuous dosing regimen also included a cohort with type 2 diabetes. Mouse models of type 2 diabetes showed that TKI treatment inhibited tumor growth in these diabetic animals (6). In this study, there was a modest further elevation of glucose, which was also seen in this human study. Notably, marked elevations of serum insulin in these diabetic animals were seen as an endocrine response to further insulin resistance. Insulin levels in the human phase I trials were not reported.

All of the regimens demonstrated evidence of clinical benefit as reflected by disease control rates (percentage of patients with stable disease compared with total number of patients) of about 40%. Although objective responses were rare, a number of patients achieved more than 6 months of disease stability. In the intermittent dosing study, 7 of 66 evaluable patients had stability for more than 6 months. For the continuous dosing regimen, 2 of

30 patients remained on therapy for more than 39 weeks. Remarkably, a patient with metastatic melanoma achieved a pathologic complete response on the continuous regimen. The authors conclude that OSI-906, as a single agent, has activity in cancer and the intermittent regimens suggest the potential for combination therapy.

These promising phase I results suggest a role for the dual tyrosine kinase inhibition of insulin and IGF1R. This dual inhibition may overcome the potential limitation of elevated serum levels after IGF1R mAb therapy. Although hyperinsulinemia was very likely in the OSI-906-treated patients, the drug can suppress any physiologic effects of insulin on tumor cells, as shown in the mouse models of hyperinsulinemia (6).

Although the overall response rate was low for this therapy, it is remarkable that any responses were documented in this phase I study in the absence of biomarker selection. Although we believe we understand the targets for this dual kinase inhibitor, we have not been successful in identifying cancers

that are dependent upon insulin/IGF signaling. Notably, insulin and IGF1R activation require ligand binding, and it has been suggested that serum levels of the ligands might play a role in predicting response to an IGF1R mAb (13). This study did not measure serum insulin levels, and future studies should measure this other ligand when developing predictive biomarkers.

In the end, the failure of the IGF1R mAbs has shed light onto the putative importance of insulin receptor signaling in cancer. In *A Tale of Two Cities*, two very similar appearing men with different properties are the focus of the story. In this novel, Sydney Carton dies to save Charles Darnay. Perhaps the

"death" of IGF1R mAbs could pave a way forward for the IGF1R/insulin receptor TKIs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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