Abstract

Oral sub-mucous fibrosis, a potential pre-cancerous condition, significantly progresses into oral squamous cell carcinoma but diagnostic ambiguity prevails for malignant potentiality progression in dysplastic and non-dysplastic conditions. In addressing diagnostic ambiguity, multidimensional (viz. structural, multi-level molecular pathology, metabotypes) evaluation of this pathosis may be contributory. This study evaluates oral epithelial nano-architectures, expression changes in epithelial master regulator (p63 and its oncogenic isoform ΔNp63) and markers of epithelial coherence (E-cadherin, β-catenin), maturation (cytokeratin 10) and proliferation (cytokeratins 5/6, Ki67) including exploration of key glycolytic enzyme alteration and metabolomic signatures in oral pre-cancer and cancer. Scanning electron microscopy revealed significant deviations in surface nano-architecture (pit and ridge) and up-regulation in p63, ΔNp63, CK-5/6 including cytoplasmic E-cadherin and β-catenin in dysplasia and cancer. But CK-10 was down-regulated in dysplasia. Positive correlation between ridges to pit ratio and expressions of p63 as well as CK-5/6 noted in both dysplasia and cancer. Graph theoretic analysis on immunohistochemical expression and distribution pattern of p63 along with corroborative FTIR signatures and molecular pathology findings on Ki67 distinctly demonstrated differential molecular pathology status with special reference to cellular proliferation in cancer and pre-cancer. Further, this study for first time documented higher expression of key glycolytic enzyme (α-enolase) as a malignant potentiality marker in dysplastic sub-mucous fibrosis. NMR studies indicated ‘no prominent Warburg Effect’ in oral cancer by documenting status quo in lactate profile but increase in malate production which is again linked to enhancement in fatty acid synthesis required for membrane production of proliferating cells. It also documented abnormal choline metabolism. Again, comparative quantification of metabotypes from minimal tissue extracts (<10µl) by NanoLC MALDI MS studies demonstrated up-regulated lipid phenotypes in such pre-cancer and cancer. Hence, this study provided valuable multi-level information for addressing diagnostic ambiguities of such oral pre-cancer progression and also illustrated their metabolic dimensions.