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Commentary

Predictive biomarkers for targeting insulin-like growth factor-I (IGF-I) receptor

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The development of anticancer drugs remains slow and costly. Use of predictive biomarkers has been postulated to not only accelerate this process but also increase the odds of drug approval (1). Despite concerns about the validation of the insulin-like growth factor receptor type I (IGF-IR) as an important target for anticancer drugs, many drugs targeting this receptor are currently being evaluated in clinical trials (2). IGF-IR is highly expressed on many human cancers, with its ligands IGF1 and IGF2 also being commonly overexpressed in many malignancies (3). IGF1 increases cancer-cell proliferation *in vitro,* and importantly knockout of IGF-IR makes nonmalignant cells highly resistant to oncogenic transformation (4). Clinical evidence for the validity of this target is also now emerging, with early evidence of antitumor activity in patients with Ewing's sarcoma, adrenocortical carcinoma (ACC), and non-small cell lung (NSCLC) carcinoma (5–8).

Both small molecule inhibitors and therapeutic antibodies blocking IGF-IR are in clinical development, with the former also often targeting the insulin receptor (IR). This edition of *Molecular Cancer Therapeutics* includes an important report detailing a comprehensive preclinical evaluation of predictive biomarkers for h10H5 (Genentech, South San Francisco, CA), a humanized monoclonal antibody to IGF-IR (9). The identification of such biomarkers remains arguably the most important issue in development of drugs targeting IGF-IR. Previous studies have reported on the expression of IGF1-R, phospho-IGF-IR, insulin receptor substrates-1 (IRS1), and -2 (IRS2), and predictive gene expression signatures (10–13). This report describes a detailed assessment of certain elements of the pathway, including an evaluation of the receptor and its ligands, and its proximal and distal signaling proteins with expression array profiles, focusing exclusively on breast and colorectal cancer (CRC) models. The authors conclude that for sensitivity to h10H5, IGF-IR overexpression is necessary but not sufficient, requiring between 1,300 to 10,000 receptors per cell for sensitivity. These data also indicate that IGF2, IRS1, and IRS2 protein expression may be important for patient selection, supporting previously published findings.

Other studies suggest that IGF-IR expression correlates with response to IGF-IR blockade (10). IGF1, IGF2, and IGF-IR were also highly expressed in sarcoma cell lines sensitive to the tyrosine kinase inhibitor BMS 536924, whereas those resistant to this drug expressed high levels of IGF binding protein-3 (IGFBP-3) and -6 (IGFBP-6), and of epidermal growth factor receptor (EGFR; ref. 11). Studies of an IGF-IR tyrosine kinase inhibitor, NVP-AEW541, reported high levels of IGF-IR in all breast cancer cell lines evaluated with a high level of IRS1-I in the most sensitive of the cells (13). Zha and colleagues report differences in predictors of sensitivity for breast cancer and CRC cell lines, with IGF-IR mRNA expression being more predictive in breast cancer than in CRC (9). Furthermore, a 60-gene predictive expression signature was identified for the CRC cell lines with no predictive signature being identified for the breast cancer cell lines. Further studies led to IRS1 and IRS2 being shown to also be important in assessing likelihood of response. The authors also described a significant correlation between IGF-IR expression and signaling, and estrogen receptor (ER) function, supporting an evaluation of these agents in this subgroup of breast cancers.

Despite the substantial number of experiments reported in this report, however, the authors may not have fully dissected the complexity of the IGF-IR pathway. IGF-IR ligands can also bind IR, although with lower affinity than IGF-IR (2). The role of IR or of the IGFBPs as mediators of drug resistance has not been evaluated here. Furthermore, the relationships between IGF-IR phosphorylation, IGF-IR overexpression, and IRS1 and IRS2 were not clear from this work. Finally, although the authors identify ER-positive breast cancer as an important area for future research, the significance of IGF-IR being previously implicated as an important target in triple-negative and HER2-positive breast cancer is not addressed (14).

The authors suggest ways in which the predictive biomarkers identified in their preclinical experiments can be deployed in clinical trials, proposing the prospective treatment of different cohorts of ER-positive breast cancer patients positive or negative for IGF-IR staining by immunohistochemistry. One important issue with these studies in patients with metastatic cancer is that they usually use the evaluation of

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IGF-IR expression on archival tumor tissue, frequently acquired many years before. To resolve this problem, immunofluorescence studies of IGF-IR expression on circulating tumor cells (CTC), in addition to analysis of archival tumor tissue, could be undertaken as we have previously described (15), although further studies correlating IGF-IR expression in tumor biopsies and CTC taken from the same patient at the same time are required to clinically qualify this approach. This technique also allows an evaluation of the effect of the therapeutic agent on the number of IGF-IR-positive and IGF-IR-negative cancer cells detected by the assay. The preliminary clinical qualification of such predictive biomarkers should commence during phase I evaluation of these agents, with a focus on detailed evaluation in cohort expansions at higher drug dose levels across histological tumor types expressing the target of interest.

Disclosure of Potential Conflicts of Interest

Drs. C.P. Carden, L.R. Molife, and J.S. de Bono have been involved in conducting trials of IGF-1R inhibitors sponsored by Pfizer Oncology and OSI Pharmaceuticals. Dr. J.S. de Bono has served as a consultant for Merck, AstraZeneca, Novartis, Genentech, Amgen, and GlaxoSmithKline.

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