Platelet-activating Factor-receptor agonists generated by chemotherapy thwart host anti-tumor immunity

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Previous studies have established that pro-oxidative stressors suppress host immunity due to their ability to generate oxidized glycerophosphocholine (Ox-GPC) lipids with Platelet-activating Factor-receptor (PAF-R) agonist activity. Because many chemotherapeutic agents also induce reactive oxygen species, the present studies were designed to define if chemotherapeutic agents could thwart host anti-tumor immunity against melanoma via PAF-R activation. We demonstrate that treatment of melanoma cell lines *in vitro* and tumors *in vivo* with chemotherapeutic agents generates PAF-R-agonists in a process blocked by antioxidants, indicating the involvement of non-enzymatic PAF-R-agonists in this event. In a model system consisting of implantation of two tumors, we show that intratumoral chemotherapy with melphalan or etoposide of one tumor significantly augments the growth of the other (untreated) tumor in wild-type but not PAF-R-deficient hosts. Chemotherapeutic agents-mediated PAF-R-dependent increased tumor growth is blocked by systemic administration of antioxidants and cyclooxygenase-2 inhibitors. In addition, depleting antibodies against regulatory T cells (Tregs) significantly attenuated chemotherapy-mediated growth of untreated tumors, suggesting the role of Tregs in this process. Moreover, using FoxP3^{EGFP} transgenic mice, we show that COX-2 inhibitor blocked intratumoral Tregs, indicating that Tregs are downstream to COX-2. Furthermore, PAF-R agonists were identified in perfusates of patients undergoing isolated limb chemoperfusion for melanoma with melphalan chemotherapy. Finally, various novel Ox-GPCs are identified after chemotherapy by mass spectrometry. These findings provide evidence for a novel and previously unappreciated pathway by which Ox-GPC PAF-R agonists produced as a by-product of chemotherapy modulate tumor growth via the inhibition of anti-tumor immunity. These studies might explain some instances of chemotherapy treatment failure and offer insights into potential therapeutic strategies that could enhance the overall anti-tumor effectiveness of chemotherapy.