Editorial

Mesenchymal-Epithelial Transition in Oral Cancer

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Epithelial-mesenchymal transition (EMT) is a well-known event during cancer metastasis. Step-wise accumulation of genetic mutations during carcinogenesis leads to reduction/loss of E-cadherin in epithelial cells with eventual loss of cell-to-cell adhesion and separation of tumor cells. Thus, the epithelial cells lose their apicobasal polarity, gain motility and acquire mesenchymal phenotype which heralds metastasis. A recent hypothesis states that the disseminated metastatic cells revert back to epithelial phenotype, typically demonstrating re-expression of E-cadherin to allow efficient colonization at secondary sites. This process is termed mesenchymal-epithelial transition (MET) or mesenchymal-to-epithelial reverting transition.[1-3] MET provides survival advantage to tumor cells at a lower metabolic load due to the E-cadherin adhesions and also is the reason behind why metastases recapitulate the primary tumor pathology.[4] Brabletz *et al.* observed that metastases from tumors originally expressing nuclear β-catenin were found to re-express E-cadherin, and their β-catenin became cytoplasmic, which is indicative of an MET.[5]

Only a handful studies in exist in the current literature on MET in oral cancer. Since, oral squamous cell carcinoma (OSCC) constitutes the majority of oral cancers, OSCC, and oral cancer is used interchangeably in this manuscript. Worthy to note is the expression of E-cadherin in lymph node metastases of 2 of OSCC cases in a study by Schwock *et al.* which they attributed to MET following nodal metastasis. Another school of thought states that tumor cells may exist in "quasi-mesenchymal" states, rather than undergoing complete transition.[6]

Hong *et al.* studied induction of MET in OSCC cell lines by inhibiting Akt activity. Decreased nuclear factor-kappa B signaling and downregulation of snail and twist were observed on Akt inhibition. Hence, they proposed Akt inhibition would be a potential treatment strategy to control cancer metastasis.[2]

A study by Nguyen *et al.* investigated the role of fibroblast growth factor receptor 1 (FGFR1), a cytokine (FGF) receptor that acts as oncoprotein during head and neck SCC (HNSCC) tumorigenesis. Simultaneously, they also observed the effects of PD173074, a known selective inhibitor of FGFR1. HNSCC cases demonstrated a high expression of FGFR1 and this correlated with malignant behaviors. An interesting finding was relative overexpression of FGFR1 in EMT cell lines compared to non-EMT cell lines. Furthermore, on treatment with PD173074 cancer cells exhibited a morphological change from spindle-to cobblestone-like. Thus, the authors proposed the therapeutic significance of PD173074 inducing MET which suppressed cancer cell growth and invasion.[7]

Chang *et al.* investigated the role of multifunctional signaling modulator, connective tissue growth factor (CTGF) in HNSCC. CTGF acts as either an oncoprotein or a tumor suppressor in different cancer types. Their results revealed that CTGF promoted MET and reduced invasiveness in HNSCC cells.[8]

Recently, a study by Cheng *et al.* investigated the expression of growth differentiation factor-10 (GDF10) (a member of the transforming growth factor-β [TGF-β] superfamily) in oral cancer cell lines. They found GDF10 to be down-regulated during oral carcinogenesis. GDF10 inhibited EMT and hence authors suggested the use of TGFBR3, an upstream activator of GDF10 expression to reversing the process of EMT.[9]

Thus, induction of MET made possible in oral cancer cells due to epithelial plasticity may guide us toward novel therapeutic avenues to oral cancer. As the current research is heading toward uncovering the molecular mechanisms underlying EMT/MET, the future of EMT/MET research seems to be promising.

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