—Review—

Inflammatory mediators in ovarian follicles: the possible role of platelet-activating factor and its metabolic enzyme

Yasushi Kawano*, Emi Harada, Yuki Yamashita, Yui Itonaga, Naomi Inoue and Hisashi Narahara

Department of Obstetrics and Gynecology, Faculty of Medicine, Oita University, Oita 879-5593, Japan

Abstract: Platelet-activating factor (PAF) is a potent pro-inflammatory negotiator that shows a distinct spectrum of biological and pharmacological effects and participates in a wide range of pathophysiological conditions. In the reproductive system, PAF has been shown to have an important role in initiating ovulation, progesterone production and chemokine production. The purpose of this article was to review the roles of PAF, a well-known family of messenger phospholipids, in the reproductive process, especially in ovulation. This review highlights the interesting parallels between PAF's mechanism in ovulation and inflammatory process.

Keywords: Platelet-activating factor, PAF-acetylhydrolase, Granulosa cells, Ovulation, Chemokine

Introduction

Platelet-activating factor (PAF) was first described as a mediator that was synthesized and released from basophils which causes platelet aggregation by IgE sensitization [1]. Subsequently, Demopoulos *et al.* [2] and Benveniste *et al.* [3] reported the structure of PAF as 1-*O*-alkyl-2-*sn*-glycero-3-phosphocholine.

Since then, other roles of PAF have been discovered, and it is now also known as a potent pro-inflammatory phospholipid, which has been shown to have many physiological and pathophysiological effects beyond wound healing, including roles in physiological inflammation, apoptosis, angiogenesis, reproduction and long-term potentiation [4]. PAF's contributions to reproductive and developmental processes have been shown to include roles in ovulation [5], sperm motility [6], implantation [7], fetal lung maturation [8], and the initiation and maintenance of parturition [9–11].

This review focuses on recent discoveries about PAF and PAF-acetylhydrolase (AH) in the field of ovarian folliculogenesis, emphasizing PAF-mediated events and the importance of their tight regulation in ovarian follicles.

PAF Synthesis and Metabolism

PAF has a structure of 1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine (Fig. 1), and it comprises a family of pro-inflammatory phospholipids which exerts effects in a variety of cells and tissues [12]. PAF is synthesized in diverse cells such as neutrophils, macrophages, monocytes, eosinophils, basophils, platelets, and endothelial cells [13]. PAF is also produced in tissues including the lungs, kidney, myocardium, brain, liver, skin, saliva, retina, uterus, ovary [5] and embryo [14, 15]. PAF is known to induce many inflammatory reactions and allergic responses involving leukocyte adhesion, chemotaxis, degranulation, and increased vascular permeability [16, 17].

There are two enzymatic pathways by which PAF is physiologically and pathologically biosynthesized, namely remodeling and *de novo* pathways [18]. It has been recognized that the *de novo* pathway is a minor endogenous pathway [19], which takes three enzymatic steps to form PAF from its precursor 1-alkyl-2-lyso-sn-glycero-3-phosphate [20]: acetylation by acetyltransferase, dephosphorylation by a phosphohydrolase, and appending with choline-P [21, 22]. The other, remodeling pathway, which substitutes an acetyl residue for the long-chain fatty acyl residue of cell membrane phospholipids is recognized as the principal enzymatic pathway of PAF synthesis (Fig. 2).

Indeed, PAF synthesis in the remodeling pathway is known to begin with release of 1-*O*-alkyl- or 1-*O*-acyl-2-lyso-GPC (lyso-PAF) from 1-*O*-alkyl- or 1-*O*-ac-

Received: May 30, 2017
Accepted: July 19, 2017
*To whom correspondence should be addressed.
e-mail: kawayas@oita-u.ac.jp

1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocolin (PAF)

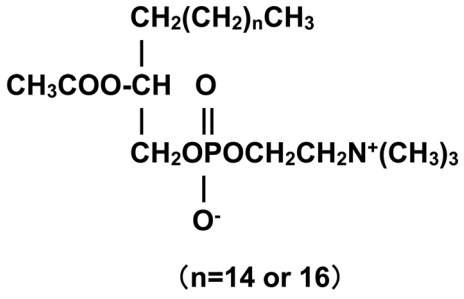

Fig. 1. The structure of platelet-activating factor [11].

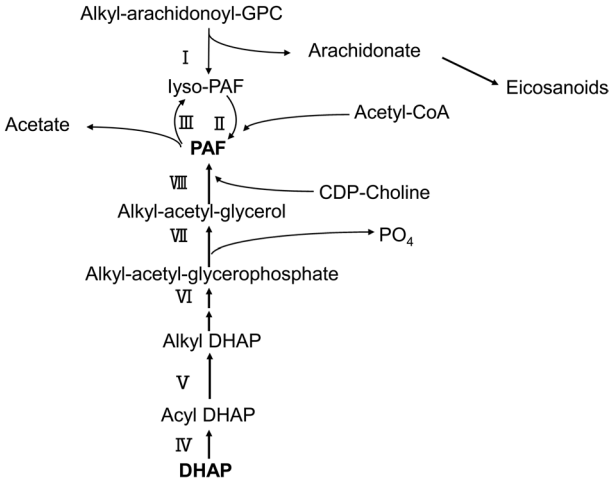

Fig. 2. Metabolism of PAF [11]. Pathways for PAF synthesis. The remodeling pathway reactions shown are: RxI, phospholipase A2 or a CoA-independent transacylase; RxII, lysoPAF: cetyl-CoA acetyl-transferase; RxIII, PAF-acetylhydrolase. The enzymes of the *de novo* pathway are: RxIV, DHAP: acyl-CoA acyltransferase; RxV, alkyl-DHAP synthase; RxVI, acetyl-CoA: 1-*O*-alkyl-2-lyso-GP acetyltransferase DHAP, and both CDP-choline dihydroxyacetone phosphate and cytidine diphosphate; RxVII, 1-alkyl-2-acetyl-glycero-3-phosphate phosphohydro-lase; and RxVIII, 1-alkyl-2-acetyl-glycerol: CDP-choline cholinephosphotransferase.

yl-2- arachidonoyl-GPC by phospholipase A2 (PLA2). Lyso-PAF is subsequently converted to PAF by acetyl-CoA and lyso-PAF acetyltransferase [23, 24]. Like the eicosanoids, PAF is not usually stored in a preformed state, but is rapidly synthesized by inflammatory cells in response to cell-specific stimuli. This step is essential for synthesizing PAF. The activation of phospholipase A2 also leads to arachidonate release resulting in eicosanoid synthesis. It has also been reported that the alkyl phosphatidylcholines are enriched to release arachidonate in leukocytes and monocytes [25, 26]. Taken together, it can be inferred that the amount of PAF present in the biological fluid or tissues may be modulated by a balance of synthesis and catabolic pathways [15, 27].

PAF is catalyzed by PAF-AH, which removes the acetyl group from the *sn-2* position, resulting in the biologically inactive form of lyso-PAF [28], which lacks PAF activity in nature. PAF-AH is known to be produced primarily by hepatocytes and macrophages, and is distributed in human plasma, blood cells and numerous tissues [11]. Human peripheral blood-derived macrophages [29], human decidual macrophages [30, 31], and phorbol ester-stimulated HL-60 cells [32] have been shown to secrete PAF-AH into plasma. Treatment of rats with either dexamethasone or medroxyprogesterone causes an increase in plasma PAF-AH activity, whereas estrogen treatment results in a decrease in the activity of the plasma enzyme [33]. If any imbalance in inflammatory reactions occurs, the amount of PAF will change and induce some pathological status. PAF-AH is believed to regulate in part the PAF concentration in the body [29].

PAF in the Ovary and Follicular Fluid

The first indication that PAF may be involved in ovulation, was based on the observation that the local administration of a PAF receptor antagonist inhibited rupture of ovarian follicles in rats [5]. The involvement of PAF in ovulation was examined by injection of a specific PAF antagonist, BN52021. This substance effectively blocked ovulation when administered concomitantly with hCG or up to 9 h after hCG treatment. On the other hand, the inhibition of follicle rupture was suppressed when BN52021 and PAF were injected into the ovarian bursa simultaneously [5]. It was shown that when BN52021 was administered bilaterally into the ovarian bursa, hCG-induced ovulation, the typical preovulatory increase in ovarian collagenolysis, and uptake of labeled bovine serum albumin were all blocked [5]. The fact that PAF partially reversed the inhibitory action of BN52021 shows that PAF has an effect on ovulation. Moreover, PAF has been shown to induce margination and activation of thrombocytes and leukocytes *in vivo* [34]. As several matrix-degrading proteases have been identified in human granulocytes [35], PAF's action on ovulation is believed to be mediated through blood cells.

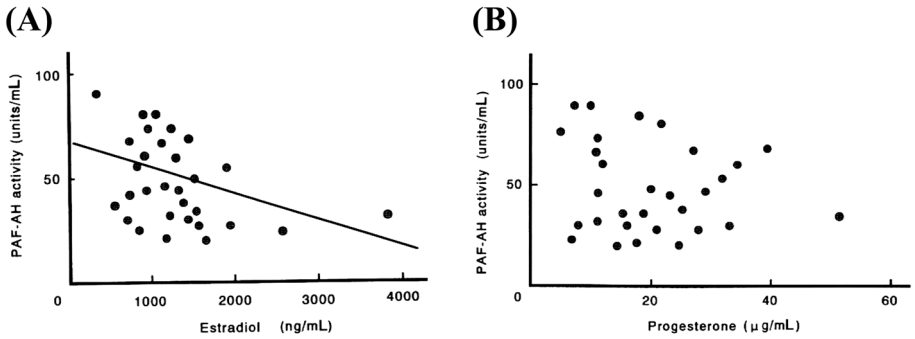

Fig. 3. PAF-AH in FF [48]. (A) Correlation between E2 levels and PAF-acetylhydrolase activity in FF. y=0.011x + 61.7; $r = 0.374$; n=30; $P < 0.05$. (B) Correlation between P levels and PAF-acetylhydrolase activity in FF. y=0.507x + 59.2; $r = 0.297$; n=30; $P < 0.11$.

Espey *et al.* [36] reported a decrease in the PAF concentration in rat ovarian tissue within several hours after the administration of human chorionic gonadotrophin (hCG). In another investigation, PAF was shown to be secreted from a cultured ovine follicular wall and to increase within 2 h after the endogeneous pre-ovulatory LH surge [37]. It has also been demonstrated that PAF is present in human follicular fluid (FF) collected near the time of ovulation [38], with levels varying from 600 to 5,000 pg/ml. There was no difference in PAF levels in FF yielding no oocyte or that yielding an oocyte capable or not capable of being fertilized. There were also no significant correlations between PAF levels and the number of retrieved oocytes or estradiol levels at the time of hCG administration [38]. Interestingly, PAF levels were different between long-protocol and short-protocol IVF procedures. Specifically, PAF levels were higher in long-protocol IVF [38].

Leukocytes are thought to arrive in and around the pre-ovulatory follicle in response to the LH surge in order to promote the release of secretory products, such as histamine, bradykinin, prostaglandins, serotonin, cytokines and chemokines, all of which play well-documented roles in the biochemistry of ovulation [39–42].

It has been suggested that the release of specific mediators or biochemical and cytologic changes in the follicular wall due to the accumulation of polynuclear leukocytes and thrombocytes before ovulation might be associated with the presence of PAF in ovarian follicles, and especially in FF [43, 44]. These observations provide support for the hypothesis that PAF activity in FF might result in local production of PAF, even if the possibility of extra-follicular production cannot be excluded. These studies indicate that chemotactic factors of these cells are necessary in the ovulatory process.

The enzymatic activity of PAF-AH in the FF, converting PAF to lyso-PAF, was first reported in 1993 [45]. The activity of PAF-AH in the hydrolyzation of [^{3}H]PAF in the FF is markedly lower than in other body fluids such as plasma or peritoneal fluid (PF). It has also been reported that the percentages of [^{3}H]PAF catalyzed after 15-min incubation in plasma, PF and FF, were 65%, 39% and 10%, respectively. Interestingly, it was shown that the estimated half-life of PAF was 7–12 min in plasma, 15–25 min in PF and 2 h in FF [45]. As PAF-AH in plasma has been shown to correlate with the levels of lipoproteins [46, 47], the specific activity of PAF-AH is reflected by the ratio of PAF-AH to cholesterol. The results of these studies show, the specific activity of PAH-AH in FF is not significantly different from that in plasma, and the lower activity in FF is probably due to the absence of LDL in FF [45].

A clinical study performed on 1995 investigated the PAF-AH activity in human FF obtained from patients who had oocytes retrieved for *in vitro* fertilization and embryo transfer (IVF-ET) [48]. Human FF aspirated from preovulatory follicles with controlled ovarian hyperstimulation (COH) had PAF-AH activity ranging from 20.2 to 89.9 units/ml. There were no differences between pregnant and non-pregnant subjects in the number of oocytes retrieved, in the rate of oocytes fertilized, or in the number of embryos transferred. However, the specific activity of PAF-AH was significantly lower in women with a successful pregnancy outcome than in the non-pregnant patients. The hormones regulating the plasma activity of PAF-AH have been examined in both rats and humans [49]. An assessment of the relationship between the specific activities of PAF-AH and ovarian steroid hormones in FF was performed. E2 levels negatively correlated with the PAF-AH activity in FF. However, the levels of progesterone showed no correlation with the PAF-AH activity in FF (Fig. 3).

PAF and Granulosa Cell Function

PAF receptor

It has been reported that PAF interacts with a specific G-protein-coupled transmembrane receptor, PAF-R [50]. The activated PAF-R is linked to a myriad of signal transduction pathways in its downstream, such as phospholipase A2, phospholipase C, phospholipase D, mitogen-activated protein (MAP) kinase cascades, and adenylate cyclase [51]. The PAF receptor also couples with both pertussis toxin-sensitive and -insensitive G proteins [50, 52].

PAF-R primarily contributes to the activation of extracellular signal-regulated kinase (ERK) and p38 MAP kinase in numerous tissues. However, ERK and p38 activation by PAF differs among species according to the cell type in which its receptor is located. For example, PAF activates ERK through a protein kinase C-dependent, Ras-independent pathway in Chinese hamster ovary cells [50]. On the other hand, ERK via MEK1/2, a downstream target of Ras, is activated by PAF in human neutrophils [53].

A DNA variant in which an aspartic acid is substituted for an alanine residue at position 224 (A224D) has been identified in the putative third cytoplasmic loop in the human PAF receptor gene [54]. Interestingly, this mutation has been reported as being present in a Japanese population at an allele frequency of 7.8%. The mutant PAF receptor expressing A224D exhibits partial but significant reduction not only in the intracellular signaling for calcium mobilization and inositol phosphate production, but also in the inhibition of adenylyl cyclase and the chemotactic effects elicited by PAF stimulation [54]. The consistency of the variant receptor may be the principal mechanism behind the inter-individual variations in PAF-related physiological responses, disease predisposition or phenotypes and drug responsiveness [4].

Progesterone production

It has been demonstrated that PAF, produced during the inflammation-like reaction in ovulatory processes, affects granulosa cell function and corpus luteum formation *in vitro* [55].

PAF at a dose of 500 ng or greater per ml of media caused a marked decrease in the production of progesterone by cells cultured in media containing 0.25% BSA. In media containing 1% FBS, PAF at 500 ng/ml or greater decreased production of progesterone, but this effect was greatly attenuated compared to cultures without serum [56]. These results suggest this effect may be due to the presence of enzymes in FBS that inactive PAF.

Progesterone secretion as well as morphological change are found in human luteinized granulosa cells. The decrease in progesterone production elicited by PAF treatment may reflect a cytotoxic effect. PAF could have an indirect stimulating effect on granulosa or luteal cells *in vivo*. Even though no direct effect of PAF has been demonstrated *in vitro*, the situation *in vivo* with platelets present is quite different. PAF activates platelets which in turn release 5-hydroxytryptamine and PDGF and thereby alter granulosa cell function [56].

PAF and chemokine

Chemokines are secreted by resident tissue cells such as endothelial cells, leukocytes or adipocytes, and contribute to the recruitment and activation of circulating leukocytes. Ovulation is similar to an inflammatory reaction and the leukocytes around the follicle may play an important role in ovulation [43, 57]. The involvement of chemokines in ovarian function is becoming more evident as research in this area progresses [58, 59]. Chemokines has been directly and indirectly implicated in follicular development and atresia, ovulation, steroidogenesis, and corpus luteum function (including formation, development, and regression).

Experimental evidence suggests that there is a 3-fold increase in the density of neutrophils in the medullary region of the rat ovary during the ovulatory phase, and a corresponding 8-fold increase in the density of this cell type in the theca layer of the ovulating follicles [60]. The neutrophils tended to concentrate around the inner parts of the theca interna with a large number around the apex of the ovulating follicle. In humans, a marked increase in the neutrophil density in the theca compartment is also seen after the onset of the LH-surge, with further accumulation just after follicle rupture [61, 62]. Indirect evidence for an increase in this cell type is provided by the fact that ovarian concentrations of neutrophil elastase, a marker enzyme that reflects neutrophil activity, increase to a similar extent in the rabbit ovary about 9 h after hCG injection [63]. Ovulation has many features in common with inflammatory reactions, including the participation of leukocytes and classical inflammatory mediators.

It has been suggested that IL-8 and GROα may be important modulators of preovulatory events, not only through the attraction and activation of neutrophils that eventually play roles in timely follicular rupture, but also through the stimulation of new blood vessel formation for the corpus luteum [64]. PAF is known to be a potent pro-inflammatory mediator, and it exerts its effects via specific receptors in a variety of cell types [20, 29, 65]. It has been reported that the addition of a PAF antagonist into

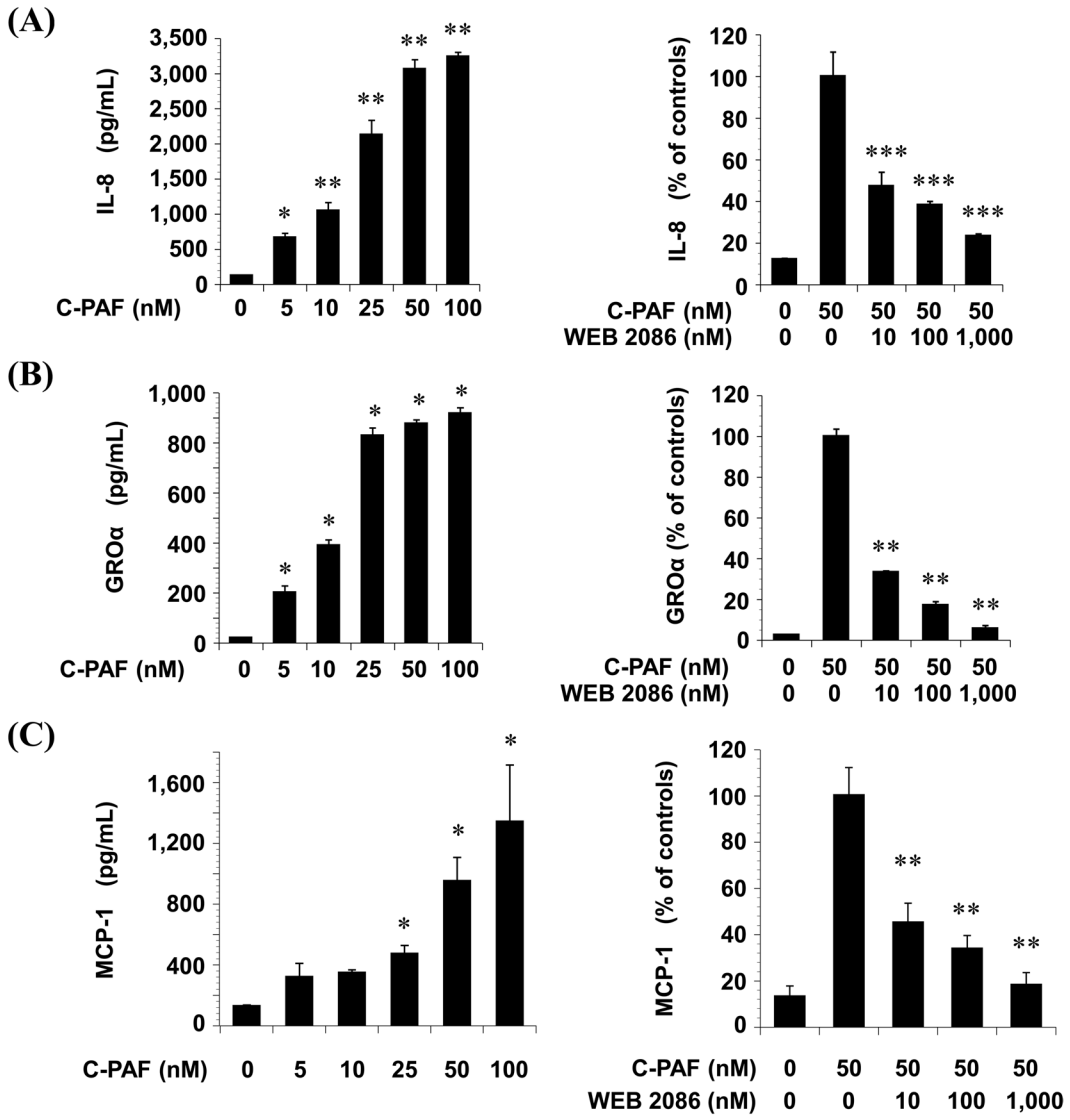

Fig. 4. GC1a data [73]. IL-8 (A), GROα (B) and MCP-1 (C) (unpublished data) concentrations in culture media of GC1a after 24 h stimulation with various concentrations of C-PAF and WEB 2086 (PAF-receptor antagonist). GC1a cells were treated with human C-PAF at concentrations of 5 nM to 100 nM, C-PAF (50 nM) and WEB 2086 at concentrations of 10 nM to 1,000 nM. * P<0.01, ** P<0.001 vs. unstimulated control, *** P<0.001 vs. C-PAF (50 nM) stimulation (A). * P<0.001 vs. unstimulated control, ** P<0.001 vs. C-PAF (50 nM) stimulation (B, C).

the bursa of the rat ovary resulted in a marked reduction in the frequency of ovulation, and this inhibition was partially reversed by simultaneous administration of PAF [5]. PAF has been shown to be secreted from a cultured ovine follicular wall, and PAF levels increase within 2 h after the endogenous pre-ovulatory LH surge [37]. The detection of PAF in human FF collected near the time of ovulation indicates the local ovarian production of PAF [38]. These observations provide support for the hypothesis that PAF plays a role in the ovulatory mechanism [43].

Although it has been shown that human FF has chemotactic activity with respect to neutrophils, [66, 67] specific chemotactic factors responsible for the recruitment and activation of neutrophils in and around pre-ovulatory follicles have not been identified. The neutrophil chemotactic activity in preovulatory follicular fluid is higher in conceptual cycles than in non-conceptual cycles [66]. One of the candidates for this activity is IL-8, a chemoattractant and cytokine that activates neutrophils [68], as

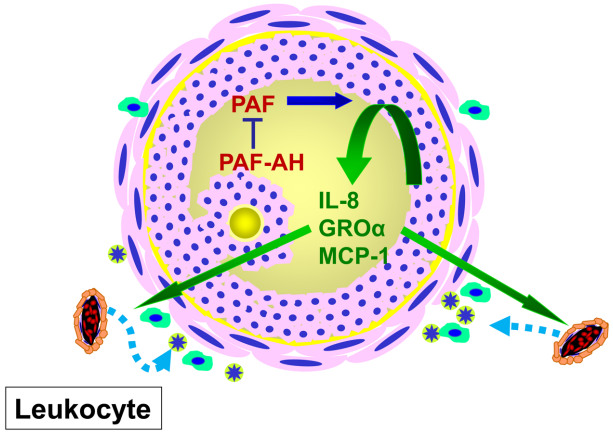

Fig. 5. The hypothetical roles of PAF in peri-ovulatory processes are shown. Monocytes, macrophages and neutrophilic granulocytes are recruited from the blood by the action of chemokines such as MCP-1, IL-8 and GROα.

well as a potent angiogenic agent [69]. IL-8 has been found in large amounts in human follicles [64]. GROα, another chemoattractant of neutrophils has also been found in human FF [70].

The stimulation of GC1a, a granulosa cell line [71], by inflammatory cytokines such as IL-1α and TNF-α [58], or growth factors such as epidermal growth factor and transforming growth factor-α [72] is known to induce the production of IL-8 and GROα. The production of IL-8 and GROα in GC1a is also observed after stimulation by PAF [73]. The levels of IL-8, GROα and MCP-1 (unpublished data) were increased by treatment of C-PAF for 2–32 h in a time-dependent manner. The levels of IL-8, GROα and MCP-1 were also significantly and dose-dependently increased by treatment with C-PAF (5–100 nm) compared to controls. On the other hand, when the GC1a cells were treated with C-PAF (50 nm) and/or increasing concentrations of WEB 2086, a PAF receptor antagonist, the levels of IL-8, GROα and MCP-1 were significantly lower than those of the controls treated with C-PAF alone (Fig. 4). On the basis of these observations, I IL-8, GROα and MCP-1 in FF are thought to promote to neutrophil chemoattraction and accumulation. Our results also indicate that I IL-8, GROα and MCP-1 are regulated by a mechanism involving C-PAF; it is likely that IL-8, GROα and MCP-1 play important roles in the accumulation of neutrophils and in the subsequent induction of ovulation (Fig. 5).

PAF and cell proliferation

Some experimental findings provide substantial evidence of PAF receptor-mediated effects in cell cycle progression and exit from the proliferation cycle [74]. PAF stimulation at physiological concentrations contributes to a shift in the cell cycle phase distribution pattern, with the proportions of proliferating cells in the S and G2/M phases decreasing in favor of increasing numbers of cells entering the G0/G1 compartment. Responses to PAF treatment are rather moderate, possibly due to the typically high proportions of resting cells in pre-ovulatory granulosa cell populations [75].

Corresponding to the effect on cell cycle progression, PAF treatment also elicits a considerable increase in cell recruitment. PAF receptor knockout mice generated by targeted gene disruption, do not show gross morphological abnormalities in any organ system [76]. However, gonadotropin-induced activation of genes encoding cyclooxygenase and the progesterone receptor (essential for ovulation) occurs normally in follicles that fail to ovulate due to reduced numbers of granulosa cells [75, 77]. These observations imply that granulosa cell number is a critical factor in ovulation. PAF receptor antagonists may disturb *in vivo* proliferative regulation of granulosa cells, that is, the withdrawal from the cell cycle associated with resistance to apoptosis [78], consequently inhibiting ovulation. PAF receptor antagonists reverse or attenuate the effects of PAF on the cell cycle, cell number and PCNA expression. Overlapping but not identical pathways are activated by PAF to promote cell cycle progress subsequent to withdrawal from the cell cycle.

Conclusions

PAF is a well-known pro-inflammatory mediator, which has been identified as a factor that is active throughout the female reproductive process. Multiple lines of evidence suggest that signaling effects of PAF, which are closely associated with ovulation, are mediated by various mechanisms such as catalytic activity by PAF-AH, granulosa cell function including chemokine and progesterone production, and have an effect on the cell cycle. Being an important physiological regulator as well as an initial influencing factor in pro- or peri-ovulatory processes, PAF may be an important biomarker in ovarian follicles. However, further research is needed to understand its independent influence in reproductive processes including ovulation.

References

1) Benveniste, J., Henson, P.M. and Cochrane, C.G. (1972): Leukocyte-dependent histamine release from rabbit plate-

lets. The role of IgE, basophils, and a platelet-activating factor. J. Exp. Med., 136, 1356–1377. [Medline] [CrossRef]
2) Demopoulos, C.A., Pinckard, R.N. and Hanahan, D.J. (1979): Platelet-activating factor. Evidence for 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine as the active component (a new class of lipid chemical mediators). J. Biol. Chem., 254, 9355–9358. [Medline]
3) Benveniste, J., Tencé, M., Varenne, P., Bidault, J., Boullet, C. and Polonsky, J. (1979): [Semi-synthesis and proposed structure of platelet-activating factor (P.A.F.): PAF-acether an alkyl ether analog of lysophosphatidylcholine]. C. R. Acad. Sci. D Sci. Nat., 289, 1037–1040. (in French) [Medline]
4) Stafforini, D.M., McIntyre, T.M., Zimmerman, G.A. and Prescott, S.M. (2003): Platelet-activating factor, a pleiotrophic mediator of physiological and pathological processes. Crit. Rev. Clin. Lab. Sci., 40, 643–672. [Medline] [CrossRef]
5) Abisogun, A.O., Braquet, P. and Tsafriri, A. (1989): The involvement of platelet activating factor in ovulation. Science, 243, 381–383. [Medline] [CrossRef]
6) Ricker, D.D., Minhas, B.S., Kumar, R., Robertson, J.L. and Dodson, M.G. (1989): The effects of platelet-activating factor on the motility of human spermatozoa. Fertil. Steril., 52, 655–658. [Medline] [CrossRef]
7) O'Neill, C. (1990): PAF and the establishment of pregnancy. In: Platelet-activating Factor and Human Disease (Barnes, P.C., Page, C.P., Henson, P.S., eds.), pp. 282–296, Blackwell, Oxford.
8) Johnston, J.M., Bleasdale, J.E. and Hoffman, D.R. (1987): Function of PAF in reproduction and development: Involvement of PAF in fetal lung maturation and parturition. In: Platelet-activating Factor and Related Lipid Mediators (Snyder, F., ed.), pp. 375–402, Plenum Press, New York.
9) Toyoshima, K., Narahara, H., Furukawa, M., Frenkel, R.A. and Johnston, J.M. (1995): Platelet-activating factor. Role in fetal lung development and relationship to normal and premature labor. Clin. Perinatol., 22, 263–280. [Medline]
10) Johnston, J.M., and Miyaura, S. (1987): in PAF Antagonist: New Developments for Clinical Application, pp139–160, Portfolio Pub, Woodlands, TX.
11) Muguruma, K., Narahara, H., Kawano, Y. and Johnston, J.M. (1997): Platelet-activating factor in reproduction. Infertil Reprod Med Clin N. Am., 8, 1–24.
12) Venable, M.E., Zimmerman, G.A., McIntyre, T.M. and Prescott, S.M. (1993): Platelet-activating factor: a phospholipid autacoid with diverse actions. J. Lipid Res., 34, 691–702. [Medline]
13) Triggiani, M., Schleimer, R.P., Warner, J.A. and Chilton, F.H. (1991): Differential synthesis of 1-acyl-2-acetyl-sn-glycero-3-phosphocholine and platelet-activating factor by human inflammatory cells. J. Immunol., 147, 660–666. [Medline]
14) Francescangeli, E., Freysz, L. and Goracci, G. (1996): PAF-synthesizing enzymes in neural cells during differentiation and in gerbil brain during ischemia. Adv. Exp. Med. Biol., 416, 21–27. [Medline] [CrossRef]
15) Palur Ramakrishnan, A.V., Varghese, T.P., Vanapalli, S., Nair, N.K. and Mingate, M.D. (2017): Platelet activating factor: A potential biomarker in acute coronary syndrome? Cardiovasc. Ther., 35, 64–70. [Medline] [CrossRef]
16) Reznichenko, A. and Korstanje, R. (2015): The role of platelet-activating factor in mesangial pathophysiology. Am. J. Pathol., 185, 888–896. [Medline] [CrossRef]
17) Braquet, P., Hosford, D., Braquet, M., Bourgain, R. and Bussolino, F. (1989): Role of cytokines and platelet-activating factor in microvascular immune injury. Int. Arch. Allergy Appl. Immunol., 88, 88–100. [Medline] [CrossRef]
18) Snyder, F. (1985): Chemical and biochemical aspects of platelet activating factor: a novel class of acetylated ether-linked choline-phospholipids. Med. Res. Rev., 5, 107–140. [Medline] [CrossRef]
19) Snyder, F., Fitzgerald, V. and Blank, M.L. (1996): Biosynthesis of platelet-activating factor and enzyme inhibitors. Adv. Exp. Med. Biol., 416, 5–10. [Medline] [CrossRef]
20) Snyder, F. (1990): Platelet-activating factor and related acetylated lipids as potent biologically active cellular mediators. Am. J. Physiol., 259, C697–C708. [Medline]
21) Snyder, F. (1994): Metabolic processing of PAF. Clin. Rev. Allergy., 12, 309–327. [Medline]
22) Liu, Y., Shields, L.B.E., Gao, Z., Wang, Y., Zhang, Y.P., Chu, T., Zhu, Q., Shields, C.B. and Cai, J. (2017): Current understanding of platelet-activating factor signaling in central nervous system diseases. Mol. Neurobiol., 54, 5563–5572. [Medline] [CrossRef]
23) Shindou, H., Hishikawa, D., Nakanishi, H., Harayama, T., Ishii, S., Taguchi, R. and Shimizu, T. (2007): A single enzyme catalyzes both platelet-activating factor production and membrane biogenesis of inflammatory cells. Cloning and characterization of acetyl-CoA:LYSO-PAF acetyltransferase. J. Biol. Chem., 282, 6532–6539. [Medline] [CrossRef]
24) Harayama, T., Shindou, H., Ogasawara, R., Suwabe, A. and Shimizu, T. (2008): Identification of a novel noninflammatory biosynthetic pathway of platelet-activating factor. J. Biol. Chem., 283, 11097–11106. [Medline] [CrossRef]
25) Nakagawa, Y., Kurihara, K., Sugiura, T. and Waku, K. (1986): Relative degradation of different arachidonoyl molecular species of choline glycerophospholipids in opsonized zymosan-stimulated rabbit alveolar macrophages. Biochim. Biophys. Acta., 876, 601–610. [Medline] [CrossRef]
26) Chilton, F.H. and Connell, T.R. (1988): 1-ether-linked phosphoglycerides. Major endogenous sources of arachidonate in the human neutrophil. J. Biol. Chem., 263, 5260–5265. [Medline]
27) Narahara, H., Kawano, Y., Nasu, K., Yoshimatsu, J., Johnston, J.M. and Miyakawa, I. (2003): Platelet-activating factor inhibits the secretion of platelet-activating factor acetylhydrolase by human decidual macrophages. J. Clin. Endocrinol. Metab., 88, 6029–6033. [Medline] [CrossRef]
28) Farr, R.S., Wardlow, M.L., Cox, C.P., Meng, K.E. and Greene, D.E. (1983): Human serum acid-labile factor is an acylhydrolase that inactivates platelet-activating factor. Fed. Proc., 42, 3120–3122. [Medline]
29) Prescott, S.M., Zimmerman, G.A. and McIntyre, T.M.

(1990): Platelet-activating factor. J. Biol. Chem., 265, 17381–17384. [Medline]
30) Narahara, H., Nishioka, Y. and Johnston, J.M. (1993): Secretion of platelet-activating factor acetylhydrolase by human decidual macrophages. J. Clin. Endocrinol. Metab., 77, 1258–1262. [Medline]
31) Kawano, Y., Narahara, H. and Johnston, J.M. (1999): Inhibitory effect of interleukin-8 on the secretion of platelet-activating factor acetylhydrolase by human decidual macrophages. J. Soc. Gynecol. Investig., 6, 328–332. [Medline] [CrossRef]
32) Narahara, H., Frenkel, R.A. and Johnston, J.M. (1993): Secretion of platelet-activating factor acetylhydrolase following phorbol ester-stimulated differentiation of HL-60 cells. Arch. Biochem. Biophys., 301, 275–281. [Medline] [CrossRef]
33) Toyoshima, K., Narahara, H., Furukawa, M., Frenkel, R.A. and Johnston, J.M. (1995): Platelet-activating factor. Role in fetal lung development and relationship to normal and premature labor. Clin. Perinatol., 22, 263–280. [Medline]
34) Issekutz, A.C., Ripley, M. and Jackson, J.R. (1983): Role of neutrophils in the deposition of platelets during acute inflammation. Lab. Invest., 49, 716–724. [Medline]
35) Tschesche, H., Fedrowitz, J., Kohnert, U., Michaelis, J. and Macartney, H.W. (1986): Matrix degrading proteinases from human granulocytes: type I, II, III collagenase, gelatinase and type IV, V-collagenase. A survey of recent findings and inhibition by gamma-anticollagenase. Folia Histochem. Cytobiol., 24, 125–131. [Medline]
36) Espey, L.L., Tanaka, N., Woodard, D.S., Harper, M.J.K. and Okamura, H. (1989): Decrease in ovarian platelet-activating factor during ovulation in the gonadotropin-primed immature rat. Biol. Reprod., 41, 104–110. [Medline] [CrossRef]
37) Alexander, B.M., Van Kirk, E.A. and Murdoch, W.J. (1990): Secretion of platelet-activating factor by periovulatory ovine follicles. Life Sci., 47, 865–868. [Medline] [CrossRef]
38) Amiel, M.L., Testart, J. and Benveniste, J. (1991): Platelet-activating factor-acether is a component of human follicular fluid. Fertil. Steril., 56, 62–65. [Medline] [CrossRef]
39) Norman, R.J., and Brannstrom, M. (1994): White cells and the ovary--incidental invaders or essential effectors? J. Endocrinol., 140, 333–336. [Medline] [CrossRef]
40) Kawasaki, F., Kawano, Y., Kosay Hasan, Z., Narahara, H. and Miyakawa, I. (2003): The clinical role of interleukin-6 and interleukin-6 soluble receptor in human follicular fluids. Clin. Exp. Med., 3, 27–31. [Medline] [CrossRef]
41) Kawano, Y., Kawasaki, F., Nakamura, S., Matsui, N., Narahara, H. and Miyakawa, I. (2001): The production and clinical evaluation of macrophage colony-stimulating factor and macrophage chemoattractant protein-1 in human follicular fluids. Am. J. Reprod. Immunol., 45, 1–5. [Medline] [CrossRef]
42) Kawano, Y., Fukuda, J., Nasu, K., Nishida, M., Narahara, H. and Miyakawa, I. (2004): Production of macrophage inflammatory protein-3α in human follicular fluid and cultured granulosa cells. Fertil. Steril., 82,(Suppl 3): 1206–1211. [Medline] [CrossRef]
43) Espey, L.L. (1980): Ovulation as an inflammatory reaction--a hypothesis. Biol. Reprod., 22, 73–106. [Medline] [CrossRef]
44) Thibault, C. and Levasseur, M.C. (1988): Ovulation. Hum. Reprod., 3, 513–523. [Medline] [CrossRef]
45) Lepage, N., Miron, P., Hemmings, R., Roberts, K.D. and Langlais, J. (1993): Distribution of lysophospholipids and metabolism of platelet-activating factor in human follicular and peritoneal fluids. J. Reprod. Fertil., 98, 349–356. [Medline] [CrossRef]
46) Stafforini, D.M., McIntyre, T.M., Carter, M.E. and Prescott, S.M. (1987): Human plasma platelet-activating factor acetylhydrolase. Association with lipoprotein particles and role in the degradation of platelet-activating factor. J. Biol. Chem., 262, 4215–4222. [Medline]
47) Stafforini, D.M., Carter, M.E., Zimmerman, G.A., McIntyre, T.M. and Prescott, S.M. (1989): Lipoproteins alter the catalytic behavior of the platelet-activating factor acetylhydrolase in human plasma. Proc. Natl. Acad. Sci. USA., 86, 2393–2397. [Medline] [CrossRef]
48) Narahara, H., Tanaka, Y., Kawano, Y., Gholbzouri, K., Miyakawa, I. and Johnston, J.M. (1995): Platelet-activating factor-acetylhydrolase activity in follicular fluid of patients undergoing in vitro fertilization and embryo transfer. Fertil. Steril., 64, 1172–1176. [Medline] [CrossRef]
49) Yasuda, K., Eguchi, H., Narahara, H. and Johnston, J.M. (1993): Platelet activating factor: its regulation in parturition. In: Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Radiation Injury. (Nigam S, Honn KV, Marnett LJ, Walden TL, eds.), pp. 727–730, Kluwer Academic Publications, Boston.
50) Honda, Z., Takano, T., Gotoh, Y., Nishida, E., Ito, K. and Shimizu, T. (1994): Transfected platelet-activating factor receptor activates mitogen-activated protein (MAP) kinase and MAP kinase kinase in Chinese hamster ovary cells. J. Biol. Chem., 269, 2307–2315. [Medline]
51) Marques, S.A., Dy, L.C., Southall, M.D., Yi, Q., Smietana, E., Kapur, R., Marques, M., Travers, J.B. and Spandau, D.F. (2002): The platelet-activating factor receptor activates the extracellular signal-regulated kinase mitogen-activated protein kinase and induces proliferation of epidermal cells through an epidermal growth factor-receptor-dependent pathway. J. Pharmacol. Exp. Ther., 300, 1026–1035. [Medline] [CrossRef]
52) Dupré, D.J., Le Gouill, C., Rola-Pleszczynski, M. and Stanková, J. (2001): Inverse agonist activity of selected ligands of platelet-activating factor receptor. J. Pharmacol. Exp. Ther., 299, 358–365. [Medline]
53) Coffer, P.J., Geijsen, N., M'rabet, L., Schweizer, R.C., Maikoe, T., Raaijmakers, J.A., Lammers, J.W. and Koenderman, L. (1998): Comparison of the roles of mitogen-activated protein kinase kinase and phosphatidylinositol 3-kinase signal transduction in neutrophil effector function. Biochem. J., 329, 121–130. [Medline] [CrossRef]
54) Fukunaga, K., Ishii, S., Asano, K., Yokomizo, T., Shiomi, T., Shimizu, T. and Yamaguchi, K. (2001): Single nucleotide polymorphism of human platelet-activating factor receptor impairs G-protein activation. J. Biol. Chem., 276, 43025–43030. [Medline] [CrossRef]

55) Rabinovici, J. and Angle, M.J. (1991): Platelet-activating factor induces progesterone secretion and changes in morphological appearance in luteinizing granulosa cells in vitro. Fertil. Steril., 55, 1106–1111. [Medline] [CrossRef]
56) Kang, K.C., Haering, P.L., Miller, K.F. and Kim, M.H. (1990): Effect of a synthetic platelet activating factor on steroidogenesis of cultured porcine granulosa cells. Life Sci., 47, 891–895. [Medline] [CrossRef]
57) Brännström, M., Wang, L. and Norman, R.J. (1993): Ovulatory effect of interleukin-1 beta on the perfused rat ovary. Endocrinology., 132, 399–404. [Medline] [CrossRef]
58) Zeineh, K., Kawano, Y., Fukuda, J., Nasu, K., Narahara, H. and Miyakawa, I. (2003): Possible modulators of IL-8 and GRO-α production by granulosa cells. Am. J. Reprod. Immunol., 50, 98–103. [Medline] [CrossRef]
59) Kawano, Y., Fukuda, J., Itoh, H., Takai, N., Nasu, K. and Miyakawa, I. (2004): The effect of inflammatory cytokines on secretion of macrophage colony-stimulating factor and monocyte chemoattractant protein-1 in human granulosa cells. Am. J. Reprod. Immunol., 52, 124–128. [Medline] [CrossRef]
60) Brännström, M., Mayrhofer, G. and Robertson, S.A. (1993): Localization of leukocyte subsets in the rat ovary during the periovulatory period. Biol. Reprod., 48, 277–286. [Medline] [CrossRef]
61) Brännström, M., Pascoe, V., Norman, R.J. and McClure, N. (1994): Localization of leukocyte subsets in the follicle wall and in the corpus luteum throughout the human menstrual cycle. Fertil. Steril., 61, 488–495. [Medline] [CrossRef]
62) Takaya, R., Fukaya, T., Sasano, H., Suzuki, T., Tamura, M. and Yajima, A. (1997): Macrophages in normal cycling human ovaries; immunohistochemical localization and characterization. Hum. Reprod., 12, 1508–1512. [Medline] [CrossRef]
63) Ujioka, T., Matsukawa, A., Tanaka, N., Matsuura, K., Yoshinaga, M. and Okamura, H. (1998): Interleukin-8 as an essential factor in the human chorionic gonadotropin-induced rabbit ovulatory process: interleukin-8 induces neutrophil accumulation and activation in ovulation. Biol. Reprod., 58, 526–530. [Medline] [CrossRef]
64) Arici, A., Oral, E., Bukulmez, O., Buradagunta, S., Engin, O. and Olive, D.L. (1996): Interleukin-8 expression and modulation in human preovulatory follicles and ovarian cells. Endocrinology., 137, 3762–3769. [Medline] [CrossRef]
65) Braquet, P., Touqui, L., Shen, T.Y. and Vargaftig, B.B. (1987): Perspectives in platelet-activating factor research. Pharmacol. Rev., 39, 97–145. [Medline]
66) Herriot, D.M., Warnes, G.M. and Kerin, J.F. (1986): Pregnancy-related chemotactic activity of human follicular fluid. Fertil. Steril., 45, 196–201. [Medline] [CrossRef]
67) Harkin, D.G., Bignold, L.P., Herriot-Warnes, D.M. and Kirby, C.A. (1994): Chemotaxis of polymorphonuclear leukocytes towards human pre-ovulatory follicular fluid and serum using a 'sparse-pore' polycarbonate filtration membrane. J. Reprod. Immunol., 27, 151–155. [Medline] [CrossRef]
68) Baggiolini, M., Walz, A. and Kunkel, S.L. (1989): Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. J. Clin. Invest., 84, 1045–1049. [Medline] [CrossRef]
69) Koch, A.E., Polverini, P.J., Kunkel, S.L., Harlow, L.A., DiPietro, L.A., Elner, V.M., Elner, S.G. and Strieter, R.M. (1992): Interleukin-8 as a macrophage-derived mediator of angiogenesis. Science., 258, 1798–1801. [Medline] [CrossRef]
70) Karström-Encrantz, L., Runesson, E., Boström, E.K. and Brännström, M. (1998): Selective presence of the chemokine growth-regulated oncogene alpha (GROalpha) in the human follicle and secretion from cultured granulosa-lutein cells at ovulation. Mol. Hum. Reprod., 4, 1077–1083. [Medline] [CrossRef]
71) Havelock, J.C., Rainey, W.E. and Carr, B.R. (2004): Ovarian granulosa cell lines. Mol. Cell. Endocrinol., 228, 67–78. [Medline] [CrossRef]
72) Kawano, Y., Zeineh, K., Furukawa, Y., Utsunomiya, Y., Okamoto, M. and Narahara, H. (2012): The effects of epidermal growth factor and transforming growth factor-α on secretion of interleukin-8 and growth-regulated oncogene-α in human granulosa-lutein cells. Gynecol. Obstet. Invest., 73, 189–194. [Medline] [CrossRef]
73) Kawano, Y., Furukawa, Y., Fukuda, J., Matsumoto, H., Yuge, A. and Narahara, H. (2007): The effects of platelet-activating factor on the secretion of interleukin-8 and growth-regulated oncogene α in human immortalized granulosa cell line (GC1a). Am. J. Reprod. Immunol., 58, 434–439. [Medline] [CrossRef]
74) Viergutz, T. and Löhrke, B. (2007): Role of the platelet-activating factor and its receptor in the proliferative regulation of bovine ovarian granulosa cells. Cell Prolif., 40, 949–960. [Medline] [CrossRef]
75) Robker, R.L. and Richards, J.S. (1998): Hormonal control of the cell cycle in ovarian cells: proliferation versus differentiation. Biol. Reprod., 59, 476–482. [Medline] [CrossRef]
76) Ishii, S. and Shimizu, T. (2000): Platelet-activating factor (PAF) receptor and genetically engineered PAF receptor mutant mice. Prog. Lipid Res., 39, 41–82. [Medline] [CrossRef]
77) Lydon, J.P., DeMayo, F.J., Funk, C.R., Mani, S.K., Hughes, A.R., Montgomery, C.A. Jr., Shyamala, G., Conneely, O.M. and O'Malley, B.W. (1995): Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. Genes Dev., 9, 2266–2278. [Medline] [CrossRef]
78) Quirk, S.M., Cowan, R.G. and Harman, R.M. (2004): Progesterone receptor and the cell cycle modulate apoptosis in granulosa cells. Endocrinology., 145, 5033–5043. [Medline] [CrossRef]