HNSCC cells resistant to EGFR pathway inhibitors are hypermutated and sensitive to DNA damaging substances.

Abstract:

Despite remarkable successes with targeted therapies in the treatment of cancer, resistance can occur which limits the clinical outcome. In this study, we generated and characterized resistant cell clones derived from two different head and neck squamous cell carcinoma (HNSCC) cell lines (Cal27, UD-SCC-5) by long-term exposure to five targeted- and chemotherapeutics (afatinib, MK2206, BEZ235, olaparib and cisplatin). The resistant tumor cell clones showed an increased ERK1/2 expression and an altered expression of the stem-cell markers CD44, ALDH1, Oct4, Sox2, Nanog and Bmi1. None of the single markers alone was predictive for resistance to all five targeted- and chemotherapeutics. Furthermore, long-term exposure of tumor cells to these five drugs resulted in an eightfold increase in the mutational rate compared to untreated cells. Interestingly, targeted- and chemotherapy resistant cell clones remained sensitive to irradiation. Lastly, clones that were resistant to afatinib, MK2206 or BEZ235 showed cross-resistance to further treatment with therapeutics that affect the same signaling pathway, but remained sensitive to those affecting different pathways such as cisplatin and olaparib. In contrast, cell clones which were once resistant to cisplatin or olaparib were found to be
multidrug-resistant. These data might indicate that patients with HNSCC benefit more by a first line targeted therapy followed by cisplatin as a second line therapy.

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