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Role Of Cdc25a, Limd1 And Rbsp3 In The Development Of Head And Neck Squamous Cell Carcinoma.

Shreya Sarkar

The study aims at understanding the importance of the candidate genes LIMD1, RBSP3 and CDC25A in the development of Head and Neck Squamous Cell Carcinoma (HNSCC). To this end, profiling of molecular signature (expression/ promoter methylation) was first performed in basal/parabasal and spinous layers of normal epithelium, followed by deciphering the mechanism of alterations (expression/ promoter methylation/ deletion/ mutation) during tumorigenesis and clinico-pathological correlation. Different alleles of markers of the genes were determined in normal specimens, followed by deletion of different sized alleles in HNSCC and correlation with expression in normal epithelium. Finally, the interplay of the genes was assayed in an in vitro model using pre- and post-neoadjuvant chemotherapy treated paired tumour/ adjacent normal specimens from the same patients to understand their significance in tumorigenesis.

The candidate genes, although tumour suppressors in function show distinct molecular signatures in the basal layer of normal oral epithelium and alteration during tumorigenesis. RBSP3 maintained its low expression/ high promoter methylation during tumorigenesis through further methylation/ deletion. Conversely, LIMD1 and CDC25A showed loss of high expression with/without promoter methylation respectively through deletion/promoter methylation. Both alterations and patient outcome were associated with the etiological factors tobacco and HPV.

Susceptible (CA) alleles of the candidate genes showed differential presence in the normal population. Most markers showed loss of the larger sized allele in tumours, although there was similar levels of expression of the genes in normal epithelium irrespective of allele size.

Study of interplay showed that compared to pre-therapeutic tumours, post-therapy tumours revealed diminished proliferation index/ enhanced apoptotic index, indicating halting of the cell cycle. RBSP3 and LIMD1 showed increased expression in post-therapy tumours, validating their tumour suppressive role in the cell cycle. Similarly, cMYC showed reduced expression with increased in RB/pRB ratio. Enhanced BAX/ BCL2 ratio in post therapy tumours indicated induction of apoptosis. Therefore, the candidate genes and their associated alleles were important, not only in development and progression of HNSCC, but also in inducing shrinkage of tumours during neoadjuvant chemotherapy. Assessment of their alterations and their outcome to therapy might prove to be valuable in their use as diagnostic and prognostic tools in head and neck cancers.

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24/11/2015