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Platelet-Activating Factor-Receptor and Tumor Immunity

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Abstract

First described in 1972 by Benveniste and colleagues, platelet-activating factor (PAF) remains one of the potent phospholipid known to date. The role of PAF produced enzymatically in mediating diverse biological and pathophysiological processes including inflammatory and allergic diseases and cancers in response to various stimuli has been extensively studied. However, little is known about the role of non-enzymatically-generated PAF-like lipids produced in response to pro-oxidative stressors, particularly in modulating the host immune responses to tumor immunity, which is the focus of this review.

INTRODUCTION

PAF (1-0-alkyl-2-acetyl-sn-glycero-3-phosphorylcholine) is cellular membrane derived phospholipids that mediate its effects via binding to a seven transmembrane G-protein coupled receptor, the PAF-receptor (PAF-R). The expression of the PAF-R has been identified on various immune and non-immune cell types including epithelial, endothelial and cancer cells [1–3]. Enzymatic PAF synthesis is a tightly regulated process that utilizes two different pathways (*de novo and remodeling*) [4]. In contrast, the exposure to ubiquitous pro-oxidative stressors capable of producing reactive oxygen species (ROS) generate non-enzymatically cleaved oxidized glycerophosphocholines (Ox-GPCs) directly from parent membrane glycerophosphocholines (GPCs) that exhibit PAF-R agonistic activity [5–8]. These pro-oxidative stressors include environmental exposures such as ultraviolet B (UVB) radiation, aryl hydrocarbons from jet fuel to cigarette smoke. Moreover, clinically relevant chemotherapeutic agents, and radiation and photodynamic therapies can also generate Ox-GPCs [5–12]. The activity of both enzymatic PAF as well as Ox-GPCs is thought to be regulated by the major PAF-metabolizing enzyme, serum PAF-acetyl hydrolase (PAF-AH) [2].

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PAF and tumor immunity

Several research groups including ours have investigated the role of Ox-GPCs/PAF-R agonists in modulating cutaneous inflammation and host immunity [5–12]. To emphasize, we and others have demonstrated that Ox-GPCs generated via pro-oxidative stressors including UVB and cigarette smoke exposure mediate systemic immunosuppression via a mechanism that involves PAF-R dependent induction of cyclooxygenase type 2 (COX-2) and related prostaglandins and eicosanoids, immunosuppressive cytokine, interleukin 10 (IL-10) and tumor growth factor beta (TGFβ) [7–9,13]. Of significance, our recent studies have demonstrated that these Ox-GPCs/PAF-R agonists mediated systemic immunosuppression augment the growth of experimental murine B16F10 melanoma tumors. This latter process requires host stromal-PAF-R dependent modulation of tumor microenvironment associated suppressive immunophenotype, regulatory T cells (Tregs) [13]. Of importance, PAF-R signaling has been implicated in promoting angiogenesis and metastasis via its direct effects on tumor cell PAF-R [14]. Notably, our studies have shown that systemic PAF-R agonists augments the growth of PAF-R negative experimental murine Lewis Lung Cancer (LLC1) growth and metastasis via activating host cell-PAF-R rather tumor cell-PAF-R [15]. These studies indicate that the implications of Ox-GPCs effects on tumor immunity are not limited to melanoma but can also be applied to lung cancer as wells as its metastatic ability.

The induction of the PAF-R expression on melanoma cells has been shown to be modulated by chemotherapy and this act to mediate a prosurvival response of tumor cells by chemotherapy and is attenuated by PAF-R antagonists [16]. However, whether or not chemotherapy-mediated effects are via the modulation of the host immune responses is not clear. In our recently completed studies, we demonstrated that treatments with chemotherapeutic agents to murine or human melanoma cells lines in vitro or in vivo generate several novel Ox-CPCs with the PAF-R agonists activity in a process blocked by antioxidants. The expression of the PAF-R in tumor cells resulted in enhanced production of Ox-GPCs compared to the PAF-R-deficient tumor cells (studies submitted for publication). The dual tumor model, where implantation of two tumors in PAF-R expressing and deficient syngeneic mice followed by intratumoral treatment of one tumor with the chemotherapeutic agents and measuring the growth of other (secondary) tumor has allowed us the direct assessment of the host anti-tumor immune responses to chemotherapy in the modulation of melanoma tumor growth. We demonstrated that chemotherapy mediated generation of Ox-GPCs augments the growth of secondary tumors in a PAF-R dependent manner. These effects are blocked by the antioxidants, COX-2 inhibitors and depleting antibodies against Tregs. Importantly, several novel Ox-GPCs were detected in the perfusates of melanoma patients undergoing isolated limb chemoperfusion with melphalan chemotherapy. These findings indicate that chemotherapeutic agents due to their ability to act as potent pro-oxidative stressors can modulate the growth of melanoma tumors via affecting the adaptive arm of the host immune system mediated through the generation of non-enzymatic oxidized PAF-R agonists.

Myeloid derived suppressor cells (MDSCs), an immature population of myeloid progenitor cells have been shown to exert potent suppressive activity towards the innate and adaptive arm of the host immune system and promote carcinogenesis. Our ongoing studies have

discovered that MDSCs mediate PAF-R agonists induced systemic immunosuppressive effects. Nevertheless, the cross talk between MDSCs and Tregs in mediating PAF-R agonists induced augmentation of cancer growths are under investigation in our laboratory. Since, tumor associated suppressive type 2 macrophages (M2) share the common profile with MDSCs, particularly the activation markers such as arginase 1, inducible nitric oxide synthetase (iNOS), IL-10, mgl1, fizz1 and ccl2, the clear demonstration of whether M2 macrophages are being recruited by MDSCs into tumor microenvironment will further shed a light into the mechanisms of PAF-R agonists mediated tumor growth.

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