Abstract

Title of the thesis: Signaling Mechanism in Regulating Vasculogenic Mimicry of Oral Squamous Cell Carcinoma and Combating with Phytochemicals at Transcription and Post Transcription Level

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Vasculogenic mimicry (VM) is an angiogenesis independent alternative mechanism of tumor perfusion through generating blood containing pseudo-vascular channels, associated with high tumor grade, metastasis, chemo-resistance and prone to poor prognosis in genetically dysregulated and highly aggressive cancers including oral squamous cell carcinoma (OSCC). Understanding the underlying mechanism associated with VM and combating with phytochemical may help scientists and clinicians for better prognosis and development of new anticancer therapy against OSCC. Our research work revealed that the expression of HIF-1α and the extracellular matrix protein Laminin-5γ2 coordinated with VM are significantly associated with tumor grade, primary tumor size, lymph node metastasis and TNM stage. Co-expression of Vasculogenic mimicry with HIF-1α and Laminin-5γ2 significantly correlates with the decreased disease free and overall survival in OSCC patients with the more specific emphasis on VM- Laminin-5γ2 duality as an independent prognostic biomarker for OSCC. The study also concluded HIF-1 α as a key regulator of vasculogenic mimicry formation by modulating EphA2-Laminin 5γ2 cascade in the hypoxic microenvironment of OSCC. The phytochemical Lupeol in association with the common chemotherapeutic drug Paclitaxel resulted into apoptosis and the disruption of VM along with associated EMT and CSC phenotypes in-vitro. We further validated the impact of this novel interventional approach in a patient derived tumor explant culture model of oral malignancy. The ex-vivo tumor model mimicked the in-vitro anti-VM potential of Lupeol-Paclitaxel combination through down-regulating HIF-1α/EphA2/Laminin5γ2 cascade. So Lupeol in synergistic association with Paclitaxel will emerge as a new direction of cancer treatment for OSCC progression and after series of clinical trials this potential drug combination may be used as an effective and definitive therapeutic modality against OSCC.

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