Metabolic Stress Triggers CD36 Activity in Tumour Initiation in Oral Submucous Fibrosis

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Metabolic stress at the cellular and organismal level may play a significant role in oncogenesis. Lipid-dependent metabolic stress in the extracellular matrix (ECM) has been linked with tumour initiation and metastasis. Previous work has identified the involvement of certain lipid raft molecules like Caveolin-1 in educating sites for metastasis. The fat receptor CD36 in lipid rafts similarly interacts with several ECM molecules, including integrins and is a key upstream regulator in lipid metabolism and collagen degradation leading to the pathogenesis of CD36-mediated signalling that disrupts ECM homeostasis. Oral Submucous Fibrosis (OSF) is a debilitating, potentially malignant condition of the mouth with 7-13% transformation rate, which is frequently found in South Asia and in the Western-Pacific. It is caused by Areca-nut chewing, which progressively restricts mouth opening that contributes to diet-related metabolic stress leading to anaemia and vitamin and protein deficiencies. OSF is marked by epithelial atrophy and fibrosis with accumulated type I collagen in the submucosa undergoing inflammation and reactive immune responses but little is known about the process of malignant transformation. We hypothesized that dysregulated fat metabolism might be a key denominator in the malignant transformation of OSF and CD36 as a fat biosensor may play a pivotal role in the intracellular and extracellular signalling pathways. We analysed patient data with quid chewing frequency and restricted mouth opening and found that the clinical presentation of malignant transformation was strongly associated with the number of betel quids (7-12 or more) used per day. Epithelial thickness increased in 3 folds with the development of oral cancer compared with OSF and OSF-dysplastic stages predominantly characterised by atrophy. Immunohistochemistry with CD36 in OSF showed localization with epithelial cell nuclei adjacent to the basement membrane, while a remarkable elevation of CD36 was seen across tumour cell cytoplasm in the invading islands. Taken together, these suggested how a functional shift in CD36 may result in the malignant transformation of those cells undergoing metabolic stress. Further studies will validate how CD36-dependent cancer initiation favours tumour cell survival and metastasis under metabolic stress conditions.

Keywords: *OSF, Malignant transformation, Metabolic stress, CD36*