Commentary

PTK2/FAK: a new predictive biomarker for response to radiotherapy in head and neck squamous cell carcinoma

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With over 600,000 new cases per year worldwide, head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy in developed countries (1). However, despite numerous developments in treatment modalities, the disease-free and overall survival of head and neck cancer patients barely improved over the last decades (2). Radiotherapy plays an indispensable role in the treatment of HNSCC, but mortality among patients because of locoregional failure remains high (3). Therefore, the identification of molecular pathways, involved in resistance to radiation as well as the development of agents enhancing the radiosensitivity of tumor cells, deserves great attention.

The first molecular biomarker to be associated with radioresistance was infection with the human papillomavirus (HPV). HPV-positive tumor cells have been shown to respond better to radiation *in vitro* as well as *in vivo* (4). Besides HPV infection, other molecular biomarkers involved in radioresistance have been identified as well. For example, tumor hypoxia was shown to increase resistance to radiation and biomarkers for tumor hypoxia, such as HIF1alpha, GLUT1 or CAIX protein expression, have been associated to worse disease-free and overall survival of HNSCC patients (5). Also elevated EGFR expression and mutations in TP53 were associated with radioresistance (6).

So far, only one targeted, radiosensitizing agent has been approved for the treatment of HNSCC: cetuximab, an inhibitor of the Epidermal Growth Factor Receptor (EGFR). However, adding cetuximab to radiotherapy is only beneficial in less than 20% of all patients that qualify for this treatment modality (7) and despite numerous studies, robust predictive biomarkers for response to cetuximab are still lacking. So the clear need remains to identify novel biological pathways involved in radioresistance to provide additional therapeutic targets.

Recently, Skinner *et al*. performed a broad, comprehensible study on radiosensitivity, in which they aimed to identify novel biomarkers for radioresistance, as well as potential targets for radiosensitization in HPV-negative HNSCC (8). Candidate biomarkers were identified using a reverse phase protein assay (RPPA) that compared the differential expression of 177 proteins and phosphoproteins between 49 radiosensitive and radioresistant HNSCC cell lines. The authors chose a practical approach in which only directly targetable proteins were included, meaning that proteins with a lower expression in radioresistant tumor cells as well as proteins with no available inhibitor were excluded from further analysis.

The RPPA yielded five proteins that were upregulated in radioresistant cell lines versus radiosensitive cell lines: phosphorylated EGFR, EN1, ERK1, FAK and FGFR1. The authors focused their attention to PTK2/FAK, a cytosolic protein tyrosine kinase that might be involved in cancer because of its pro-proliferative and anti-apoptotic functions (9). They demonstrated that FAK protein expression was upregulated in radioresistant tumor cells and this was highly correlated to PTK2/FAK mRNA expression and copy number. The authors studied the relation between PTK2/FAK and locoregional failure in two separate cohorts of surgically treated patients, who received postoperative radiotherapy. They identified amplification and mRNA overexpression of PTK2/FAK as an independent negative predictor for disease-free survival in both cohorts. The authors confirmed these findings in patient data obtained from the TCGA database.

This study of Skinner *et al*. addressed the great need for new, clinically validated biomarkers for radiotherapy response. With their broad, unbiased approach, the authors were not only able to study biomarkers already associated with radioresistance, but also had the opportunity to identify novel biomarkers. In this way, they were able to associate PTK2/FAK, which was already known to be involved in tumor proliferation and metastasis (10), to radioresistance as well.

The authors used a variety of different techniques to support their findings: not only did they identify PTK2/FAK as a potential, novel biomarker for radioresistance using protein, mRNA, and copy number analysis, they also successfully validated this biomarker in a clinical study, showing the clinical relevance of PTK2/FAK as predictor of radiotherapy outcome in HNSCC patients.

Despite their outstanding work in elucidating a new pathway involved in radioresistance, Skinner *et al*. left some opportunities unexploited. The authors studied the radiosensitizing role of PTK2/FAK in cell-line experiments and validated this potential biomarker in patient cohorts. They correlated mRNA expression and copy number variation with disease-free survival, which indeed yielded a significant association. However, although their initial identification of potential biomarkers for radioresistance was based on a protein expression assay, they did not study protein expression *in vivo*. It would be of added value to confirm these findings by immunohistochemical staining for FAK protein in patient material, especially because FAK inhibitor PF-00562271, which was used in their radiosensitivity assay, acts on a protein level (11).

Furthermore, Skinner *et al*. showed in a clonogenic radiosensitivity assay that FAK inhibitor PF-00562271 sensitizes tumor cell lines for the effects of radiation. However, they did not show that this effect was reached by actual inhibition of the function of FAK. Assessing mRNA or protein expression of (phosphorylated) downstream targets of FAK might indeed prove whether PF-00562271 exerts an on-target effect on the FAK pathway. This way, the authors could have further strengthened their conclusion that inhibiting FAK sensitizes tumor cells for radiation. Ultimately, FAK inhibition should be evaluated in a mouse model to prove more robustly its role as radiosensitizer in the treatment of head and neck cancer *in vivo* and to clear the way for further assessment of FAK inhibition in clinical trials.

In conclusion, resistance of tumor cells to radiation plays an important role in locoregional failure of radiotherapy in the head and neck area. Skinner *et al*. recently made a great contribution to further unraveling the tumor biology behind this phenomenon by identifying a novel pathway involved in radioresistance. With PTK2/FAK, the authors identified a promising, new biomarker for radiotherapy response in HNSCC patients, which might enable clinicians to predict radiotherapy outcome more accurately, and might provide a new therapeutic target for radiosensitizing tumor cells.

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Footnote

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