Integr(at)in(g) EGFR therapy in HNSCC

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Patients with locally advanced head and neck squamous cell carcinomas (HNSCCs) are usually addressed to surgery and/or radiotherapy. The addition of chemotherapy to radiotherapy has also been extensively investigated, but treatment outcome often remained disappointing (1). Based on high levels of epidermal growth factor (EGFR) expression detected in approximately 90% of HNSCC, and associated to worse clinical outcome and decreased response to radiotherapy (2), the anti-EGFR monoclonal antibody cetuximab has been approved for treatment of patients with HNSCC (1). A paper recently published in Journal of National Cancer Institute by Eke and colleagues (3) demonstrated that simultaneous targeting of β1 integrin and EGFR is a promising approach to overcome radioresistance in preclinical HNSCC models. Mechanistically, radioresistance depends on pro-survival signalling transduced by a protein complex of focal adhesion kinase (FAK) and extracellular signal-regulated kinase (ERK1): combined β1 integrin/EGFR blocking is able to interfere with these signals.

Integrins are heterodimeric cell-surface molecules (formed by α and β subunits) that mediate cell-matrix interactions. In addition, even if not provided with intrinsic kinase activity, integrins mediate from the extracellular space into the cell through adaptor molecules such as FAK, p130Cas, Src-family kinases and GTPases of the Rho family (4,5). Via these molecules, integrin cooperatively interacts with receptor tyrosine kinase (RTK) to regulate cell survival, proliferation, adhesion, and migration (6). In HNSCC, β1 integrin overexpression has been found and related to tumour therapy resistance (7,8).

Eke and colleagues (3) reported that β1 integrin inhibition, by either the antibody AIIB2 or silencing with β1 integrin siRNA, activates EGFR associated signalling in HNSCCs. Particularly, the authors observed an increase of ERK1/2 phosphorylation and a dissociation of the FAK-ERK1 protein complex, both in vitro and in vivo (Figure 1). It is known that the Ras/Raf/MEK/ERK pathway is one of the signalling pathways activated downstream to EGFR (9) as well as to integrins (10). Similarly, FAK transduces signal from β1 integrins and EGFR (11) through autophosphorylation of tyrosine 397 (12), thus inducing cell motility, proliferation, and the stress response to ionizing radiation and chemotherapy (13-15). Shibue et al. (16) showed that β1 integrin-FAK signalling directs the proliferation of metastatic cancer cells disseminated in the lungs: β1 integrins regulate FAK activation in these metastatic cells, and inhibition of both proteins reduces cell proliferation (16).

A relationship between EGFR and β1 integrin pathway has been also demonstrated in lung cancer. Morello et al. (17) reported that β1 integrin controls EGFR signalling and tumorigenic properties of lung cancer cells. Ju et al. (18) showed that β1 integrin over-expression is associated with acquired resistance to tyrosine kinase inhibitor gefitinib in non-small cell lung cancer (NSCLC), accompanied with increase of the cells’ adhesion and migration. Moreover, the sensitivity of NSCLC cells to gefitinib is negatively correlated with levels of β1 integrin protein expression (18). In another study (19), the integrin β1/Src/Akt signalling pathway has been identified as a key mediator of acquired resistance to erlotinib in lung cancer: gene silencing of β1 integrin restored sensitivity to erlotinib and reduced Src and Akt phosphorylation/activation after erlotinib treatment. In tumour samples from patients with lung cancer refractory to erlotinib and/or gefitinib, increased expression of integrin β1, α5, and/or α2 was also observed (19).

Other studies reported that EGFR inhibition is related to
different negative feedback loops involving MEK1/2 and other bypass signalling, often mediated by β1 integrin (20). Conversely, the work by Eke et al. (3) demonstrated that β1 integrin inhibition induces EGFR activation, with consequent overactivation of components of the Ras pathway. Based on these data, Eke and colleagues (3) tested the combination of β1 integrin inhibition by AIIB2 and EGFR inhibition by cetuximab in HNSCC models. They found that the combined treatment is more effective than single agents in inducing cytotoxicity and radiosensitization of HNSCC cell lines (Figure 2). In tumour xenografts, the combination AIIB2/cetuximab/radiotherapy produced higher tumour control rates compared to single anti-β1 integrin treatment. On the other hand, in a different tumour model, Poschau and colleagues demonstrated that both β1 integrin and EGFR targeting are inefficient to radiochemosensitize colorectal cancer cells (21).

Ionizing radiations are able to induce damages to several sub-cellular structures, from the plasma membrane to the cell nucleus. Particularly, in cancer therapy, radiation-induced cytotoxicity is closely linked to DNA damage (22). In this respect, several studies report the involvement of nuclear EGFR in DNA repair, for both non-homologous end joining (via DNA-protein kinase) and homologous recombination (via Rad51) (23-25). The role of β1 integrins in this context is less known. However, several studies have reported that β1 integrin targeting enhances radiochemosensitivity in different tumour types (13,26-28). In fact, β1 integrins may regulate chromatin structure by increasing acetylation of the core histone H3 and by reducing the interaction of the linker histone H1 with DNA (29). Moreover, they have been involved in the protection from bleomycin-induced DNA breakage (30). The results obtained by Eke and colleagues (3) suggest that cooperative EGFR/β1 integrins interactions may play a critical role in DNA damage repair; therefore, the simultaneous inhibition of both signalling pathways may significantly improve radiosensitization of HNSCC models.
of cetuximab to AIIB2 prevents the AIIB2-induced hyperphosphorylation of Raf/MEK/ERK and FAK signalling. In different human cancer cell lines including ovarian, lung and HNSCC cells, FAK has been described downstream to Ras/Raf/MEK/ERK pathway (11,12,14,32).

In order to evaluate the role of FAK downstream to β1 integrin and EGFR, as well as its interaction with the Ras pathway, the authors performed modulation (down-regulation/overexpression) of both FAK and ERK1 by siRNAs or by expression vectors. They found that FAK plays a key role in the radiosensitization of HNSCC cell lines. Moreover, the authors concluded that FAK operates downstream to ERK1, regulating the DNA damage and survival response controlled by β1 integrin and EGFR (3).

Altogether, the results by Eke demonstrate the efficacy of simultaneous β1 integrin/EGFR targeting in combination with radiotherapy in HNSCC tumours and propose this strategy as a reasonable and feasible option to overcome tumour radioresistance and diminish tumour recurrence in patients. However, the feasibility of β1 integrin targeting in cancer patients needs further evaluation. In 2014, a first-in-human clinical trial testing Fc-engineered IgG1 monoclonal antibody targeting integrin α5β1 was performed to evaluate tolerability, maximum tolerated dose, pharmacokinetics, pharmacodynamics and preliminary anti-tumour activity in patients with advanced solid tumours. Unfortunately, the trial was prematurely terminated without reaching end-points for the high toxicity (33). Moreover, since Eke and colleagues found that two out of the ten tested models do not respond to combination therapy, further studies will be required to understand the mechanisms of nonsusceptibility for β1 integrin/EGFR targeting. The knowledge of molecular determinants of response, i.e., FAK phosphorylation/dephosphorylation after exposition to AIIB2/cetuximab, could allow a selection of patients who will potentially benefit from this kind of therapy.

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