Cigarette smoke exposure mediated generation of Platelet-activating factor agonists induces systemic immunosuppression.

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The ubiquitous environmental pollutant cigarette smoke (CS) is known to exert immodulatory effects. CS also acts as a potent pro-oxidative stressor. Several studies including ours have characterized the importance of various pro-oxidative stressors including UVB to inhibit host immunity and an importance of the platelet-activating factor (1-alkyl-2-acetyl-glycerophosphocholine; PAF), a potent lipid mediator in this process. PAF is produced enzymatically in a tightly-controlled process. In addition, oxidative stressors can act directly on glycerophosphocholines (GPC) to produce oxidized GPC which are potent PAF-R agonists. The present studies employed model systems consisting of PAF-receptor (PAF-R)-expressing (KBP) and–deficient (KBM) cells and mice (wild type [WT] and *Pafr-/-*) to determine whether CS exposure could generate PAF-R agonists in blood and whether it could suppress contact hypersensitivity reactions in a PAF-R-dependent manner. We show that lipid extracts derived from the blood of CS-treated WT mice resulted in immediate intracellular calcium (Ca_2^+) mobilization response only in KBP cells. However, no Ca_2^+mobilization response was detected with lipid extracts from non-smoked (sham) mice both in KBP and KBM cells. In addition, lipid extracts only from CS-treated mice induced an increase in IL-8 secretion in KBP cells indicating that CS generates systemic PAF-R agonists. CS exposure also inhibited contact hypersensitivity to the allergen dinitrofluorobenzene (DNFB) selectively in WT but not in*Pafr-/-* mice. This inhibitory effect of CS in WT mice were similar to those induced by a PAF-R agonist, CPAF or histamine. Furthermore, this inhibition of CHS by CS in WT mice was blocked by antioxidants vitamin C and N-acetyl cysteine. These findings indicate that CS exposure induces systemic immunosuppression in a PAF-R-dependent manner. These studies provide the first evidence that the pro-oxidative stressor CS can modulate cutaneous immunity via the generation of PAF agonists through lipid oxidation.