TITLE

Targeting Cancer Stem Cells and tumor-stromal cross talk: Strategy to reverse drug resistance in Oral Cancer?

ABSTRACT

Chemoresistance leading to disease relapse is one of the major challenges in improving treatment outcome in head and neck cancers. Evidences point out that current chemopreventive and therapy approaches induce an initial response but witha subsequent relapse, in many cases the recurrent tumour being a more aggressive one. Inherent tissue heterogeneity, mirrored in the premalignant lesions as well as in the carcinomas and which includes the stromaand stem cells along with the highly dividing malignant cells, is now considered a major causal factor. Targeting the tumour in its entiretyoughtto be the focus of treatment strategies; Cancer Stem Cells (CSCs) are increasingly being part of such attempts to improve treatment response.Further, analogous to the stromal role in maintaining normal stem cell populations, tumour-stroma interactions are considered to provide a niche to cultivate CSC behaviour thereby promoting tumorigenic behaviour. Accordingly targeting CSCs and tumour-stroma interactions in conjunction with the current standard of care needs to be explored as a treatment strategy.

4NQO-mice oral cancer models and primary cell lines derived from the mice, indicate CSCs to be an integral part of the oral carcinogenic process, thereby advocating the anti-CSC targeting strategy in chemoprevention. This is also mirrored in *in vitro* human cell line models. Accordingly, targeting NOTCH1, one of the markers upregulated during dysplasia, resulted in downregulation of CSC properties as well as dysplastic characteristics. The application of this concept in chemotherapy was tested in drug resistant cell line models developed in the lab; anti-ALDH1A1 targeting as well as inducing pro-apoptotic pathways improved the efficacy of Cisplatin treatment *in vitro* and *in vivo*. Tumour-stromal cross talk has been a known determinant of cancer cell behaviour, studies in the lab provide evidence for enriched CSC behaviour and drug resistance under the effect of cross talk with cancer associated fibroblasts (CAF). Targeting the cross-talk pathways enabled an abrogation of this effect and induced sensitivity to existing oral cancer chemo-preventive and chemo-therapy drugs. Given these evidences, CSCs and the CSC-enriching effect of tumor-stromal cross talk in oral cancer needs to be explored towards identifying underlying molecular mechanisms. Targeting the pathways that mediate the tumour-stromal cross talk is a major step towards reversing resistance to chemotherapy and prevention, further preclinical and clinical studies

will establish the clinical relevance and utility of these targets in oral cancer, either individually or in adjunct with existing chemopreventive/chemotherapy drugs.