EGFR regulation by microRNA in lung cancer: a rose by any other name ... is an increasingly complicated rose

Since it was first described 40 years ago, the epidermal growth factor (EGF) and its receptor (EGFR) has become one of the most studied entities in all human biology [1, 2]. The potent role of EGF in transforming normal cells into tumors was an early observation with specific implications for lung cancer clear by the early 1980s [3, 4]. In 1980, the gene was localized to chromosome 7, opening the door for consideration of the complex set of genetic aberrations now described for the EGFR locus [5]. In the intervening quarter century, many downstream regulatory and signaling events have been reported, most notably through RAS, PI3K, and AKT [6]. Despite the progress that has been made, however, much uncertainty remains for the role of EGFR in human cancer.

In consideration of EGFR regulation, its pathways, and associated targeted therapies, investigators in the current issue of Annals of Oncology turn their attention to a relatively new class of biomolecules, the microRNAs (miRNA). MicroRNAs are abundant short nontranslated RNA species that bind to the 3’-untranslated regions (UTRs) of target messenger RNA transcripts, thereby inhibiting their translation into protein. Weiss et al. use a rational approach to select candidate miRNAs theoretically capable of EGFR regulation, focusing on miR128b as a prime suspect on the basis of a high degree of matching to target sequence and its genomic coordinates on 3p22, a region frequently lost in lung cancer. Using cell line experiments, the authors demonstrate convincingly that the 3’-UTRs of EGFR is a likely target of miR128b and establish that regulation of the protein product is also a possibility. This finding is the most significant and novel contribution of the current work. Although not conclusive, the authors support the regulation of protein levels by miR128b by correlating aberrations of the 3p22 locus in a limited number of cell lines with lower miR128b levels compared with cells in which the locus is preserved. In each case of 3p22 alteration, EGFR abundance as measured by immunohistochemistry (IHC) corresponds to the abundance miR128b, although admittedly the small number of model systems might obscure other mechanisms by which EGFR protein abundance is regulated. In clinical samples, however, the predicted correlation between loss of heterozygosity (LOH) at 3p22 and IHC for EGFR was not observed, suggesting that protein regulation in patients is more complex than documented in the model system. Nonetheless, the evidence for regulation of EGFR by miR128b is certainly intriguing and an important observation by these investigators.

In addition to considering the pathologic processes related to miRNA regulation of EGFR, the authors of the current manuscript evaluate miR128b in the context of an already complex catalogue of biomarkers. With so many lines of evidence pointing to EGFRs importance in cancer, scores of investigators have postulated its role as a biomarker of prognosis and predictive response to therapy. The interest in biomarkers is intensified since both the primary protein EGFR and its downstream elements have been targeted by a range of therapeutics [7]. Most notably, two classes of drugs, oral tyrosine kinase inhibitors and mAbs, have been developed and approved for the treatment of a range of EGFR-driven tumors, most notably lung, colon, pancreatic, and head and neck cancer.

Certainly, the most obvious biomarker would be the protein itself, and there is a large body of work reporting associations between EGFR IHC staining in human cancer prognosis [8]. Increased expression of EGFR and its phosphorylated targets has generally been associated with less favorably prognosis across many tumor types, although controversy is such that there remains little role for IHC in the clinical management of patients. One notable exception is that IHC positivity is a component of the FDA indication for anti-EGFR therapy in colon cancer with the anti-EGFR mAb cetuximab in the United States.

Enthusiasm for IHC has largely been supplanted in lung cancer by reports of mutations in tumor EGFR and associated improvements in survival and response to tyrosine kinase inhibitor therapies. Since the initial reports of near universal response to therapy in patients harboring mutation, a more complex picture has emerged in which not all mutations convey drug sensitivity and gene amplification appears to play a role as well. Further complicating the picture is the repeated observation that the survival benefit of anti-EGFR therapy in lung cancer is of the same order of magnitude in patients with and without mutation. In summary, consensus EGFR biomarkers have not emerged in lung cancer, inspiring leaders in the field to convene a working group on the topic [9]. One observation that has gained some acceptance is that patients with KRAS mutation appear to be the least likely to benefit from anti-EGFR therapy in both lung and colon cancer. Interestingly, in the face of (or perhaps because of) the considerable complexity of these biomarkers, a sense of ambivalence as to their use has emerged on the part of clinicians. It has generally been easier to administer the therapy and await a response (or failure) than to seek additional information from biomarkers. In part, this may relate to the limitations of acquiring usable specimens for analysis in many patients, although this is likely not the only reason.
Among the group of authors reporting the role of miR128b in lung cancer are several with clear experience in the field of EGFR biomarkers, particularly in regards to EGFR amplification. Appropriately they investigate in the current issue the potential prognostic and predictive role of miR128b, with intriguing results. In this small retrospective cohort of Asian ethnicity, LOH at the miR128b locus was associated with increased disease control in response to anti-EGFR therapy by the oral tyrosine kinase inhibitor gefitinib compared with patients without LOH at the locus. In addition, survival was also significantly longer in these same patients, with LOH of mir128b again conveying the favorable outcome. Given the nature and size of the data, this finding can only be considered hypothesis generating at this stage. However, recent studies have also implicated a miRNA signature in association with relapse and survival, provoking additional interest in the clinical impact of this biological phenomenon [10].

So, 40 years after the first reports of its ligand, it appears as though a new chapter may have opened for the well-studied EGFR gene, now as a target of miRNA regulation. Accordingly, new insights wait for cancer biology with potential benefits for patients as new targets are unveiled and biomarkers emerge. A rose by any other name …

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