Published in final edited form as:

Handb Exp Pharmacol. 2020 ; 259: 185–203. doi:10.1007/164_2019_218.

Platelet-activating Factor as an Effector for Environmental Stressors

Jeffrey B. Travers, M.D., Ph.D.

Wright State University Department of Pharmacology & Toxicology, and Dayton Veterans Administration Medical Center, Dayton OH.

I. Introduction

Environmental influences upon the human host are profound. For example, ultraviolet radiation from sunlight not only is needed for plant photosynthesis, ultraviolet B radiation (UVB) is necessary for human vitamin D synthesis [Wacker and Holick 2013; Leitenberger et al. 2007]. Yet, many environmental agents exert pro-carcinogenic effects. In particular, UVB is responsible for the majority of skin cancers, including malignant melanoma [Leitenberger et al. 2007; Ullrich 2005]. Polycyclic aromatic hydrocarbons (e.g., benzo[a]pyrene) found in coal tar, and in the atmosphere from combustion of petrochemicals and wood, has also been demonstrated to be both a mutagen and is highly carcinogenic [Ramesh et al. 2004; Haritash and Kaushik 2009]. It should be noted that the polycyclic aromatic hydrocarbons were amongst the first agents associated with cancer, from the increased incidence of scrotal carcinomas amongst British chimney sweepers in the 1700s. Other pro-carcinogenic environmental agents from sunlight to cigarette smoke have been known to also induce immune suppression [Walterscheid et al. 2002; Wolf et al. 2006; Zhang et al. 2008; Sahu et al. 2013; Ferracini et al. 2015]. The exact mechanisms by which environmental stressors generate both beneficial and injurious outcomes continues to serve as active areas of investigation.

Though environmental agents are a heterogeneous group, many agents with harmful effects have in common the ability to generate and/or bind to reactive oxygen species (ROS). As will detail in this review, the class of glycerophosphocholine-based lipid mediators collectively known as Platelet-activating Factor can serve as an effector between many pro-oxidative stressors and the human host. In particular, PAF agonists have the ability to be produced rapidly in response to numerous stimuli, which have in common ROS and/or cell membrane disruption. PAF agonists generate both an early pro-inflammatory and a delayed immune suppressive response, which provides many opportunities to serve as effectors for environmental agents, especially pro-oxidative stressors.

II. PAF generation

Platelet-activating Factor (PAF) is the term given by Jacques Benveniste and colleagues in the early 1970s for the substance released by activated leukocytes which induced platelet-

aggregation [Benveniste et al. 1972]. The structure of this activity was elucidated in 1979, and was found to be a glycerophosphocholine with a short-chained fatty acid at the *sn*-2 position [Demopoulos et al. 1979]. In regards to structure-activity relationships, for maximal PAF activity, a long-chained saturated fatty acid (hexadecyl or octadecyl) is at the *sn*-1 position, and a short-chained (usually acetate) is needed at the *sn*-2 position. Glycerophosphocholines with *sn*-1 acyl group have approximately 1–10% of the biological activity of the alkyl-containing species [Demopoulos et al. 1979; Braquet et al. 1987]. Regarding *sn*-2 species, a 3 carbon ester appears to be as potent as 2 carbon, with decreased activity for 4 or 5 carbon *sn*-2 species.

a. Enzymatic synthesis

PAF is synthesized enzymatically via two separate pathways [Braquet et al. 1987; Nakanishi et al. 2006; Shimizu 2009; Morimoto et al. 2010]. The remodeling pathway (see Figure 1) which is associated with cellular stimulation from a variety of sources, consists of PLA₂ (often cytosolic PLA₂) followed by an acetyl-CoA-dependent acetyltransferase (LPCAT) which acetylates a lyso-PAF intermediate to form PAF. Two LPCATs have been implicated in PAF biosynthesis, with LPCAT1 more constitutively active, with LPCAT2 more associated with inflammatory cells [Shimizu 2009; Morimoto et al. 2010]. Cellular stimuli which activate PAF biosynthesis via the remodeling pathway usually involve induction of intracellular calcium mobilization. The ability of PAF to be generated rapidly in response to intracellular calcium provides an important mechanism by which a cell can respond rapidly to disruption of the cellular membrane, which allows a tremendous gradient from the millimolar levels of extracellular calcium to the 100–250 nanomolar intracellular levels. As shown in Figure 2, damage to cellular membranes can serve as a rapid mechanism to provide PAF agonists. Many cellular receptors can also generate PAF biosynthesis, including activation of many G-protein coupled receptors (such as the PAF receptor) [Travers et al. 1996].

A second pathway for PAF synthesis involves a de novo pathway, which consists of three separate enzymes: 1-alkyl-2-lyso-*sn*-glycero-3-phosphate (alkyllyso-GP): acetyl-CoA acetyltransferase, 1-alkyl-2-acetyl-*sn*-glycero-3-phosphate phosphohydrolase, and 1-alkyl-2-acetyl-*sn*-glycerol (alkylacetyl-G):CDP-choline cholinephosphotransferase. This de novo pathway appears to be more constitutive active, though it can be activated by phorbol esters [Shimizu 2009; Snyder et al. 1996].

b. Non-enzymatic synthesis

PAF agonists can also be generated non-enzymatically via direct attack of free radicals on the *sn*-2 long-chained unsaturated fatty acids on glycerophosphocholines [Marathe et al. 2001; Konger et al. 2008]. Oxidation of esterified fatty acyl residues introduces oxy functions, rearranges bonds and results in the fragmentation of carbon–carbon bonds by β -scission that generates a myriad of phospholipid reaction products, including ones that exert PAF-R agonistic activity. In this regard, cellular and potentially nuclear membranes serve as the source of oxidized phospholipids and are thus the sources of reactive oxygen species (ROS)-mediated PAF-R agonist formation. In contrast to the tightly regulated enzymatic PAF production, generation of oxidized glycerophosphocholines (Ox-GPC) is relatively

unregulated. The likely factors in Ox-GPC generation include the nature and amount of ROS, the host antioxidant defenses, and the amounts of sn-2 unsaturated fatty acids (associated with diet). Only a handful of these Ox-GPC PAF-R agonists have been structurally characterized [Marathe et al. 2001; Konger et al. 2008]. Stimuli which have been demonstrated to generate Ox-GPC include cigarette smoke [Sahu et al. 2013], chemotherapeutic agents [Sahu et al. 2014], chronic ethanol exposure [Yang et al. 2010], radiation therapy [Sahu et al. 2016], and ultraviolet B radiation [Marathe et al. 2005].

c. PAF metabolism

Though glycerophosphocholines can be metabolized via multiple phospholipases (e.g., PLA₁, PLA₂, PLC, PLD), PAF and Ox-GPC are inactivated predominantly via removal of the *sn*-2 group by specialized PLA₂ enzymes known as PAF-acetylhydrolases (PAF-AH). The major types relevant for PAF metabolism are the serum form, PAF-AH type I, and cell-associated PAF-AH type II. Genetic deficiencies in PAF-AH type I (also known as lipoprotein-associated PLA₂) have been described, and have been associated with pathologies including atherosclerotic disease [Rosenson and Stafforini 2012; Zalewski and Macphee 2005; Min et al. 2001; Yamada and Yokota 1997]. Consistent with PAF elevation in various disorders, PAF-AH type I levels have been demonstrated to be decreased following sepsis or acute allergic reactions in humans [Franck Trimoreau et al. 2000; Vadas et al. 2008].

III. PAF Receptor

The PAF receptor (PAFR) is a member of the G protein-coupled receptor family [Shimizu 2009; Honda et al. 1991]. The PAFR is widely expressed, including in cells of the immune system (e.g., neutrophils, eosinophils, mast cells, macrophages, B cells) as well as in other cell types (e.g., keratinocytes, fibroblasts, platelets). Creation of PAFR knockout mice has confirmed that a single receptor mediates all PAF effects [Ishii et al. 1998]. Two different PAFR mRNA transcripts with open identical reading frames are generated via the use of separate promoters. Expression of transcript I is regulated by estrogen, and transcript II is regulated by the PKC-NFkB pathway. Consistent with the ability of the PAFR to activate a myriad of responses, this receptor is coupled to G proteins Gi, Gq, and G12/13. In addition, the PAFR has been demonstrated to transactivate the epidermal growth factor receptor through its ability to release heparin-binding EGF [Marques et al. 2002]. Activation of the PAFR results in an intracellular calcium mobilization, activation of mitogen-activated protein kinases, NF-kB pathway activation, and inhibition of cyclic AMP formation. In addition to PAFR effects alone, activation of the PAFR will synergize with other stimuli ranging from ultraviolet radiation to retinoids and other agents [Wolverton et al. 2010]. It has been hypothesized that PAFR on the cellular membrane which appears to be coupled to Gq and the nuclear membrane receptor to Gi/o can activate distinct signaling pathways [Bazan et al. 1994; Marrache et al. 2002]. A mutant PAFR has been reported whereby the alanine residue at position 224 is substituted by aspartic acid (A224D) in the putative third intracellular loop. This mutation is observed at a 7.8% allele frequency in Japanese populations [Fukunaga et al. 2001]. The functional consequences of this structural alteration indicated from the cellular *in vitro* studies suggest that this naturally occurring mutation

exhibits impaired coupling of PAFR to G-proteins. Thus, this receptor mutation may serve as a basis for inter-individual variation in PAFR related processes, including physiological responses, disease predisposition or phenotypes, and drug responsiveness.

IV. Acute PAF Effects

Inasmuch as the PAF-R is expressed in endothelial, inflammatory and innate immunity cells, it is not surprising that activation of the PAF-R is linked to acute inflammation. Engagement of PAFR induces multiple biochemical pathways. These include phosphatidylinositol turnover, increase in intracellular calcium, activation of kinases and anti-apoptotic pathways and transcription of several genes coding for pro- and anti-inflammatory cytokines as well as for cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [Travers et al. 1996; Honda et al. 1991; Marques et al. 2002; Zimmerman et al. 2002]. PAFR activation also induces eicosanoids and PAF production, indicating a positive feed-forward loop. The cellular response to PAFR activation seems to depend on the type of G protein linked to the receptor. As outlined above, as the cellular membrane PAFR is coupled to Gq and the nuclear membrane receptor to Gi/o it can allow a single receptor type to trigger distinct signaling pathways [Bazan et al. 1994; Marrache et al. 2002]. It has been suggested that the activation of the cell membrane receptor linked to Gq would generate early pro-inflammatory responses and synthesis of PAF which would in turn activate the nuclear PAF-R linked to Gi/o to induce transcription of genes for COX-2, iNOS and cytokines [Zimmerman et al. 2002]. Moreover, the cell response to PAFR also depends on the type of ligand and on the interaction with other receptors. This response may be adverse or beneficial; indeed, during infections, production of PAF was shown to mediate resistance to various pathogens including *Leishmania amazonensis* [Lonardoni et al. 2000], *Trypanosoma cruzi* [Aliberti et al. 1999] and gram-negative bacterial *Klebsiella pneumoniae* [Soares et al. 2002] infections. Pharmacologic inhibitors of the PAFR have been reported to increase the local and systemic infection in these model systems. Of note, PAFR KO mice infected with *T. cruzi* exhibit higher blood parasitemia, parasite load in lymph nodes and spleen and mortality [Talvani et al. 2003]. The emerging view is that endogenous PAF appears vital in controlling certain infections in part via facilitation of optimal macrophage activation. It should be noted that concomitant activation of PAFR and other receptor types such as Toll-like receptors (TLRs) results in augmented pro-inflammatory effects. Thus, the PAFR can act in cooperation with other macrophage receptors inducing either suppression or activation, affecting both innate and adaptive immunity [Lefebvre et al. 2010].

Injection of low doses of PAF into skin results in an urticarial eruption in both rodents and humans [Archer et al. 1984; Hellewell and Williams 1989; Travers et al. 1998a]. PAF injection also induces itching and pain in these models. Of interest, PAF has been reported to be measured in the blood of patients with active cold urticaria [Grandel et al. 1985]. Systemic PAF exerts acute effects on the cardiopulmonary system and has been shown to mimic sepsis. Of interest, PAFR KO mice are protected against LPS-induced lethality [Ishii et al. 1998]. PAF can be found in association with multiple acute inflammatory states ranging from sepsis to the blistering disease bullous pemphigoid [Travers et al. 1998b; Mallet and Cunningham 1985]. Hence, PAF in theory could contribute to all of the classic

acute inflammatory features of calor (heat), rubor (redness), tumor (swelling), and dolor (pain).

V. Chronic PAF Effects

In contrast to the overall “pro-inflammatory” effects ascribed to acute PAF, chronic effects of PAF appear to be more “anti-inflammatory”. For example, PAF has been demonstrated to inhibit delayed type hypersensitivity reactions to *Candida* antigens and the chemical dinitrofluorobenzene [Walterscheid et al. 2002; Zhang et al. 2008]. This process has been studied in some detail, and appears to be due to PAF interacting with the mast cell PAFR, resulting in the upregulation of regulatory T cells (Treg) in a COX-2-dependent manner [Chacon-Salinas et al. 2014]. As will detail elsewhere in this review, this PAF→Mast cell→Treg process appears to be responsible for the systemic immunosuppressive effects of multiple environmental stressors ranging from cigarette smoke [Sahu et al. 2013] to ultraviolet B radiation [Walterscheid et al. 2002; Zhang et al. 2008].

In addition to immune effects of chronic PAF exposure, several studies have implicated PAF in chronic ethanol toxicity. In particular, chronic ethanol administration in rats and mice results in increased levels of oxidized glycerophosphocholines and PAF in plasma [Yang et al. 2010; Liu et al. 2013]. Moreover, PAFR-deficient mice are protected from chronic ethanol-mediated kidney damage [Latchoumycandane et al. 2015]. In these chronic ethanol models, non-enzymatic oxidized glycerophosphocholine PAF agonists appear to play important roles. Finally, PAF has been identified in multiple chronic conditions involving numerous organ types including experimental cerebral malaria [Lacerda-Queiroz et al. 2012] and necrotizing enterocolitis [Lefebvre et al. 2010]. Thus, the PAF system has been implicated in both pro- as well as anti-inflammatory chronic pathologies.

VI. PAF system and Environmental Stressors

Given that PAF and Ox-GPC PAFR agonists are generated in response to multiple environmental stressors, this class of lipid mediators could play important roles in the effects of these agents. This review will focus on recent findings providing evidence linking the PAF system with pro-oxidative stressors UVB, photodynamic therapy, and cigarette smoke. The potential implications of PAF in how the host interacts with these stressors will be outlined, with an eye towards translational modulation.

a. Ultraviolet B radiation

Ultraviolet B radiation (290–320 nm; UVB) is a pro-oxidative stressor which has profound effects upon human skin [Wacker and Holick 2013; Leitenberger et al. 2007]. These “burning rays” of sunlight are critical for vitamin D metabolism, yet, also induce sun burns as well as both melanoma and non-melanoma skin cancer [Ullrich 2005]. Given that UVB generates anti-inflammatory effects in skin, phototherapy is used clinically to treat a myriad of skin diseases including psoriasis [Leitenberger et al. 2007]. UVB stimulates the production of PAF and Ox-GPC with PAFR agonistic activity [Marathe et al. 2005]. PAFR signaling is involved in two separate aspects of photobiology. First, PAFR activation appears important in the early acute responses of UVB. In a murine model of photosensitivity due to

deficiency of the DNA repair enzyme xeroderma pigmentosum type A (XPA), UVB treatment results in increased levels of PAF and Ox-GPC formation [Yao et al. 2012]. Moreover, the exaggerated pro-inflammatory response to UVB in XPA-deficient mice is blocked by PAFR antagonists [Yao et al. 2012]. It should be noted that PAFR-deficient mice exhibit decreased acute inflammation as well as decreased production of cytokines such as tumor necrosis factor in response to UVB [Yao et al. 2012; Travers et al. 2008]. Second, the systemic immunosuppression induced by UVB has been demonstrated to involve PAFR signaling via Ox-GPCs [Walterscheid et al. 2002; Zhang et al. 2008]. Of interest, UVB can induce both local immunosuppression (where the UVB-treated site is anergic) as well as systemic immunosuppression (where non-treated UVB site is tested). Local immunosuppression appears to involve decreasing dendritic cell function, whereas systemic immunosuppression involves mast cells and Tregs (see Figure 3). It has been demonstrated that UVB-induced systemic immunosuppression is defective in PAFR deficient mice [Zhang et al. 2008]. However, local immunosuppression is normal in PAFR KO mice [Sahu et al. 2012a]. Finally, systemic PAFR antagonists inhibit tumor formation in a murine model of UVB photocarcinogenesis [Sreevidya et al. 2008].

Other agents such as organic solvents found in jet fuel have also been demonstrated to act upon the skin to induce systemic immunosuppression via PAF/Ox-GPC PAFR agonists [Ramos et al. 2004]. Thus, PAFR signaling appears to play an important role in inflammatory processes in the skin, and this system can be activated by a wide range of pro-oxidative stressors.

b. Photodynamic therapy

Photodynamic therapy (PDT) combines the phototoxic effects of porphyrin and a compatible light source. Photodynamic therapy using topical 5-aminolevulinic acid is a commonly used procedure in dermatology to treat patients with extensive areas of actinic damage (pre-cancerous actinic keratosis) and also has efficacy against superficial basal cell carcinomas (BCC) [Lee and Baron 2011; Gold 2011]. Regular PDT treatments have also been championed as a strategy for management of high-risk populations, including immunosuppressed (e.g. organ transplant recipients) due to their tremendous burden of actinic neoplasia [Basset-Seguin et al. 2013]. However, relatively little is known regarding PDT, in particular the long-term effects of this treatment modality that thousands of patients are being exposed to annually.

Acute responses to PDT include a potent phototoxic reaction. Studies have demonstrated that PDT is immunosuppressive in both mice [Ferracini et al. 2015; Hayami et al. 2007] and humans [Matthews and Damian 2010; Frost et al. 2011]. Consistent with PDT being immunosuppressive, there are reports of skin cancers and herpes simplex recurrences developing following PDT [Gogia et al. 2013; Varma et al. 2000; Fiechter et al. 2012; Wolf et al. 1997; Nobbe et al. 2011]. However, under certain conditions, PDT can be immune enhancing [St Denis et al. 2011; Krosi et al. 1996; Kabingu et al. 2009]. In particular, Dr. Sandra Gollnick's group has reported that PDT of skin BCC generated a cytotoxic immune response with enhanced gamma-interferon production to the BCC-associated protein Hedgehog-interacting protein 1 (Hip1) [Kabingu et al. 2009]. Inasmuch as PDT is a

commonly used procedure, investigations as to its effects on the human skin immune system and their consequences and potential manipulation to allow enhanced therapeutic effects are highly warranted. Our group has discovered that PDT of keratinocytes is a potent inducer of PAFR agonists, and that standard doses of PDT resulted in systemic immunosuppression in wild-type, but not PAFR-deficient mice [Ferracini et al. 2015]. Additionally, studies in humans suggest that high fluence rates of topical PDT (which would likely generate more PAF agonists) are more immunosuppressive than lower rates [Frost et al. 2011]. Moreover, PDT appears less effective in patients who are already immunosuppressed [Dragieva et al. 2004]. Of interest, a few reports indicate in preclinical models that COX-2 inhibitors augment PDT anti-tumor responses [Ferrario and Gomer 2010; Makowski et al. 2003]. Given that PAF-induced immunosuppression is blocked by COX-2 inhibitors [Walterscheid et al. 2002; Wolf et al. 2006; Zhang et al. 2008; Sahu et al. 2013], it is indeed possible that the PAF agonists produced as a by-product of PDT could be exerting immunomodulatory effects.

c. Cigarette Smoke

Affecting approximately one in six humans, tobacco smoke is one of the most significant environmental exposures [Hatsukami et al. 2008; Stampfli and Anderson 2009]. Many adverse effects of cigarette smoke (CS) on immune responses have been reported, which have far-reaching effects on increased infections, vaccine failures, and tumor generation [Stampfli and Anderson 2009; Finklea et al. 1971; Esber et al. 1973; SucIU-Foca et al. 1974; Winter et al. 1994]. Cigarette smoke generates isoprostanes in humans blocked by vitamin C [Pryor and Stone 1993; Morrow et al. 1995; Lehr et al. 1997; Obwegeser et al. 1999; Imaizumi et al. 1991; Dietrich et al. 2002; Geng et al. 1996; Dillon et al. 2002; Revathikumar et al. 2016]. As isoprostanes are prostaglandin-like compounds formed by the free radical-catalyzed peroxidation of arachidonic acid non-enzymatically, this fits with the notion that CS can generate enough ROS to induce lipid oxidation (and thus Ox-GPC formation). Indeed, PAF-R agonistic activity has been identified in both hamsters and humans following CS exposure [Morrow et al. 1995; Lehr et al. 1997; Obwegeser et al. 1999; Imaizumi et al. 1991]. Vitamin C supplementation blocked this PAF-R agonistic activity in hamsters suggesting Ox-GPC PAFR agonist involvement. Our group has reported that CS generates PAF-R agonistic activity in mice, which can be blocked by placement of the mice on an experimental diet of vitamin C-enriched (10g/kg) chow and 5 mM N-acetylcysteine (NAC) in water for 10 d prior to CS exposure [Sahu et al. 2013]. CS exposure also inhibited CHS to DNFB in PAFR-positive but not PAFR KO mice [Sahu et al. 2013]. Of importance, CS-induced immunosuppression was blocked by antioxidants, COX-2 inhibitors, as well as depleting Tregs [Sahu et al. 2013].

Though nicotine has been implicated in some aspects of CS-mediated immunosuppression [Dillon et al. 2002; Revathikumar et al. 2016; Reale et al. 2015; Nouri-Shirazi et al. 2015], nicotine itself has been reported to not exert systemic immunosuppressive effects in humans. It should be noted that our preclinical studies revealed that CS derived from low-nicotine cigarettes resulted in similar levels of PAF agonists as normal cigarettes [Sahu et al. 2013].

The proposed mechanism by which CS generates PAFR agonists via ROS suggests that many other potential environmental exposures (*e.g., air pollutants*) could also exert similar effects. Further studies are warranted to potentially understand how lung tumors associated with CS use evade immune-mediated clearance and how host and environmental factors influence this process.

VII. PAF system and Cancer Therapy

The immune system plays an important role in cancer development and progression [reviewed in Marin-Acevedo et al. 2018; Passarelli et al. 2017]. Indeed, therapeutics designed to enhance immunity such as CTLA4 and PD-1 inhibitors are now being used to treat cancers, especially melanoma. We have demonstrated that systemic exposure of PAF augments experimental tumor growth in mice [Sahu et al. 2012b, 2014]. Similar to systemic immunosuppressive effects of PAFR activation, PAF-augmented tumor growth is blocked by COX-2 inhibitors and is dependent upon Tregs. Thus, systemic PAFR activation inhibits tumor immunity.

Chemotherapeutic agents are known to act as pro-oxidative stressors. We have demonstrated that chemotherapeutic agents including etoposide, dacarbazine, cisplatin, and melphalan all generate PAF and Ox-GPC PAFR agonists [Sahu et al. 2014]. Consistent with the ability of these chemotherapeutic agents to induce ROS, this PAF agonist generation is partially inhibited by antioxidants. Of importance, chemotherapeutic agent-induced PAF is increased in tumor cells expressing a PAFR [Sahu et al. 2014]. Using a novel model system of subcutaneous placement of two B16F10 syngeneic melanoma tumors, intratumoral injection of etoposide or melphalan into one tumor resulted in the enhanced growth of the second tumor, a process not seen in PAFR KO mice [Sahu et al. 2014]. These findings fit with the notion that PAF agonists produced by the chemotherapy-treated tumor inhibit tumoral immunity. Of translational importance, high levels of PAF are measured in human subjects undergoing regional chemotherapy with melphalan [Sahu et al. 2014].

Radiation therapy is also commonly used to treat tumors [Citrin 2017]. Localized radiation therapy has been demonstrated to exert immunosuppressive effects [Wara 1977; Wara et al. 1975]. Moreover, radiation can induce Tregs [Schaue et al. 2012]. Recently, radiation therapy was demonstrated to induce PAF agonists both in cell lines, in experimental tumors, as well as in human patients undergoing localized radiation to tumors [Sahu et al. 2016]. Similar to the two tumor model used to study intratumoral chemotherapy [Sahu et al. 2014], localized radiation of one tumor resulted in increased growth of the second tumor in a PAFR-dependent manner [Sahu et al. 2016]. Again, COX-2 inhibitors blocked this PAFR-dependent inhibition of anti-tumor immunity.

VIII. PAF and Microvesicle Particles

Microvesicle particles (MVP) are defined as submicron vesicles generated from cellular membranes via exocytosis. They are irregularly shaped and range from ~100–1000 nm in size. MVP generation occurs in response to various stimuli, many involving intracellular calcium mobilization [Xiao et al. 2015; Camussi et al. 2010]. Once released into the

circulation (blood and urine), MVP can then exert functional effects on various cell types. MVP have different functions which depend on the cell of origin and stimuli. Moreover, MVP are thought to be able to target other cell types through surface membrane interactions that then allow fusion of the MVP to the target cell membrane and subsequent delivery of the intravesicular contents. The pathways by which MVP are released from cells have been studied, and are cellular- and stimulus-dependent [Norling and Dalli 2013]. For example, in endothelial cells, MVP release in response to agents like TNF- α are due to P38 MAPK signaling, whereas in THP-1 monocytes both Erk 1/2 (p42/44) and P38 MAPK pathways are involved [Norling and Dalli 2013; Vion et al. 2013; Li et al. 2010; Herring et al. 2013]. Ceramides appear to play an important role in MVP generation and release. In particular, blocking the enzyme acid sphingomyelinase either via pharmacologic tools or genetic strategies inhibits MVP generation [Serban et al. 2016].

The functions of various MVP in physiological and pathological processes depend on their carried contents (proteins, lipids and nucleic acids) [Camussi et al. 2010]. One advantage of this arrangement is that metabolically unstable compounds inside MVP can be somewhat protected from enzymatic degradation. Studies have reported that circulating MVP are increased in inflammatory skin diseases such as psoriasis, in which many cytokines are also elevated [Tamagawa-Mineoka et al. 2010; Liu et al. 2016; Takeshita et al. 2014]. In translational studies, elevated levels of MVP have been documented in vascular diseases and correlated with the severity of disease.

Recent studies by our group have demonstrated that activation of the keratinocyte PAFR induces MVP release [Bihl et al. 2016; Fahy et al. 2017]. Of interest, UVB radiation also induces MVP in a PAFR-dependent manner (see Figure 4). These studies indicate the possibility MVP could serve as effectors linking environmental stressors that act upon the skin, with the PAF system playing an intermediary role. If this is the case, then, novel therapeutic strategies aimed at MVP could be useful in conditions such as photosensitivity.

IX. Future Directions

Environmental stressors play important roles in human biology and pathology. Accumulating evidence links PAF with multiple stressors, which have in common the ability to generate cell damage and ROS. Given that PAF agonists are produced in response to multiple therapeutic agents, it is possible that this could be exploited. For example, chemotherapy-generated PAF agonists could be exerting an adverse effect on the cancer patient by blocking anti-tumor immunity. If this is the case, then strategies such as antioxidants to block PAF agonist generation, or COX-2 inhibitors to block the downstream pathways which induce Tregs could be valuable adjuncts for chemotherapy. Another potential strategy to modulate effects of PAF agonists could be to further study MVP as potential carriers of metabolically labile PAF agonists. Thus, future directions in this arena will be to first define the PAF system as it relates to human-based interactions with environmental agents to assess whether this could be exploited pharmacologically.

Acknowledgements

The PI wishes to acknowledge the support by grants from the National Institutes of Health grant R01 HL062996, R21 AR070010, and Veteran's Administration Merit Award 5I01BX000853.

REFERENCES

- Aliberti JC, Machado FS, Gazzinelli RT, Teixeira MM, Silva JS (1999) Platelet-activating factor induces nitric oxide synthesis in *Trypanosoma cruzi*-infected macrophages and mediates resistance to parasite infection in mice. *Infect Immun* 67(6):2810–2814 [PubMed: 10338485]
- Archer CB, Page CP, Morley JP, MacDonald DM (1984) Inflammatory characteristics of platelet-activating factor (Pafacether) in human skin. *Br J Dermatol* 110:45–49 [PubMed: 6581831]
- Basset-Seguín N et al. (2013) Photodynamic therapy for actinic keratosis in organ transplant patients. *J Eur Acad Dermatol Venereol* 27(1):57–66 [PubMed: 22151793]
- Bazan NG, Fletcher BS, Herschman HR, Mukherjee PK (1994) Platelet-activating factor and retinoic acid synergistically activate the inducible prostaglandin synthase gene. *Proc Natl Acad Sci U S A* 91(12):5252–5256 [PubMed: 8202477]
- Benveniste J, Henson PM, Cochrane CG (1972) Leukocyte-dependent histamine release from rabbit platelets. The role of IgE, basophils, and a platelet-activating factor. *J Exp Med* 136 (6):1356–1377 [PubMed: 4118412]
- Bihl JC, Rapp CM, Chen Y, Travers JB (2016) UVB generates microvesicle particle release in part due to platelet-activating factor signaling. *Photochem Photobiol* 92(3):503–506 [PubMed: 26876152]
- Braquet P, Touqui L, Shen TY, Vargaftig BB (1987) Perspectives in platelet-activating factor research. *Pharmacol Rev* 39:97–145 427 [PubMed: 3303066]
- Camussi G, Deregibus MC, Bruno S, Cantaluppi V, Biancone L (2010) Exosomes/microvesicles as a mechanism of cell-to-cell communication. *Kidney Int* 78(9):838–848 429 [PubMed: 20703216]
- Chacon-Salinas R, Chen L, Chavez-Blanco AD, Limon-Flores AY, Ma Y, Ullrich SE (2014) An essential role for platelet-activating factor in activating mast cell migration following ultraviolet irradiation. *J Leukoc Biol* 95:139–148 [PubMed: 24009177]
- Citrin DE (2017) Recent developments in radiotherapy. *N Engl J Med* 377(11):1065–1075 [PubMed: 28902591]
- Demopoulos CA, Pinckard RN, Hanahan DJ (1979) Platelet-activating factor. Evidence for 1-O-alkyl-2-acetyl-sn-glycerol-3-phosphorylcholine as the active component (a new class of lipid chemical mediators). *J Biol Chem* 254(19):9355–9358 [PubMed: 489536]
- Dietrich M, Block G, Hudes M, Morrow JD, Norkus EP, Traber MG, Cross CE, Packer L (2002) Antioxidant supplementation decreases lipid peroxidation biomarker F(2)-isoprostanes in plasma of smokers. *Cancer Epidemiol Biomarkers Prev* 11(1):7–13 [PubMed: 11815395]
- Dillon SA, Lowe GM, Billington D, Rahman K (2002) Dietary supplementation with aged garlic extract reduces plasma and urine concentrations of 8-iso-prostaglandin F(2 alpha) in smoking and nonsmoking men and women. *J Nutr* 132(2):168–171 [PubMed: 11823573]
- Dragieva G, Hafner J, Dummer R et al. (2004) Topical photodynamic therapy in the treatment of actinic keratosis and Bowen's disease in transplant recipients. *Transplantation* 77:115–121 4441. [PubMed: 14724445]
- Esber HJ, Menninger FF Jr, Bogden AE, Mason MM (1973) Immunological deficiency associated with cigarette smoke inhalation by mice. Primary and secondary hemagglutinin response. *Arch Environ Health* 27(2):99–104 [PubMed: 4721205]
- Fahy K, Langni L, Rapp CM, Borchers C, Bihl JC, Chen Y, Simman R, Travers JB (2017) UVB-generated microvesicle particles: a novel pathway by which a skin-specific stimulus could exert systemic effects. *Photochem Photobiol* 93(4):937–942 [PubMed: 28039861]
- Ferracini M, Sahu RP, Harrison KA, Waeiss RA, Murphy RC, Jancar S, Konger RL, Travers JB (2015) Topical photodynamic therapy induces systemic immunosuppression via generation of platelet-activating factor agonists. *J Invest Dermatol* 135:321–323 [PubMed: 25050596]

- Ferrario A, Gomer CJ (2010) Targeting the tumor microenvironment using photodynamic therapy combined with inhibitors of cyclooxygenase-2 or vascular endothelial growth factor. *Methods Mol Biol* 635:121–132 [PubMed: 20552344]
- Fiechter ZS, Skaria A, Nievergelt H et al. (2012) Facial basal cell carcinomas recurring after photodynamic therapy: a retrospective analysis of histological subtypes. *Dermatology* 224:346–351 [PubMed: 22759732]
- Finklea JF, Hasselblad V, Riggan WB, Nelson WB, Hammer DI, Newall VA (1971) Cigarette smoking and hemagglutination inhibition response to influenza after natural disease and immunization. *Am Rev Respir Dis* 104:368–372 [PubMed: 5098670]
- Franck Trimoreau CA, Bruno F, Desachy A, Besse F, Vignon P, Denizot Y (2000) Platelet-activating factor acetylhydrolase and haemophagocytosis in the sepsis syndrome. *Mediators Inflamm* 9:197–200 [PubMed: 11132779]
- Frost GA, Halliday GM, Damian DL (2011) Photodynamic therapy-induced immunosuppression in humans is prevented by reducing the rate of light delivery. *J Invest Dermatol* 131(4):962–968 [PubMed: 21248771]
- Fukunaga K, Ishii S, Asano K, Yokomizo T, Shiomi T, Shimizu T, Yamaguchi K (2001) Single nucleotide polymorphism of human platelet-activating factor receptor impairs G-protein activation. *J Biol Chem* 276(46):43025–43030 [PubMed: 11560941]
- Geng Y, Savage SM, Razani-Boroujerdi S, Sopori ML (1996) Effects of nicotine on the immune response. II. Chronic nicotine treatment induces T cell anergy. *J Immunol* 156(7):2384–2390 [PubMed: 8786295]
- Gogia R, Grekin RC, Shinkai K (2013) Eruptive self-resolving keratoacanthomas developing after treatment with photodynamic therapy and microdermabrasion. *Dermatol Surg* 39 (11):1717–1720 [PubMed: 24118143]
- Gold MH (2011) Photodynamic therapy. *Curr Probl Dermatol* 42:181–192 [PubMed: 21865812]
- Grandel KE, Farr RS, Wanderer AA, Eisenstadt TC, Wasserman SI (1985) Association of platelet-activating factor with primary acquired cold urticaria. *N Engl J Med* 313(7):405–409 [PubMed: 2410790]
- Haritash AK, Kaushik CP (2009) Biodegradation aspects of polycyclic aromatic hydrocarbons (PAHs): a review. *J Hazard Mater* 169(1–3):1–15 [PubMed: 19442441]
- Hatsukami DK, Stead LF, Gupta PC (2008) Tobacco addiction. *Lancet* 371(9629):2027–2038 [PubMed: 18555914]
- Hayami J, Okamoto H, Sugihara A et al. (2007) Immunosuppressive effects of photodynamic therapy by topical aminolevulinic acid. *J Dermatol* 34:320–327 [PubMed: 17408441]
- Hellewell PG, Williams TJ (1989) Antagonism of PAF-induced oedema formation in rabbit skin: a comparison of different antagonists. *Br J Pharmacol* 97(1):171–180 [PubMed: 2720306]
- Herring JM, McMichael MA, Smith SA (2013) Microparticles in health and disease. *J Vet Intern Med* 27:1020–1033 [PubMed: 23815149]
- Honda Z, Nakamura M, Miki I, Minami M, Watanabe T, Seyama Y, Okado H, Toh H, Ito K, Miyamoto T (1991) Cloning by functional expression of platelet-activating factor receptor from guinea-pig lung. *Nature* 349(6307):342–346 [PubMed: 1846231]
- Imaizumi T, Satoh K, Yoshida H, Kawamura Y, Hiramoto M, Takamatsu S (1991) Effect of cigarette smoking on the levels of platelet-activating factor-like lipid(s) in plasma lipoproteins. *Atherosclerosis* 87(1):47–55 [PubMed: 1872924]
- Ishii S, Kuwaki T, Nagase T, Maki K, Tashiro F, Sunaga S, Cao WH, Kume K, Fukuchi Y, Ikuta K, Miyazaki J, Kumada M, Shimizu T (1998) Impaired anaphylactic responses with intact sensitivity to endotoxin in mice lacking a platelet-activating factor receptor. *J Exp Med* 187:1779–1788 [PubMed: 9607919]
- Kabingu E, Oseroff AR, Wilding GE, Gollnick SO (2009) Enhanced systemic immune reactivity to a basal cell carcinoma associated antigen following photodynamic therapy. *Clin Cancer Res* 15:4460–4466 500 [PubMed: 19549769]
- Konger RL, Marathe GK, Yao Y, Zhang Q, Travers JB (2008) Oxidized glycerophosphocholines as biologically active mediators for ultraviolet radiation-mediated effects. *Prostaglandins Other Lipid Mediat* 87(1–4):1–8 [PubMed: 18555720]

- Krosi G, Korbek M, Krosi J, Dougherty GJ (1996) Potentiation of photodynamic therapy-elicited antitumor response by localized treatment with granulocyte-macrophage colony-stimulating factor. *Cancer Res* 56(14):3281–3286 [PubMed: 8764122]
- Lacerda-Queiroz N, Rodrigues DH, Vilela MC, Rachid MA, Soriani FM, Sousa LP, Campos RD, Quesniaux VF, Teixeira MM, Teixeira AL (2012) Platelet-activating factor receptor is essential for the development of experimental cerebral malaria. *Am J Pathol* 180(1):246–255 [PubMed: 22079430]
- Latchoumycandane C, Nagy LE, McIntyre TM (2015) Myeloperoxidase formation of PAF receptor ligands induces PAF receptor-dependent kidney injury during ethanol consumption. *Free Radic Biol Med* 86:179–190 [PubMed: 26003521]
- Lee Y, Baron ED (2011) Photodynamic therapy: current evidence and applications in dermatology. *Semin Cutan Med Surg* 30(4):199–209 [PubMed: 22123417]
- Lefebvre JS, Marleau S, Milot V, Lévesque T, Picard S, Flamand N, Borgeat P (2010) Toll-like receptor ligands induce polymorphonuclear leukocyte migration: key roles for leukotriene B4 and platelet-activating factor. *FASEB J* 24(2):637–647 [PubMed: 19843712]
- Lehr HA, Weyrich AS, Saetzler RK, Jurek A, Arfors KE, Zimmerman GA, Prescott SM, McIntyre TM (1997) Vitamin C blocks inflammatory platelet-activating factor mimetics created by cigarette smoking. *J Clin Invest* 99(10):2358–2364 [PubMed: 9153277]
- Leitenberger J, Jacobe HT, Cruz PD Jr (2007) Photoimmunology – illuminating the immune system through photobiology. *Semin Immunopathol* 29:65–70 [PubMed: 17621955]
- Li M, Yu D, Williams KJ, Liu ML (2010) Tobacco smoke induces the generation of procoagulant microvesicles from human monocytes/macrophages. *Arterioscler Thromb Vasc Biol* 30 (9):1818–1824 [PubMed: 20558816]
- Liu J, Li W, Chen R, McIntyre TM (2013) Circulating biologically active oxidized phospholipids show on-going and increased oxidative stress in older male mice. *Redox Biol* 1:110–114 [PubMed: 25499575]
- Liu M-L, Williams KJ, Werth VP (2016) Chapter four-microvesicles in autoimmune diseases. *Adv Clin Chem* 77:125–175 [PubMed: 27717416]
- Lonardoni MV, Russo M, Jancar S (2000) Essential role of platelet-activating factor in control of Leishmania (Leishmania) amazonensis infection. *Infect Immun* 68(11):6355–6361 [PubMed: 11035745]
- Makowski M et al. (2003) Inhibition of cyclooxygenase-2 indirectly potentiates antitumor effects of photodynamic therapy in mice. *Clin Cancer Res* 9(14):5417–5422 [PubMed: 14614028]
- Mallet AI, Cunningham FM (1985) Structural identification of platelet-activating factor in psoriatic scale. *Biochem Biophys Res Commun* 126:192–196 [PubMed: 3970690]
- Marathe GK, Prescott SM, Zimmerman GA, McIntyre TM (2001) Oxidized LDL contains inflammatory PAF-like phospholipids. *Trends Cardiovasc Med* 11:139–142 [PubMed: 11686003]
- Marathe GK, Johnson C, Billings SD, Southall MD, Pei Y, Spandau D, Murphy RC, Zimmerman GA, McIntyre TM, Travers JB (2005) Ultraviolet B radiation generates platelet-activating factor-like phospholipids underlying cutaneous damage. *J Biol Chem* 280:35448–35457 [PubMed: 16115894]
- Marin-Acevedo JA, Soyano AE, Dholaria B, Knutson KL, Lou Y (2018) Cancer immunotherapy beyond immune checkpoint inhibitors. *J Hematol Oncol* 11(1):8 10.1186/s13045-017-0552-6 [PubMed: 29329556]
- Marques SA, Dy L, Southall MD, Yi Q, Smietana E, Kapur R, Marques M, Travers JB, Spandau D (2002) The platelet-activating factor receptor activates the ERK MAP kinase and induces proliferation of epidermal cells through an EGF receptor-dependent pathway. *J Pharmacol Exp Ther* 300:1026–1035 [PubMed: 11861812]
- Marrache AM, Gobeil F, Bernier SG, Stankova J, Rola-Pleszczynski M, Choufani S, Bkaily G, Bourdeau A, Sirois MG, Vazquez-Tello A et al. (2002) Proinflammatory gene induction by platelet-activating factor mediated via its cognate nuclear receptor. *J Immunol* 169 (11):6474–6481 [PubMed: 12444157]
- Matthews YJ, Damian DL (2010) Topical photodynamic therapy is immunosuppressive in humans. *Br J Dermatol* 162(3):637–641 [PubMed: 19863500]

- McAllister-Sistilli CG, Caggiula AR, Knopf S, Rose CA, Miller AL, Donny EC (1998) The effects of nicotine on the immune system. *Psychoneuroendocrinology* 23(2):175–187 [PubMed: 9621397]
- Min JH, Wilder C, Aoki J, Arai H, Inoue K, Paul L, Gelb MH (2001) Platelet-activating factor acetylhydrolases: broad substrate specificity and lipoprotein binding does not modulate the catalytic properties of the plasma enzyme. *Biochemistry* 40(15):4539–4549 [PubMed: 11294621]
- Morimoto R, Shindou H, Oda Y, Shimizu T (2010) Phosphorylation of lysophosphatidylcholine acyltransferase 2 at Ser34 enhances platelet-activating factor production in endotoxin-stimulated macrophages. *J Biol Chem* 285:29857–29862 [PubMed: 20663880]
- Morrow JD, Frei B, Longmire AW, Gaziano JM, Lynch SM, Shyr Y, Strauss WE, Oates JA, Roberts LJ 2nd. (1995) Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. *N Engl J Med* 332(18):1198–1203 [PubMed: 7700313]
- Nakanishi H, Shindou H, Hishikawa D, Harayama T, Ogasawara R, Suwabe A, Taguchi R, Shimizu T (2006) Cloning and characterization of mouse lung-type acylCoA:lysophosphatidylcholine acyltransferase 1 (LPCAT1). Expression in alveolar type II cells and possible involvement in surfactant production. *J Biol Chem* 281(29):20140–20147 [PubMed: 16704971]
- Nobbe S, Trueb RM, French LE, Hofbauer GFL (2011) Herpes simplex virus reactivation as a complication of photodynamic therapy. *Photodermatol Photoimmunol Photomed* 27:51–52 [PubMed: 21198884]
- Norling LV, Dalli J (2013) Microparticles are novel effectors of immunity. *Curr Opin Pharmacol* 13:570–575 [PubMed: 23742926]
- Nouri-Shirazi M, Kahlden C, Nishino P, Guinet E (2015) Nicotine exposure alters the mRNA expression of Notch ligands in dendritic cells and their response to Th1-/Th2-promoting stimuli. *Scand J Immunol* 81(2):110–120 [PubMed: 25418282]
- Obwegeser R, Oguogho A, Ulm M, Berghammer P, Sinzinger H (1999) Maternal cigarette smoking increases F2-isoprostanes and reduces prostacyclin and nitric oxide in umbilical vessels. *Prostaglandins Other Lipid Mediat* 57(4):269–279 [PubMed: 10402220]
- Passarelli A, Mannavola F, Stucci LS, Tucci M, Silvestris F (2017) Immune system and melanoma biology: a balance between immunosurveillance and immune escape. *Oncotarget* 8 (62):106132–106142 [PubMed: 29285320]
- Pryor WA, Stone K (1993) Oxidants in cigarette smoke. *Ann N Y Acad Sci* 686:12–28 [PubMed: 8512242]
- Ramesh A, Walker SA, Hood DB, Guillén MD, Schneider K, Weyand EH (2004) Bioavailability and risk assessment of orally ingested polycyclic aromatic hydrocarbons. *Int J Toxicol* 23 (5):301–333 [PubMed: 15513831]
- Ramos G, Kazimi N, Nghiem DX, Walterscheid JP, Ullrich SE (2004) Platelet activating factor receptor binding plays a critical role in jet fuel-induced immune suppression. *Toxicol Appl Pharmacol* 195(3):331–338 [PubMed: 15020195]
- Reale M, Di Bari M, Di Nicola M, D'Angelo C, De Angelis F, Velluto L, Tata AM (2015) Nicotinic receptor activation negatively modulates pro-inflammatory cytokine production in multiple sclerosis patients. *Int Immunopharmacol* 29(1):152–157 [PubMed: 26209886]
- Revathikumar P, Bergqvist F, Gopalakrishnan S, Korotkova M, Jakobsson PJ, Lampa J, Le Maître E (2016) Immunomodulatory effects of nicotine on interleukin 1 β activated human astrocytes and the role of cyclooxygenase 2 in the underlying mechanism. *J Neuroinflammation* 13(1):256 [PubMed: 27681882]
- Rosenson RS, Stafforini DM (2012) Modulation of oxidative stress, inflammation, and atherosclerosis by lipoprotein-associated phospholipase A2. *J Lipid Res* 53(9):1767–1782 [PubMed: 22665167]
- Sahu RP, Yao Y, Konger RL, Travers JB (2012a) Platelet-activating factor does not mediate UVB-induced local immune suppression. *Photochem Photobiol* 88:490–493 [PubMed: 22211638]
- Sahu RP, Turner MJ, DaSilva SC, Rashid BM, Ocana JA, Perkins SM, Konger KL, Touloukian CE, Kaplan MH, Travers JB (2012b) The environmental stressor ultraviolet radiation inhibits murine anti-tumor immunity through its ability to generate platelet-activating factor agonists. *Carcinogenesis* 33(7):1360–1367 [PubMed: 22542595]
- Sahu RP et al. (2013) Cigarette smoke exposure inhibits contact hypersensitivity via the generation of platelet-activating factor agonists. *J Immunol* 190(5):2447–2454 [PubMed: 23355733]

- Sahu RP, Ocana JA, Harrison KA, Ferracini M, Touloukian CE, Al-Hassani M, Sun L, Loesch M, Murphy RC, Althouse SK, Perkins SM, Speicher PJ, Tyler DS, Konger RL, Travers JB (2014) Chemotherapeutic agents subvert tumor immunity by generating agonists of platelet-activating factor. *Cancer Res* 74(23):7069–7078 [PubMed: 25304264]
- Sahu RP, Harrison KA, Weyerbacher J, Murphy RC, Konger RL, Garrett JE, Chin-Sinex HJ, Johnston ME II, Dynlacht JR, Mendonca M, McMullen K, Li G, Spandau DF, Travers JB (2016) Radiation therapy generates immunosuppressive platelet-activating factor agonists. *Oncotarget* 7:20788–20800 [PubMed: 26959112]
- Schaue D, Ratikan JA, Iwamoto KS, McBride WH (2012) Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys* 83:1306–1310 [PubMed: 22208977]
- Serban KA, Rezanian S, Petrusca DN, Poirier C, Cao D, Justice MJ, Patel M, Tsvetkova I, Kamocki K, Mikosz A, Schweitzer KS, Jacobson S, Cardoso A, Carlesso N, Hubbard WC, Kechris K, Dragnea B, Berdyshev EV, McClintock J, Petrache I (2016) Structural and functional characterization of endothelial microparticles released by cigarette smoke. *Sci Rep* 6:31596 [PubMed: 27530098]
- Shimizu T (2009) Lipid mediators in health and disease: enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation. *Annu Rev Pharmacol Toxicol* 49:123–150 [PubMed: 18834304]
- Snyder F, Fitzgerald V, Blank ML (1996) Biosynthesis of platelet-activating factor and enzyme inhibitors. *Adv Exp Med Biol* 416:5–10 [PubMed: 9131118]
- Soares AC, Pinho VS, Souza DG, Shimizu T, Ishii S, Nicoli JR, Teixeira MM (2002) Role of the platelet-activating factor (PAF) receptor during pulmonary infection with gram negative bacteria. *Br J Pharmacol* 137(5):621–628 [PubMed: 12381675]
- Sreevidya CS, Khaskhely NM, Fukunaga A, Khaskina P, Ullrich SE (2008) Inhibition of photocarcinogenesis by platelet-activating factor or serotonin receptor antagonists. *Cancer Res* 68(10):3978–3984 [PubMed: 18483284]
- St Denis TG, Aziz K, Waheed AA et al. (2011) Combination approaches to potentiate immune response after photodynamic therapy for cancer. *Photochem Photobiol Sci* 10(5):792–801 [PubMed: 21479313]
- Stampfli MR, Anderson GP (2009) How cigarette smoke skews immune responses to promote infection, lung disease and cancer. *Nat Rev Immunol* 9(5):377–384 [PubMed: 19330016]
- SucIU-Foca N, Molinaro A, Buda J, Reemtsma K (1974) Cellular immune responsiveness in cigarette smokers. *Lancet* 1:1062–1064
- Takeshita J, Mohler ER, Krishnamoorthy P, Moore J, Rogers WT, Zhang L, Gelfand JM, Mehta NN (2014) Endothelial cell-, platelet-, and monocyte/macrophage-derived microparticles are elevated in psoriasis beyond cardiometabolic risk factors. *J Am Heart Assoc* 3(1):e000507 [PubMed: 24584739]
- Talvani A, Santana G, Barcelos LS, Ishii S, Shimizu T, Romanha AJ, Silva JS, Soares MB, Teixeira MM (2003) Experimental *Trypanosoma cruzi* infection in platelet-activating factor receptor-deficient mice. *Microbes Infect* 5:789–796 [PubMed: 12850205]
- Tamagawa-Mineoka R, Katoh N, Kishimoto S (2010) Platelet activation in patients with psoriasis: increased plasma levels of platelet-derived microparticles and soluble P-selectin. *J Am Acad Dermatol* 62:621–626 [PubMed: 19962788]
- Travers JB, Harrison KA, Johnson CA, Clay KL, Morelli JG, Murphy RC (1996) Platelet-activating factor biosynthesis induced by various stimuli in human HaCaT keratinocytes. *J Invest Dermatol* 107:88–94 [PubMed: 8752845]
- Travers JB, Pei Y, Morin M, Hood A (1998a) Antiinflammatory effects of the platelet-activating factor receptor antagonist A85783. *Arch Dermatol Res* 290:569–573 [PubMed: 9836508]
- Travers JB, Murphy RC, Johnson CA, Pei Y, Morin SM, Barber LA, Clay K, Hood AF, Morelli JG, Williams DA (1998b) Identification and pharmacological characterization of PAF and 1-acyl species found in human inflammatory blistering diseases. *Prostaglandins* 56:305–324
- Travers JB, Edenberg HJ, Zhang Q, Al-Hassani M, Yi Q, Baskaran S, Konger RL (2008) Augmentation of UVB radiation-mediated early gene expression by the epidermal platelet-activating factor receptor. *J Invest Dermatol* 128(2):455–460 [PubMed: 17928889]

- Ullrich SE (2005) Mechanisms underlying UV-induced immune suppression. *Mutat Res* 571:185–205 [PubMed: 15748647]
- Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T, Simons FER, Simons KJ, Cass D, Yeung J (2008) Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med* 358:28–35 [PubMed: 18172172]
- Varma S, Holt PJ, Anstey AV (2000) Erythroplasia of queyrat treated by topical aminolaevulinic acid photodynamic therapy: a cautionary tale. *Br J Dermatol* 142:825–826 [PubMed: 10792247]
- Vion A-C, Ramkhelawon B, Loyer X et al. (2013) Shear stress regulates endothelial microparticle release. *Circ Res* 112:1323–1333 [PubMed: 23536307]
- Wacker M, Holick MF (2013) Sunlight and vitamin D. *Dermato-Endocrinol* 5(1):51–108
- Walterscheid JP, Ullrich SE, Nghiem DX (2002) Platelet-activating factor, a molecular sensor for cellular damage, activates systemic immune suppression. *J Exp Med* 195:171–179 [PubMed: 11805144]
- Wara WM (1977) Immunosuppression associated with radiation therapy. *Int J Radiat Oncol Biol Phys* 2:593–596 [PubMed: 301876]
- Wara WM, Phillips TL, Wara DW, Ammann AJ, Smith V (1975) Immunosuppression following radiation therapy for carcinoma of the nasopharynx. *Am J Roentgenol Radium Ther Nucl Med* 123:482–485
- Winter AP, Follett EA, McIntyre J, Stewart J, Symington IS (1994) Influence of smoking on immunological responses to hepatitis B vaccine. *Vaccine* 12(9):771–772 [PubMed: 7975854]
- Wolf P, Fink-Puches R, Reimann-Weber A et al. (1997) Development of malignant melanoma after repeated topical photodynamic therapy with 5-aminolevulinic acid at the exposed site. *Dermatology* 194:53–54 [PubMed: 9031792]
- Wolf P et al. (2006) Platelet-activating factor is crucial in psoralen and ultraviolet A-induced immune suppression, inflammation, and apoptosis. *Am J Pathol* 169(3):795–805 [PubMed: 16936256]
- Wolverton JE, Al-Hassani M, Yao Y, Travers JB (2010) Epidermal platelet-activating factor activation and ultraviolet B radiation result in synergistic tumor necrosis factor alpha production. *Photochem Photobiol* 86:231–235 [PubMed: 19769579]
- Xiao X, Ma X, Liu L, Wang J, Bi K, Liu Y, Fan R, Zhao B, Chen Y, Bihl JC (2015) Cellular membrane microparticles: potential targets of combinational therapy for vascular disease. *Curr Vasc Pharmacol* 13(4):449–458 [PubMed: 25360845]
- Yamada Y, Yokota M (1997) Loss of activity of plasma platelet-activating factor acetylhydrolase due to a novel Gln281-->Arg mutation. *Biochem Biophys Res Commun* 236(3):772–775 [PubMed: 9245731]
- Yang L et al. (2010) Chronic alcohol exposure increases circulating bioactive oxidized phospholipids. *J Biol Chem* 285(29):22211–22220 [PubMed: 20460374]
- Yao Y, Harrison KA, Al-Hassani M, Murphy RC, Rezaia S, Konger RL, Travers JB (2012) Platelet-activating factor agonists mediate xeroderma pigmentosum A photosensitivity. *J Biol Chem* 287:9311–9321 [PubMed: 22303003]
- Zalewski A, Macphee C (2005) Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. *Arterioscler Thromb Vasc Biol* 25(5):923–931 [PubMed: 15731492]
- Zhang Q, Yao Y, Konger RL, Sinn AL, Cai S, Pollok KE, Travers JB (2008) UVB radiation-mediated inhibition of contact hypersensitivity reactions is dependent on the platelet-activating factor system. *J Invest Dermatol* 128:1780–1787 [PubMed: 18200048]
- Zimmerman GA, McIntyre TM, Prescott SM, Stafforini DM (2002) The platelet-activating factor signaling system and its regulators in syndromes of inflammation and thrombosis. *Crit Care Med* 30(5 Suppl):S294–S301 [PubMed: 12004251]

Figure 1.
Biosynthesis of PAF and eicosanoids via the remodeling pathway.

Figure 2. Model for how acute damage elevates intracellular calcium levels.

Resting cellular Ca^{2+} levels are at least $10,000 \times$ lower than extracellular levels. Disruption of the cellular membrane results in an increase in intracellular Ca^{2+} which then activates numerous enzymes, including phospholipases which can stimulate eicosanoids and PAF.

Figure 3.
Model for how environmental stressors can induce immunosuppression via PAFR-mediated generation of regulatory T cells

Figure 4. Model for how UVB and potentially other environmental stressors can generate microvesicle particles via PAFR signalling in a process dependent upon the enzyme acid sphingomyelinase.