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Unraveling the role of p21 activated kinase 1 (Pak1) in UV-B induced premalignant skin lesions

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Non-melanoma skin cancer (NMSC) which includes both squamous cell carcinoma and basal cell carcinoma has become an increasing health problem over the recent years and is mainly caused by overexposure to Ultraviolet (UV) light. P21 activated kinase 1 (Pak1), a major mitogen responsive serine/threonine signaling kinase is a well known regulator of cytoskeletal remodeling that contributes to tumor formation. Alterations in Pak1 expression has been documented in many type of cancers. However, the contribution and direct role of Pak1 signaling to the etiology of Non-melanoma skin cancer has not yet been studied. In the current study, upon UV-B irradiation, we observed a significant increase in Pak1 activity and subsequently its nuclear localization in cell lines and mouse models. Further to understand the role of Pak1 in UV-B induced DNA damage response and survival, Pak1 overexpression and knockdown clones were generated in keratinocytes using viral transduction. Functional assays using these Pak1 modulated systems showed that Pak1 plays a significant role in cell survival upon UV-B exposure. Further, we elucidate the molecular mechanism of Pak1 activation by UV-B in keratinocyte cell lines is mediated by both the CPDs (Cyclo Pyrimidine Dimers) and EGFR pathway. In addition, we validated the above findings in a clinical setting by perceiving for Pak1 in various pre-malignant lesions of NMSC and observed that Pak1 expression is associated with histological evidence of chronic sun damage. We intend to focus on molecular mechanism and contribution of Pak1 to the transforming properties that promote the progression of skin lesions to more invasive tumors.

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Development of *in vitro* three-dimensional (3D) culture models of hepatocyte-like cells (HLC) using polymer scaffolds

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Stem cell-based tissue engineering has emerged as a promising avenue for treatment of liver diseases and as drug metabolism and toxicity models in drug discovery and development. *In vitro* simulation of microenvironment niche for hepatic differentiation remains elusive, due to lack of information about crucial factors for the stem cell niche. For generation of functional hepatocytes, an *in vivo* three-dimensional (3D) microenvironment and architecture should be reproduced. Towards this, we fabricated three scaffolds as DG1 (Dextran-Gelatin), CH1 (Chitosan-Hyaluronic acid) and GEVAC (Gelatin-Vinyl Acetate). Hepatic differentiation of human umbilical cord derived mesenchymal stem cells (hUC-MSCs) was induced by culturing hUC-MSCs on these scaffolds. The scaffolds support hepatic differentiation by mimicking the native extracellular matrix (ECM) microenvironment and architecture to facilitate 3D cell-cell and cell-matrix interactions. The expression of hepatic markers, glycogen storage, urea production, albumin secretion and cytochrome P450 (CYP450) activity indented hepatic differentiation of hUC-MSCs. The differentiated hUC-MSCs on the 3D scaffolds formed hepatospheroids (three dimensional hepatocyte aggregate) as illustrated by scanning electron microscopy, immunoflourescent staining and cytoskeleton organization. It was observed that the 3D scaffolds supported improved cell morphology, expression of hepatic markers and metabolic activities as compared to matrigel coated plates. To the best of our knowledge, this is the first report demonstrating the use of well characterized scaffold (GEVAC) for enhanced differentiation of hUC-MSCs to hepatocyte-like cells (HLCs).

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