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Mechanisms determining efficacy of tyrosine kinase-targeting anti-cancer drugs

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ABSTRACT

The expanding field of cancer research and the introduction of multiple molecular biology techniques have significantly improved cancer drug discovery, presented new drugs, including tyrosine kinase inhibitors, and thereby gave new hope to the cancer patients and their oncologists. Using this knowledge it is now becoming increasingly possible to determine outcome of malignant disease more accurately, to estimate response to specific therapies and to get closer to the ideal of personalized targeted therapy adjusted to each patient, and to the specific cancer type and its unique genetic profile. This thesis tries to explain some mechanisms lying behind the sensitivity or the resistance to new targeted therapies of two cancer types: glioblastoma (GBM) and colorectal cancer (CRC).

The IGF-1- and PDGF- receptor tyrosine kinases are widely expressed in GBMs and involved in their self-sustained proliferation, glioblastoma tissue invasion, resistance to apoptotic stimuli, insensitivity to growth control signals and are thus potential therapeutical targets. The first study of the thesis analyzed the sensitivity of GBM cultures to the IGF-1 receptor inhibitor NVP-AEW541. This small molecule caused variable reduction in growth of GBM cultures, allowing grouping of cultures as “responders” and “non-responders” . Use of the IGF-1 receptor siRNA gave very similar result. The sensitivity to NVP-AEW541 was significantly reduced in cultures with PIK3CA mutations or ligand-independent Akt phosphorylation and in a “responder cell culture” treated with PTEN siRNA as well. Combination treatments with either PI3 kinase- or mTOR-inhibitors together with NVP-AEW541 resulted in prominent reduction in growth of “non-responders”. In the second study, the prognostic or predictive potential of PDGFRs status was evaluated, as a translational part of the randomized CSTI571BDE40 trial, which compared hydroxyurea monotherapy and a combination of hydroxyurea and imatinib, a small molecule targeting PDGFRs in recurrent glioblastoma patients. Both PDGFR alpha protein expression and phosphorylation correlated with worse outcome, but did not define a group that showed benefit from the combination therapy with hydroxyurea and imatinib. The third study deals with putative cancer stem cells, associated with radio- and chemo-resistance of GBMs. Gene expression analyses of 11 GBM cell cultures identified two subsets - designated type I and type II cultures. The type I cultures showed high expression of CXCR4, SOX2, EAAT1 and GFAP and low expression of CNP, PDGFRB, CXCL12 and extracellular matrix proteins. Type I cultures had a higher capacity to form xenograft tumors and neurospheres, displayed low or no sensitivity to mono-treatment with PDGF- and IGF-1-receptor inhibitors, but were growth inhibited by combination treatment with low concentrations of the two inhibitors. SOX2 down-regulation conferred sensitivity to PDGF- and IGF-1-receptor inhibitors.

The fourth study describes the influence of one part of the tumor microinviroment, activated fibroblasts, on sensitivity of colorectal cancer cells to cetuximab, a monoclonal EGFR-targeting antibody. LIM1215 colorectal cancer cells were growth-inhibited by cetuximab. However, when co-cultured with PDGF stimulated fibroblasts they become significantly less sensitive to cetuximab with regard to inhibition of growth, migration and invasion. LIM1215 cells co-cultured with activated fibroblasts displayed increased c-met phosphorylation suggesting fibroblast-produced HGF as a mediator of the protective effects of fibroblasts.

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