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Genomics Reloaded: Rise of the Expression Profiles

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In this issue of Oncology Scan we examine the use of genomic signatures to predict response to head and neck cancer therapy [1–3]. In the past decade-in-a-half, multiple teams have identified and developed gene expression profile signatures capable of subclassifying head and neck cancer, prognosticating outcome, and predicting treatment response. We discuss the implications of these genomic signatures for head and neck cancer patients, how these signatures can be applied to other therapies, their use to assist in pre-clinical studies, and suggestions on how this work can move the field forward not just for head and neck cancer but potentially for all types of cancers.

Klinghammer, *et al.* Basal subtype is predictive for response to cetuximab treatment in patient-derived xenografts of squamous cell head and neck cancer. *International Journal of Cancer* 2017 [2].

Summary:

This translational genomics paper hypothesized that basal subtype tumors (which are known to have epidermal growth factor receptor (EGFR) pathway activation) would be preferentially sensitive to anti-EGFR therapy. In order to test response to common chemotherapies (e.g. carboplatin, cisplatin, or cetuximab), the authors used patient-derived xenografts (PDXs). PDXs are a powerful pre-clinical model system in which fragments of a patient tumor are engrafted onto an immunocompromised mouse in order to test novel therapeutics or investigate tumor biology [4, 5]. Tumors were harvested 3 weeks after initial treatment and analyzed using Next Generation Sequencing to assess for mutational differences between tumors and using gene expression microarrays. They performed a number of analyses [6–8], to classify the PDXs into one of three subtypes (i.e. basal, classical, and mesenchymal/inflamed). The only correlation between treatment and subtype was seen for cetuximab treatment. Tumors of the basal subtype, enriched for the EGFR pathway, responded favorably to cetuximab. Tumors of the mesenchymal/inflamed subtype, demonstrated negative enrichment for the EGFR pathway and, did not respond to cetuximab. Mutational analysis demonstrated no significant differences between subtypes but among the most frequently altered genes overall were TP53 and PI3KCA consistent with previously published work [9, 10]. While the authors noted enrichment in mutated PI3KCA within the mesenchymal/inflamed subtype, no association between systemic therapy and mutational status was observed, consistent with other studies [11].

Bossi, *et al.* Functional genomics uncover the biology behind the responsiveness of head and neck squamous cell cancer patients to cetuximab. *Clinical Cancer Research* 2016 [1].

Summary:

In this retrospective, genomic analysis paper, patients treated with chemotherapy and cetuximab between 2008 and 2012 were identified. A total of 40 patients with recurrent or metastatic head and neck squamous cell carcinoma were included in the analysis. Patients were stratified into two groups: long-progression-free survival (PFS) (n=14) or short-PFS (n=26). Whole genome gene-expression profiling was performed on formalin-fixed, paraffin-embedded tumor specimens. Importantly, the authors rigorously assessed their dataset using modeling-prediction software, existing validation datasets, and technical validation for gene expression. A gene signature based on over 500 differentially expressed genes was independently validated against a metastatic colorectal cancer dataset from patients treated with cetuximab. The identified signature was able to demonstrate a significant difference between short and long-PFS in the colorectal cancer dataset suggesting a robust signature with relevance across tumor types. Further stratification of the data-set into molecular subtype's (see above) demonstrated that the long-PFS group most closely resembled the basal subtype consistent with the work of Klinghammer and colleagues. Bossi, *et al* also demonstrated up-regulation of RAS pathway, particularly oncogenic KRAS mutants, within the short-PFS signature, consistent with studies in other types of cancers in which RAS activation correlates with cetuximab resistance [12, 13]. They validated these findings in HNSCC cell lines that were either sensitive or resistant to cetuximab treatment.

Scott, *et al.* A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncology* 2016

This large-scale retrospective study introduced the concept of genome-based adjustment of radiotherapy dose (GARD) using patient gene expression profiles to help predict an optimal radiation dose. GARD was derived using a previously established gene-expression-based radiation-sensitivity index and the linear quadratic model. Using primary tumor samples prospectively collected through the Total Cancer Care protocol, this study drew from over 8,000 tissue samples representing 20 different tumor types that underwent gene expression analysis. Based on their stratified gene expression profile, tissue groups were assigned a GARD score based on their sensitivity to 3 different radiation dose ranges – 45, 60 or 70 Gy and higher. Patients with high GARD scores exhibited improved distant-metastasis-free survival rates and GARD remained an independent prognostic (and predictive) factor after controlling for known variables. They tested GARD against 5 different publically available expression profiles and for each dataset, GARD remained highly predictive of local control, relapse-free and overall survival [3]. In particular, samples drawn from the TCC demonstrated that cervical and oropharyngeal squamous cell carcinoma patients had a high GARD score while non-oropharyngeal head and neck cancer was associated with a lower GARD score.

Comments:

Therapies targeting EGFR represented the first “breakthrough” molecularly targeted drugs for head and neck cancer. In randomized studies, the addition of cetuximab to radiation [14] or systemic chemotherapy [15] improved outcomes. There remains significant uncertainty as to how to use these drugs to deliver personalized treatment to head and neck cancer patients: the right therapy to the right patient at the right time. Simple approaches such as stratifying patients by high versus low EGFR status have failed to demonstrate any correlation with outcome and cetuximab use [16].

These first two papers demonstrate the potential power of genomic data to predict responses to anticancer drugs. Klinghammer and colleagues demonstrated through molecular subtyping of their head and neck cancer PDXs that they can predict response to cetuximab therapy and that a favorable response was strongly correlated with basal subtype. Bossi, *et al* developed a gene expression profiles that could stratify cetuximab treated patients into long and short PFS (19 vs. 3 months, respectively). Together, these studies suggest that we may be able to identify a group of patients most likely to benefit from the use of cetuximab and illustrate how the use of preclinical model systems can enable us to identify predictors of therapy response. Given the significant cost of prospective therapeutic trials and the critical metric of improving patient overall survival, the need to design rationale, data-driven clinical studies is paramount. We hope that the use of pre-clinical models such as these could be used to inform patient selection criteria for future clinical trials. Had this approach been used for trials such as RTOG 0522, perhaps the results of the study would have been different as investigators could have the group of patients most likely to benefit from a novel therapy. To be sure, genomic analyses must be tested in prospective trials in order to demonstrate their true value in cancer care. These studies also demonstrate ways in which powerful preclinical model systems can be used to move the field forward.

In the third paper, the group of Javier Torres-Roca sought to use their radiation sensitivity index to personalize radiation dose using GARD [3, 17]. This paper strongly suggests that precision medicine, traditionally associated with Medical Oncology and systemic therapy, may yet find an important role in Radiation Oncology. While Radiation Oncologists have long personalized radiation fields to individual patients, we have largely left the radiation dose used to treat a given tumor fixed. The use of GARD provides one example of how we could identify a group of patients who will respond to radiation treatment and may also enable us to identify the optimal dose for each individual patient’s cancer. Clearly the radiation sensitivity index and GARD will require further evaluation in prospective trials to validate our ability to continue to cure cancer patients while personalizing the radiation dose they receive.

It is easy to envision a day when gene expression profiles will be used to personalize therapy for our patients. These gene expression profiles are not the end, but really, a new beginning and will serve as a jump point for clinicians and scientists to make additional discoveries that will continue to advance the field of medicine. Radiation has been used to cure cancer patients for over a century. By embracing the personalization of cancer care, we will continue to provide valuable, effective care for the next 100 years.

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