Intervention of lipid mediator based pathway for skin cancer

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The occurrence of skin cancers, particularly, malignant melanoma and its associated mortality rates have risen globally over the last several decades. Among various risk factors, exposure to reactive oxygen species (ROS)-generating stimuli have been implicated in several pathophysiological processes including skin cancer. While several immune and non-immune mediated mechanisms have been proposed for skin cancer, the molecular events governing the initiation and/or progression of melanoma or non-melanoma skin cancers are yet to be fully explored, given the diverse nature of ROS-generating stimuli. Studies, including ours, have implicated the critical roles of a potent lipid mediator, Platelet-activating factor (PAF) in augmenting the growth of melanoma and non-melanoma skin cancers in various experimental models. Importantly, accumulating evidences indicate that PAF and PAF-like ligands can be produced via several ROS-generating stimuli including ultraviolet B (UVB), cigarette smoke, jet fuel, tumor promoters and therapeutic agents. Notably, our studies have demonstrated that PAF/PAF ligands produced via many of such stimuli induce systemic immune suppression in a PAF-receptor (PAF-R) dependent manner. This systemic immune suppression resulted in enhanced growth of experimental skin tumor types via mechanisms mediated by PAF-R-dependent upregulation of cyclooxygenase type 2 (COX-2), related ecosanoids and immunophenotypes such as regulatory T cells (Tregs) and cytokines including interleukin 10 (IL-10). Of importance, ours and other groups have shown that therapeutic agents (i.e. chemotherapy and radiation therapy)-generated PAF ligands impede their efficacy in experimental melanoma models, in a process pharmacologically blocked by agents including PAF- R antagonists, COX-2 inhibitors and depleting antibodies against Tregs and IL-10. Of significance, we identified increased PAF or PAF-R activity in tumor samples/perfusates collected from melanoma and non-melanoma patients, who underwent scheduled treatments with chemotherapy or radiation therapy. These findings indicate that targeting PAF-R-mediated pathway could be explored as a promising appraoch for the intervention of skin cancer.

Biography

Ravi P Sahu has completed his PhD from Sanjay Gandhi Post Graduate Institute of Medical Sciences and postdoctoral studies from the University of Pittsburgh Medical Center, Texas Tech University Health Science Center and Indiana University School of Medicine. He is currently an Assistant Professor at the Department of Pharmacology and Toxicology at Wright State University Boonshoft School of Medicine at Dayton, OH. His laboratory has been interested in defining the role and mechanisms of a potent lipid mediator, platelet-activating factor (PAF)-mediated pathway in cancer growth and efficacy of cancer therapies using various *in-vitro* and *in-vivo* experimental model systems as well as human samples. The overall goal is to delineate novel approaches based on this PAF pathway for the intervention of melanoma and non-melanoma cancers. He has published over 50 papers in reputed journals and has been serving as an editorial board member and adhoc reviewer of several journals.

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