

Potential biomarkers for radiosensitivity in head and neck cancers

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Abstract: Radiotherapy is a mainstay of treatment for head and neck cancer. However, the morbidity of treatment remains a clinical challenge. Molecular profiling has provided further insight into tumor biology and tumor sensitivity to radiation, and this information could be used to personalize treatment. In this review, we discuss published signatures of radiosensitivity and discuss the pathways that may be important in dictating radiation sensitivity. Applications of these signatures could result in less morbidity if dose de-escalation efforts are successful.

Keywords: Head and neck cancer; radiation sensitivity; microRNA; epithelial-mesenchymal transition (EMT); biomarkers

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Introduction

Head and neck cancer is the sixth most common cancer in the world with about 600,000 new cases annually, with the 5-year overall survival rates between 50–60%. Head and neck cancers comprise tumors of the oral cavity, larynx, pharynx, salivary glands, and nasal passages, with squamous cell carcinoma (SCC) being the most common histological type. Currently, the known risk factors for head and neck squamous cell carcinoma (HNSCC) in developed countries include smoking and alcohol consumption (NCI Surveillance, Epidemiology, and End Results Program, <http://seer.cancer.gov/statfacts/html/larynx.html>). These represent about 1% of all new malignancies in the United States and the cumulative cost of care for patients with head and neck cancer is estimated at over 4 billion dollars annually by the year 2020 (NCI Cancer Prevalence and Cost of Care Projections, (<https://costprojections.cancer.gov/graph.php>)). This is in part due to the side effects related to standard therapies, which consist of surgery,

chemotherapy, and/or radiation. Effective strategies to alleviate unwanted toxicities to improve patient quality of life and reduce costs are elusive.

From a biological perspective, the human epidermal growth factor receptor (EGFR) was initially shown to be a key factor in the aggressiveness of head and neck cancers and their response to radiotherapy (1). This led to the landmark study combining the EGFR inhibitor cetuximab with radiation, which showed an overall survival benefit compared to radiation alone (2). Since then, no biologic therapy against new targets has shown benefit for patients with head and neck cancer. However, in recent years, it has become evident that the human papilloma virus (HPV) is not only an important risk factor, particularly amongst non-smokers; but is also associated with radiosensitivity in oropharyngeal cancer. Nonetheless, its clinical utility in other types of HNSCC is controversial (3,4).

In this review, we discuss studies which report various biomarkers of radiation sensitivity in head and neck cancer and discuss the pathways which play important roles in the

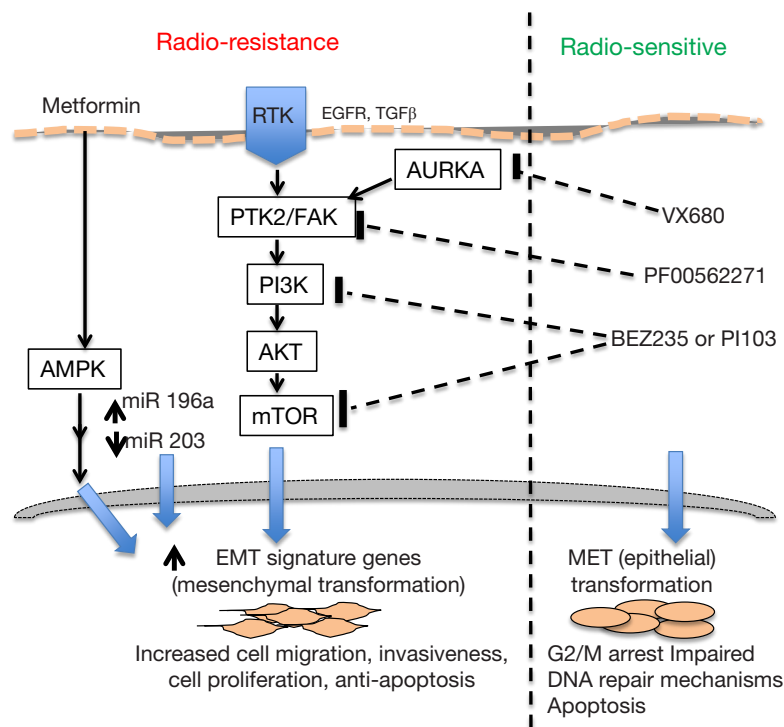


Figure 1 Targetable pathways and biomarkers of radioresistance in head and neck cancer. Relationship of various biomarkers of radioresistance and the associated signaling pathways. EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; AMPK, adenosine monophosphate-activated kinase.

regulation of radiosensitivity. An overview of pathways is shown in *Figure 1*.

Biomarkers and radiosensitivity

Radiotherapy is one of the most important treatment modalities for various types of cancers including head and neck cancer. Disease-related mortality in HNSCC is due primarily to locoregional failure, thus understanding the mechanisms of radioresistance are imperative. Irradiation is known to affect various cellular processes to promote cellular damage and thus trigger tumor death. Some of those cellular mechanisms altered by irradiation include DNA repair, cell cycle regulation, and the reoxygenation of tumors. Technological advances have achieved improvements on targeting the irradiation precisely to the gross tumor and development of different fractionation modalities to optimize the biological effects of irradiation. Nonetheless, radiosensitivity still varies between tissues and tumor types.

Irradiation induces changes in gene expression in multiple cancer cell lines including HNSCC. In the

genomic era, this type of comprehensive profiling has become more important in the pre-irradiation setting in order to identify molecular tumor signatures to predict radiosensitivity (*Table 1*). Identifying these biomarkers for various tumor types would permit a better stratification of patients based on their predicted response to irradiation. They would also increase the understanding of the intrinsic cellular mechanisms of radioresistance in cancer, thus promoting the development of adjuvant medications to personalize radiosensitization and improve patient outcomes.

To this end, the Torres Roca's group created an algorithm to assign a radiosensitivity index (RSI) to tumors based on their genomic profile, in order to predict their response to irradiation (17-19). They identified a set of genes that were strongly associated to radiosensitivity and created RSI gene signature. Their findings in various types of cancers including rectal, esophageal, head and neck cancer, and breast cancer. Gene Ontology analysis showed that these genes were involved in DNA damage response, histone deacetylation, cell-cycle regulation, apoptosis, and proliferation; all of which play important roles in radiation

Table 1 HNSCC miRNAs and their function and relationship to irradiation

microRNAs	Tissue, cell origin	Function and commentaries	References
miR-203a, miR-205-5p, miR-452-5p, miR-200b-3p, miR-429, miR-141-3p, miR-200a-3p, miR-7-5p, miR-138-5p, miR-34a-5p, miR-142-3p, miR-33b-5p	Thirty-four cell lines from laryngeal HNSCC (17 radioresistant, 17 radiosensitive). Results were validated using 32 primary tumor samples from patients prior to irradiation and no adjuvant chemotherapy, which had clinical evidence of local controls versus recurrence. The role of EMT in radioresistance was then validated using genetically modified cell lines	Loss of miR-203 expression was associated to increased expression of genes involved in EMT. Loss of miR-203 was also associated to radioresistance. Thus miR-203 upregulation can decrease EMT and improve response to radiation	(5)
miR-16, miR-29b, miR-1254, miR-150 and let-7e	A subset of 435 HNSCC patients who had radiotherapy from TCGA database. Were divided in radiosensitive and radioresistant; human lymphoblastoid from ATM patient and relative control cell line. GM0536 and GM1526, also HNSCC Cal27 cell line	Five miRNAs showed differential alteration in response to irradiation in an ATM kinase-dependent manner. ATM expression levels was correlated with radiation responsiveness. The study looks to use the miR as signature to predict clinical response of HNSCC to radiotherapy	(6)
miR-196a	Sixteen patients with OSCC were selected based on their response evidence of disease recurrence within 5 years after surgery and postoperative radiotherapy	Overexpression miR-196a in eight HNSCC cell lines result in increase of proliferation, migration, invasion and EMT. Thus increase in miR-196a was associated to radioresistance and a poor prognosis in HNSCC. This appeared to be mediated by miR-196a inhibition of ANNEXIN A1	(7)
miR-203, miR 205	Studied metastatic cells from formalin-FFPE of 49 patient lymph nodes from oral cavity tumors, and FNA biopsies from 79 patient nodules after resection of tumors in oral cavity, pharynx and larynx	miR-203 and miR 205 were up-regulated in HNSCC metastasis	(8)
miR-30a and miR-934	From the TCGA database, a cohort of 136 HNSCC patients who were alcohol drinkers vs. nondrinkers	Alcohol-induced EMT. miR-30a and miR-934 are upregulated in HNSCC samples from patients who are drinkers. miR-30a and miR-934 expression in HNSCC cell lines produced changes in cellular proliferation and invasion	(9)
miR-142-3p, miR-186-5p, miR-195-5p, miR-374b-5p; and miR-574-3p	Twenty-nine HNSCC patient plasma samples after chemical and radiation therapy; controls were plasma samples from 12 healthy volunteers matched by age and sex	Circulating in plasma miR represent a promising marker for prognosis and therapy monitoring in the plasma of HNSCC patients. They found tumor-related circulating therapy-responsive miRNAs validated them in an independent cohort of HNSCC patients	(10)
miR-26a and miR-26b	Thirty-six pairs of OSCC primary tumors with their corresponding normal epithelial tissue samples. No treatment before staging; SAS (derived from a primary tongue SCC) and HSC3 (derived from a lymph node metastasis of tongue SCC) cell lines were used	Up-regulation of both miR-26a and miR-26b in cancer cell lines inhibited cell migration and invasion. Novel transmembrane TMEM184B gene was a direct target of miR-26a/b regulation	(11)

Table 1 (continued)

Table 1 (continued)

microRNAs	Tissue, cell origin	Function and commentaries	References
miR-196a	Forty-one OSCC samples were analyzed with matched normal tissue OPM, HNSCC cell lines, primary NOKs	miR-196a and HOXB9 are highly expressed in OSCC compared to NOKs, a pattern also seen in OSCC tissues. Knock-down of miR-196a expression decreased HNSCC cell migration, invasion and adhesion, but had no effect on proliferation	(12)
miR-148a and miR-375	Seventy-nine formalin fixed paraffin embedded tissue sections of mild, moderate, severe dysplasia, cancer in situ, laryngeal cancer and normal epithelial controls	Conclude that up-regulation of miR-148a or miR-375 expression in patients with laryngeal dysplasia may predict subsequent malignant transformation	(13)
miR-10b, miR-29c, and miR-205; miR-29c and miR-205	Fifty ESCC patients and 50 healthy controls. Blood samples are collected	Diagnosis of ESCC was clinically confirmed by histo- pathology or biopsy; the research was conducted in the Asian population. Hence, it remains unknown whether microRNAs have the same diagnostic performance in Caucasian or African group	(14)
miR-193b-3p and miR-455-5p	From TCGA, OPSCC, OSCC, LSCC, 523 patients in the TCGA database; 95 OPSCC cases were included for validation; FFPE tumor tissues were collected for pathological analysis before radiotherapy or chemo-therapy	miR-193b-3p and miR-455-5p were positively associated with survival, and miR-92a-3p and miR-497-5p were negatively associated with survival in OPSCC 5 years post treatment. miRNA signature was able to further distinguish high- and low-risk patients within HPV(+) OPSCC patients	(15)
let-7f-5p, let-7e-5p, miR-130a-3p, miR-361-5p, miR-99a-5p, miR-29c-3p	FFPE samples of tumor and normal mucosa from 12 patients aged <30 years old with SCC of the tongue	Aggressive oral cavity cancer in patients <30 years old is associated with a distinctive expression pattern of the let-7 family. let-7f-5p was up-regulated in non-aggressive tumors, whereas let-7e-5p was up-regulated in aggressive tumors, compared to normal tissue	(16)

TCGA, the cancer genome atlas; ATM, Ataxia-Telangiectasia Mutated; FFPE, fixed paraffin-embedded; FNA, fine-needle aspiration; OPM, oral pre-malignant; NOKs, normal oral keratinocytes; EMT, epithelial-mesenchymal transition; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; ESCC, esophageal squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma; OSCC, oral squamous cell carcinoma; LSCC, laryngeal squamous cell carcinoma; SCC, squamous cell carcinoma.

response. The sensitivity and specificity of this molecular signature of radiosensitivity was high, and it did not correlate with response to other types of therapies.

Although the RSI has been validated in various cancer types, work from others suggests that each tumor behaves differently and thus genomic data cannot be extrapolated to all tumor types. In HNSCC, this aspect is supported by the previous findings of the positive-HPV status being associated to radiosensitivity only for oropharyngeal cancers compared to other HNSCC tumor sites. Given these limitations, the results from previous work in HNSCC (*Table 1*) are difficult to be interpreted particularly since there has been heterogeneity amongst the types and subtypes of the tumor tissues used, as well as the treatments received prior to analysis. Some studies have also suggested that a stem cell fraction within the tumors are the initiating pre-cancerous cells (20,21). These data highlight the importance of the context in which biomarkers are identified when designing signatures of radioresistance for HNSCC.

Recently, de Jong *et al.* [2015] reported a gene signature of radiosensitivity specific to laryngeal HNSCC (5). They used 32 HNSCC cell lines from primary laryngeal cancers with known radiosensitivity, which were not exposed to radiation or chemotherapy prior to collection. Their findings were then validated using patient tumor samples and genetically modified cell lines.

Statistically significant mRNA expression differences were found between cell line groups. They also observed an inverse correlation between microRNAs (miRs) relative to the cell lines' radioresistance. miRs are short segments of non-coding single-stranded RNAs composed of 21-24 nucleotides that suppress gene expression by binding to complementary segments at the 3'-untranslated region of mRNAs. Since the discovery of miRs by Victor Ambros and Gary Ruvkun in 1993, there has been extensive work to characterize their specific targets and role in human disease (22,23). A role in cancer was first suggested by Calin *et al.* [2002] reporting a deletion of miR-15 and miR-16 in B-cell chronic lymphocytic leukemia (CLL) (24,25).

Twelve miRs were identified and linked to the regulation of the differentially identified mRNAs. These findings from their *in vitro* studies were then validated using samples from 34 pts with T2-3 tumors who were treated with radiotherapy alone with a curative intent (17 with local recurrence, 17 without local recurrence). The expression levels of the most significant miRs differentially expressed in the cell lines was tested in these patient tumor samples. Patients with local recurrence were found to have low

miR-203 levels in their tumor samples. Although statistical significance was not achieved for other miRs, samples from patients with higher recurrence rates also showed lower expression of miR-452, miR-200b, and miR-141. The cellular functions associated with the differentially expressed mRNAs and miRs suggested epithelial-mesenchymal transition (EMT) mechanisms as predictive of radioresistance. However, allocation of the correct gene targets for every miR remains a challenge. Thus to validate that the differentially expressed mRNAs were involved in EMT, they used two sets of cell lines genetically modified to undergo EMT and their respective parental controls. The cells that had undergone EMT were more resistant to radiotherapy.

MicroRNAs and EMT

Multiple studies in cancer suggest that miRs play a role in cancer pathogenesis by their regulatory effects on EMT. EMT is a cellular developmental process associated with increased cellular mobility, migration, and invasion of cells. Thus EMT appears to be one important mechanism of tumor metastasis including in laryngeal cancer (26). Various pathways have been identified as potential targets to prevent EMT in cancer. Yang *et al.* [2016] recently proposed FAK/PI3K and AURKA as potential targetable pathways (27,28) (*Figure 1*).

In relation to the role of miRs in EMT, miR-200 family and miR-203 have been shown to be negative regulators of EMT (29). This appears to be mediated by a double negative feedback loop between Zeb1/2 and miR-200 family. Hypoxia and TGF β upregulate the expression of Zeb1/2 which repress miR-200 gene expression thus initiating EMT. Conversely, increased levels of miR-200 inhibit Zeb1/2 and the cell status switches from mesenchymal to an epithelial state. The role of miR-203 in laryngeal cancer as suggested by de Jong's findings are not surprising since this association with EMT has also been found in other cancers. Upregulation of Zeb1/2 and Snail1/2 suppress miR-203 in prostate and breast cancer cells, which then promotes EMT and tumor metastasis.

EMT and radiosensitivity

Recent work from Johansson *et al.* [2016] also supports a role of the EMT process in radioresistance (30). They found expression profiles of EMT signature genes, CDH1 (E-cadherin), CDH2 (N-cadherin), FOXC2, TWIST1,

VIM, and FN1 in cell lines from 25 HNSCC primary tissues. Amongst the 25 cell lines, 4 showed a higher expression of the EMT signature genes. These four lines with EMT signature showed a mesenchymal morphology, higher migratory capacity, and radioresistance. It is also important to note that the 4 lines with highest EMT signature had a CD44 high/EGFR Low pattern previously associated with stemness in HNSCC and in mammary tumor cells.

The EMT signature was similarly observed in both the radioresistant cell lines and tumors from patients in the de Jong study, which includes a list of genes that also define cancer stem cells (31). Two cell lines that showed low expression of EMT genes were induced to undergo EMT via upregulation of the TGF β pathway. Taken together, these data suggest that radioresistant cells exhibit EMT properties and biomarkers associated to EMT regulatory mechanisms.

Other pathways of radiosensitivity

One of the most common signaling pathways associated to radiosensitivity is the EGFR-PI3K/AKT pathway (32). *In vitro* exposure of prostate cancer cells to dual inhibitors of the PI3K/mTOR pathway triggered radiosensitization by shifting the cell cycle towards arrest in the G2 phase of the cell cycle. PI3K/mTOR inhibition at G2 also caused a reduction in DNA double strand base repair and non-homologous end joining repair mechanisms, repressed colony formation, and induce apoptosis.

A recent relationship was reported between adenosine monophosphate-activated kinase (AMPK) and radioresistance in colon cancer samples (33). AMPK is a known regulator of cellular energy and reprogramming metabolism. Radioresistant tumors were found to have up-regulation of the AMPK protein and AMPK mRNA levels. On the contrary radiosensitive colon cancer cells showed down regulation of AMPK mRNA and protein levels. Further, activating the AMPK pathway in cancer cells with metformin promoted radioresistance *in vitro*, while inhibition of AMPK pathway by RNAi or chemical molecules re-sensitized radioresistant cancer cells. This study demonstrates the possibility of using AMPK pathway inhibitors as targeted therapies to enhance the radiosensitivity of tumors.

A proteomic and transcriptomic analysis of HPV-negative HNSCC was also recently performed that identified several proteins that were dysregulated in radioresistant cells including FGFR, ERK1, EGFR, and PTK2/FAK (34).

In vitro inhibition of PTK2/FAK, but not FGFR, led to significant radiosensitization in several HNSCC cell lines. The mechanisms appeared to be potentiation of DNA damage by increased G2/M arrest of tumor cells. The PTK2/FAK protein expression was associated with its gene copy number, and correlated with outcomes on a cohort of HNSCC patients treated with radiation. A similar association was observed in the Head and Neck Cancer subgroup of the cancer genome atlas (TCGA). Thus, PTK2/FAK copy number could be a predictive genomic marker of radioresistance in HNSCC.

Summary

There is tremendous potential in this era of precision medicine to apply molecular signatures to predict the response of various tumors to radiotherapy. Many pathways are known to regulate radiation sensitivity, and novel biomarkers such as miRs are emerging to regulate such pathways. More evidence supports the EMT pathway in promoting radioresistance, and key players of EMT can be potentially targeted to enhance radiosensitivity of tumors including EGFR, TGF β , mTOR, PKI3 and AMPK. These findings warrant further validation studies before implementing these signatures into the clinic.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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