Intriguing issues of EGFR targeting in head and neck cancer

We have read the recent comprehensive review by Cruz et al. [1] regarding the targeting of receptor tyrosine kinases and their therapeutic perspectives in head and neck squamous cell carcinomas (HNSCC). The major focus of this report was epidermal growth factor receptor (EGFR) biology and targeting. However, we feel that some important issues of this subject have not been adequately addressed.

An important step of EGFR "life span" comprises a two-step endocytosis process [2]. In the first step, a rapid ligand-dependent internalization removes activated receptors from cell membrane and enclaves them into endosomes. In the second step, internalized receptors are either targeted to lysosomes, where they undergo degradation, or they recycle back to the membrane. Ligand-induced receptor endocytosis generally down-regulates EGFR signaling, even though there is some evidence that the internalized receptors may retain their capability of coupling effector/adaptor proteins and activating signaling cascades [3]. This is of paramount importance as it has been suggested that monoclonal antibodies can result in synergistic effects when combined with chemotherapeutic agents due to their ability to produce long-term EGFR suppression through receptor internalization and degradation, which has not been seen with EGFR-TKIs.

The implication of EGFR in HNSCC is achieved by at least four major mechanisms; three of them are reported in the present review. However, it should be stressed that among the several classes of EGFR ectodomain mutants (vI–vVII) that have been discovered, it was recently shown that EGFRvIII in HNSCC leads to constitutive ligand-independent receptor activation, enhanced downstream effects and resistance to wild-type EGFR targeting [4]. Moreover, it should be emphasized that EGFR activation can be also achieved through cross-talk interaction with other receptors, such as G-protein-coupled receptors [5], platelet-derived growth factor receptor [6], insulin-like growth factor receptor [7] and hormone receptors [8].

Finally, perhaps the most intriguing issue is to find the optimal way to intercalate EGFR inhibitors with chemotherapy and/or radiotherapy and to consider the most appropriate treatment sequence. EGFR inhibitors commonly produce cytostatic effects, characterized by cell cycle arrest in G1 phase. Preclinical data have shown that the proliferation of irradiated tumor cells is induced through EGFR stimulation [9]. Therefore, the application of EGFR inhibitors before and during radiotherapy might inhibit radiation-induced receptor activation and sensitize cancer cells to the lethal effects of ionizing radiation. It has been also suggested that better results are likely be obtained with the application of EGFR-targeted agents after chemotherapeutic agents that are cell cycle dependent, although it is still unclear if this is also the case for cytotoxic agents that are not necessarily S-phase specific (e.g. platinum compounds). Moreover, it was recently shown in vitro that the alternate sequence of chemotherapy and EGFR inhibitors might repress EGFR degradation [10]. Based on preclinical data, a few clinical trials are ongoing to test these hypotheses. If scheduling does turn out to be an important issue in HNSCC treatment, then the preference of EGFR inhibitor might be on the basis of their specific pharmacokinetic profile (e.g. half-life).

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