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Discovery of keratin fusions and their functions in oral squamous cell carcinomas

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Keratin cytoskeleton proteins form intermediate filaments in epithelial cells to regulate cell shape, mobility, membrane trafficking and cellular signaling. Although keratin-6 (K6) and 14 (K14) are highly expressed in certain squamous cell carcinomas and have been suggested as tumor markers, molecular mechanisms of how keratins contribute to cancer development still remain elusive. In this study, several novel K6-K14 chimeras were discovered in oral squamous cell carcinomas (OSCCs) by pair-ended transcriptome sequencing and subsequent validation by fluorescence in situ hybridization (FISH) and junction site mapping. Two unique fusion types (type-1 and type-2) were identified with a total of 23 in-frame fusion variants verified in OSCCs. Clinical screening confirmed high detection rate of K6-K14 fusions in tumor samples: 33% for type-1 and 25% for type-2 using fusion-specific QPCR. To know the cause for the keratin fusions, OSCC cells were treated with arecoline, 4NQO, alcohol and the combinations of these three well-known OSCC carcinogens. Our data found acrecoline as the promoter to accelerate the induction of K6-K14 fusions by 4NQO. Functional study further confirmed that the type-2 fusions can increase cell proliferation, migration and invasion via EMT and cancer stem cell formation. Our study thus uncovered a novel mechanism involved in carcinogenesis by keratin fusions.

Biography

Jim J C Sheu is a Molecular Biologist, received his PhD degree from National Tsing-Hua University, Taiwan and his Post doctorate training at the Johns Hopkins Medical Institutes, USA. Before he went to Hopkins, he has served as Director of Protein Drugs at Development Center for Biotechnology, Taiwan. Currently, his study interest is to discover novel cancer-associated genes using genome wide technologies and to define their roles in cancers. With working experiences at both academic and industrial organizations, his research team aims to develop new treatments/methods for biomedical applications.

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