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Wahid, H.H.^a, Anahar, F.N.^a, Isahak, N.H.^a, Mohd Zoharodzi, J.^a, Mohammad Khoiri, S.N.L.^a, Mohamad Zainal, N.H.^b, Kamarudin, N.^c, Ismail, H.^d, Mustafa Mahmud, M.I.A.^a

Role of Platelet Activating Factor as a Mediator of Inflammatory Diseases and Preterm Delivery
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^a Department of Basic Medical Sciences, Kulliyyah of Medicine, International Islamic University, Pahang, Malaysia

^b Faculty of Medicine and Health Sciences, Department of Human Anatomy, University of Putra Malaysia, Selangor, Malaysia

^c Department of Pathology, Kulliyyah of Medicine, International Islamic University, Pahang, Malaysia

^d Department of Obstetrics & Gynaecology, Kulliyyah of Medicine, International Islamic University, Pahang, Malaysia

Abstract

Nearly 70% of preterm deliveries occur spontaneously, and the clinical pathways involved include preterm labor and preterm premature rupture of membranes. Prediction of preterm delivery is considered crucial due to the significant effects of preterm birth on health and the economy at both the personal and community levels. Although similar inflammatory processes occur in both term and preterm delivery, the premature activation of these processes or exaggerated inflammatory response triggered by infection or sterile factors leads to preterm delivery. Platelet activating factor (PAF) is a phosphoglyceryl ether lipid mediator of inflammation that is implicated in infections, cancers, and various chronic diseases and disorders including cardiovascular, renal, cerebrovascular, and central nervous system diseases. In gestational tissues, PAF mediates the inflammatory pathways that stimulate the effector mechanisms of labor, including myometrial contraction, cervical dilation, and fetal membrane rupture. Women with preterm labor and preterm premature rupture of membranes have increased levels of PAF in their amniotic fluid. In mice, the intrauterine or intraperitoneal administration of carbamyl PAF activates inflammation in gestational tissues, thereby eliciting preterm delivery. This review summarizes recent research on PAF as an important inflammatory mediator in preterm delivery and in other inflammatory disorders, highlighting its potential value for prediction, intervention, and prevention of these diseases. © 2024 American Society for Investigative Pathology

Index Keywords

thrombocyte activating factor, thrombocyte activating factor receptor, thrombocyte activating factor; Alzheimer disease, amnion fluid, anaphylaxis, asthma, atherosclerotic plaque, bladder cancer, brain infarction, brain ischemia, breast cancer, coronary artery disease, decidua, demyelination, diabetic nephropathy, endometrium cancer, experimental autoimmune encephalomyelitis, fetus membrane, food allergy, gene expression, heart infarction, hemolytic uremic syndrome, human, immunoglobulin A nephropathy, inflammatory disease, intracellular signaling, ischemic stroke, lung adenocarcinoma, meningioma, meningoencephalitis, MPTP-induced parkinsonism, multiple sclerosis, myometrium, nonhuman, ovary cancer, ovary carcinoma, Parkinson disease, peripheral nerve injury, placenta, positive feedback, premature labor, premature myocardial infarction, protein degradation, protein expression, protein induction, protein protein interaction, protein synthesis, Review, sepsis, signal transduction, spinal cord injury, thyroid carcinoma, uterine cervix, uterine cervix cancer, animal, female, inflammation, metabolism, pathology, pregnancy, premature labor, premature rupture of membranes, prematurity; Animals, Female, Fetal Membranes, Premature Rupture, Humans, Inflammation, Obstetric Labor, Premature, Platelet Activating Factor, Pregnancy, Premature Birth

Chemicals/CAS

thrombocyte activating factor, 64176-80-3, 65154-06-5

References

- Vogel, J.P., Chawanpaiboon, S., Moller, A.-B., Watananirun, K., Bonet, M., Lumbiganon, P. **The global epidemiology of preterm birth** (2018) *Best Pract Res Clin Obstet Gynaecol*, 52, pp. 3-12.
- **Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the global burden of disease study 2015** (2016) *Lancet*, 388, pp. 1603-1658.
- Jegannathan, R., Karalasingam, S.D. **National Obstetrics Registry 6th Report 2018-2020**

(2020), Institute Clinical Research, Health Informatic Center, Ministry of Health Malaysia

- Liu, L., Oza, S., Hogan, D., Chu, Y., Perin, J., Zhu, J., Lawn, J.E., Black, R.E.
Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals
(2016) *Lancet*, 388, pp. 3027-3035.
- Cao, G., Liu, J., Liu, M.
Global, regional, and national incidence and mortality of neonatal preterm birth, 1990-2019
(2022) *JAMA Pediatr*, 176, pp. 787-796.
- Oskovi Kaplan, Z.A.
Ozgu-Erdinc AS: prediction of preterm birth: maternal characteristics, ultrasound markers, and biomarkers: an updated overview
(2018) *J Pregnancy*, 2018, p. 8367571.
- Levine, L.D., Downes, K.L., Romero, J.A., Pappas, H., Elovitz, M.A.
Quantitative fetal fibronectin and cervical length in symptomatic women: results from a prospective blinded cohort study
(2019) *J Matern Fetal Neonatal Med*, 32, pp. 3792-3800.
- van Baaren, G.-J., Vis, J.Y., Wilms, F.F., Oudijk, M.A., Kwee, A., Porath, M.M., Scheepers, H.C.J., Mol, B.W.J.
Cost-effectiveness of diagnostic testing strategies including cervical-length measurement and fibronectin testing in women with symptoms of preterm labor
(2018) *Ultrasound Obstet Gynecol*, 51, pp. 596-603.
- Amabebe, E., Chapman, D.R., Stern, V.L., Stafford, G., Anumba, D.O.C.
Mid-gestational changes in cervicovaginal fluid cytokine levels in asymptomatic pregnant women are predictive markers of inflammation-associated spontaneous preterm birth
(2018) *J Reprod Immunol*, 126, pp. 1-10.
- Huang, L., Hou, Q., Huang, Y., Ye, J., Huang, S., Tian, J., Tang, R., Mo, Z.
Serum multiple cytokines for the prediction of spontaneous preterm birth in asymptomatic women: a nested case-control study
(2019) *Cytokine*, 117, pp. 91-97.
- Fuchs, F., Houllier, M., Leparco, S., Guyot, A., Senat, M.V., Fernandez, H.
Performance of cervical pHGFBP-1 test alone or combined with short cervical length to predict spontaneous preterm birth in symptomatic women
(2017) *Sci Rep*, 7, p. 10856.
- Wing, D.A., Haeri, S., Silber, A.C., Roth, C.K., Weiner, C.P., Echebiri, N.C., Franco, A., Norton, M.E.
Placental alpha microglobulin-1 compared with fetal fibronectin to predict preterm delivery in symptomatic women
(2017) *Obstet Gynecol*, 130, pp. 1183-1191.
- Melchor, J.C., Navas, H., Marcos, M., Iza, A., De Diego, M., Rando, D., Melchor, I., Burgos, J.
Predictive performance of PAMG-1 vs fFN test for risk of spontaneous preterm birth in symptomatic women attending an emergency obstetric unit: retrospective cohort study
(2018) *Ultrasound Obstet Gynecol*, 51, pp. 644-649.
- Amabebe, E., Reynolds, S., Stern, V., Stafford, G., Paley, M., Anumba, D.O.
Cervicovaginal fluid acetate: a metabolite marker of preterm birth in symptomatic pregnant women
(2016) *Front Med (Lausanne)*, 3, p. 48.

- Ravanos, K., Dagklis, T., Petousis, S., Margioulia-Siarkou, C., Prapas, Y., Prapas, N.
Factors implicated in the initiation of human parturition in term and preterm labor: a review
(2015) *Gynecol Endocrinol*, 31, pp. 679-683.
- Shynlova, O., Nadeem, L., Zhang, J., Dunk, C., Lye, S.
Myometrial activation: novel concepts underlying labor
(2020) *Placenta*, 92, pp. 28-36.
- Lordan, R., Tsoupras, A., Zabetakis, I.
The potential role of dietary platelet-activating factor inhibitors in cancer prevention and treatment
(2019) *Adv Nutr*, 10, pp. 148-164.
- Tsoupras, A., Lordan, R., Zabetakis, I.
Inflammation, not cholesterol, is a cause of chronic disease
(2018) *Nutrients*, 10, p. 604.
- Travers, J.B., Rohan, J.G., Sahu, R.P.
New insights into the pathologic roles of the platelet-activating factor system
(2021) *Front Endocrinol (Lausanne)*, 12, p. 624132.
- Billah, M.M., Di Renzo, G.C., Ban, C., Truong, C.T., Hoffman, D.R., Anceschi, M.M., Bleasdale, J.E., Johnston, J.M.
Platelet-activating factor metabolism in human amnion and the responses of this tissue to extracellular platelet-activating factor
(1985) *Prostaglandins*, 30, pp. 841-850.
- Billah, M.M., Johnston, J.M.
Identification of phospholipid platelet-activating factor (1-O-alkyl-2-acetyl-sn-glycero-3-phosphocholine) in human amniotic fluid and urine
(1983) *Biochem Biophys Res Commun*, 113, pp. 51-58.
- Gao, L., Rabbitt, E.H., Condon, J.C., Renthal, N.E., Johnston, J.M., Mitsche, M.A., Chambon, P., Mendelson, C.R.
Steroid receptor coactivators 1 and 2 mediate fetal-to-maternal signaling that initiates parturition
(2015) *J Clin Invest*, 125, pp. 2808-2824.
- Matsubara, T., Yasuda, K., Johnston, J.M., Sanezumi, M., Okada, H., Matsuoka, S., Kanzaki, H.
Platelet-activating factor (PAF) and PAF acetylhydrolase activity in rat uterus and placenta during the late stages of pregnancy
(1997) *Biol Reprod*, 56, pp. 885-890.
- Narahara, H., Nishioka, Y., Johnston, J.M.
Secretion of platelet-activating factor acetylhydrolase by human decidual macrophages
(1993) *J Clin Endocrinol Metab*, 77, pp. 1258-1262.
- Maul, H., Shi, L., Marx, S.G., Garfield, R.E., Saade, G.R.
Local application of platelet-activating factor induces cervical ripening accompanied by infiltration of polymorphonuclear leukocytes in rats
(2002) *Am J Obstet Gynecol*, 187, pp. 829-833.
- Hoffman, D.R., Romero, R., Johnston, J.M.
Detection of platelet-activating factor in amniotic fluid of complicated pregnancies
(1990) *Am J Obstet Gynecol*, 162, pp. 525-528.

- Silver, R.K., Caplan, M.S., Kelly, A.M.
Amniotic fluid platelet-activating factor (PAF) is elevated in patients with tocolytic failure and preterm delivery
(1992) *Prostaglandins*, 43, pp. 181-187.
- Elovitz, M.A., Wang, Z., Chien, E.K., Rychlik, D.F., Phillippe, M.
A new model for inflammation-induced preterm birth: the role of platelet-activating factor and Toll-like receptor-4
(2003) *Am J Pathol*, 163, pp. 2103-2111.
- Wahid, H.H., Chin, P.Y., Sharkey, D.J., Diener, K.R., Hutchinson, M.R., Rice, K.C., Moldenhauer, L.M., Robertson, S.A.
Toll-like receptor-4 antagonist (+)-naltrexone protects against carbamyl-platelet activating factor (cPAF)-induced preterm labor in mice
(2020) *Am J Pathol*, 190, pp. 1030-1045.
- Green, E.S., Arck, P.C.
Pathogenesis of preterm birth: bidirectional inflammation in mother and fetus
(2020) *Semin Immunopathol*, 42, pp. 413-429.
- Helmo, F.R., Alves, E.A.R., Moreira, R.A.A., Severino, V.O., Rocha, L.P., Monteiro, M., Reis, M.A.D., Corrêa, R.R.M.
Intrauterine infection, immune system and premature birth
(2018) *J Matern Fetal Neonatal Med*, 31, pp. 1227-1233.
- Kim, C.J., Romero, R., Chaemsathong, P., Chaiyasit, N., Yoon, B.H., Kim, Y.M.
Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance
(2015) *Am J Obstet Gynecol*, 213 Suppl, pp. S29-52.
- Romero, R., Miranda, J., Chaemsathong, P., Chaiworapongsa, T., Kusanovic, J.P., Dong, Z., Ahmed, A.I., Kim, Y.M.
Sterile and microbial-associated intra-amniotic inflammation in preterm prelabor rupture of membranes
(2015) *J Matern Fetal Neonatal Med*, 28, pp. 1394-1409.
- Romero, R., Miranda, J., Chaiworapongsa, T., Korzeniewski, S.J., Chaemsathong, P., Gotsch, F., Dong, Z., Yeo, L.
Prevalence and clinical significance of sterile intra-amniotic inflammation in patients with preterm labor and intact membranes
(2014) *Am J Reprod Immunol*, 72, pp. 458-474.
- Menon, R., Behnia, F., Polettini, J., Richardson, L.S.
Novel pathways of inflammation in human fetal membranes associated with preterm birth and preterm pre-labor rupture of the membranes
(2020) *Semin Immunopathol*, 42, pp. 431-450.
- Vidal, M.S., Jr., Lintao, R.C.V., Severino, M.E.L., Tantengco, O.A.G., Menon, R.
Spontaneous preterm birth: involvement of multiple feto-maternal tissues and organ systems, differing mechanisms, and pathways
(2022) *Front Endocrinol (Lausanne)*, 13, p. 1015622.
- Menon, R., Boldogh, I., Urrabaz-Garza, R., Polettini, J., Syed, T.A., Saade, G.R., Papaconstantinou, J., Taylor, R.N.
Senescence of primary amniotic cells via oxidative DNA damage
(2013) *PLoS One*, 8.
- Polettini, J., Richardson, L.S., Menon, R.
Oxidative stress induces senescence and sterile inflammation in murine amniotic cavity
(2018) *Placenta*, 63, pp. 26-31.

- Behnia, F., Peltier, M., Getahun, D., Watson, C., Saade, G., Menon, R.
High bisphenol A (BPA) concentration in the maternal, but not fetal, compartment increases the risk of spontaneous preterm delivery
(2016) *J Matern Fetal Neonatal Med*, 29, pp. 3583-3589.
- Behnia, F., Peltier, M.R., Saade, G.R., Menon, R.
Environmental pollutant polybrominated diphenyl ether, a flame retardant, induces primary amnion cell senescence
(2015) *Am J Reprod Immunol*, 74, pp. 398-406.
- Dixon, C.L., Richardson, L., Sheller-Miller, S., Saade, G., Menon, R.
A distinct mechanism of senescence activation in amnion epithelial cells by infection, inflammation, and oxidative stress
(2018) *Am J Reprod Immunol*, 79.
- Adams Waldorf, K.M., Singh, N., Mohan, A.R., Young, R.C., Ngo, L., Das, A., Tsai, J., Johnson, M.R.
Uterine overdistention induces preterm labor mediated by inflammation: observations in pregnant women and nonhuman primates
(2015) *Am J Obstet Gynecol*, 213, pp. 830.e1-830.e19.
- Triggiani, M., Schleimer, R.P., Warner, J.A., Chilton, F.H.
Differential synthesis of 1-acyl-2-acetyl-sn-glycero-3-phosphocholine and platelet-activating factor by human inflammatory cells
(1991) *J Immunol*, 147, pp. 660-666.
- Shimizu, T.
Lipid mediators in health and disease: enzymes and receptors as therapeutic targets for the regulation of immunity and inflammation
(2009) *Annu Rev Pharmacol Toxicol*, 49, pp. 123-150.
- Prescott, S.M., Zimmerman, G.A., McIntyre, T.M.
Platelet-activating factor
(1990) *J Biol Chem*, 265, pp. 17381-17384.
- Zimmerman, G.A., McIntyre, T.M., Prescott, S.M., Stafforini, D.M.
The platelet-activating factor signaling system and its regulators in syndromes of inflammation and thrombosis
(2002) *Crit Care Med*, 30 Suppl, pp. S294-301.
- Honda, Z., Ishii, S., Shimizu, T.
Platelet-activating factor receptor
(2002) *J Biochem*, 131, pp. 773-779.
- Castro Faria Neto, H.C., Stafforini, D.M., Prescott, S.M., Zimmerman, G.A.
Regulating inflammation through the anti-inflammatory enzyme platelet-activating factor-acetylhydrolase
(2005) *Mem Inst Oswaldo Cruz*, 100 Suppl 1, pp. 83-91.
- Ishii, S., Nagase, T., Shimizu, T.
Platelet-activating factor receptor
(2002) *Prostaglandins Other Lipid Mediat*, 68-69, pp. 599-609.
- Palur Ramakrishnan, A.V., Varghese, T.P., Vanapalli, S., Nair, N.K., Mingate, M.D.
Platelet activating factor: a potential biomarker in acute coronary syndrome?
(2017) *Cardiovasc Ther*, 35, pp. 64-70.
- Deng, M., Guo, H., Tam, J.W., Johnson, B.M., Brickey, W.J., New, J.S., Lenox, A., Ting, J.P.
Platelet-activating factor (PAF) mediates NLRP3-NEK7 inflammasome induction

independently of PAfR(2019) *J Exp Med*, 216, pp. 2838-2853.

- Lordan, R., Tsoupras, A., Zabetakis, I., Demopoulos, C.A.
Forty years since the structural elucidation of platelet-activating factor (PAF): historical, current, and future research perspectives
(2019) *Molecules*, 24, p. 4414.
- Snyder, F.
Metabolic processing of PAF
(1994) *Clin Rev Allergy*, 12, pp. 309-327.
- Renooij, W., Snyder, F.
Biosynthesis of 1-alkyl-2-acetyl-sn-glycero-3-phosphocholine (platelet activating factor and a hypotensive lipid) by cholinophosphotransferase in various rat tissues
(1981) *Biochim Biophys Acta*, 663, pp. 545-556.
- Ashraf, M.A., Nookala, V.
Biochemistry of platelet activating factor
(2003) *StatPearls [Internet]*,
StatPearls Publishing Treasure Island, FL Available at: (last update April 10, 2023)
- Shindou, H., Hishikawa, D., Harayama, T., Eto, M., Shimizu, T.
Generation of membrane diversity by lysophospholipid acyltransferases
(2013) *J Biochem*, 154, pp. 21-28.
- Tsoupras, A.B., Fragopoulou, E., Nomikos, T., Iatrou, C., Antonopoulou, S., Demopoulos, C.A.
Characterization of the de novo biosynthetic enzyme of platelet activating factor, DDT-insensitive cholinophosphotransferase, of human mesangial cells
(2007) *Mediators Inflamm*, 2007, p. 27683.
- Blank, M.L., Lee, T., Fitzgerald, V., Snyder, F.
A specific acetylhydrolase for 1-alkyl-2-acetyl-sn-glycero-3-phosphocholine (a hypotensive and platelet-activating lipid)
(1981) *J Biol Chem*, 256, pp. 175-178.
- Stafforini, D.M.
Biology of platelet-activating factor acetylhydrolase (PAF-AH, lipoprotein associated phospholipase A2)
(2009) *Cardiovasc Drugs Ther*, 23, pp. 73-83.
- Horkheimer, I., Schuster, D.
The role of platelet-activating factor in sepsis: a bench-to-bedside review
(2002) *Adv Sepsis*, 2, pp. 2-7.
- Arai, H., Koizumi, H., Aoki, J., Inoue, K.
Platelet-activating factor acetylhydrolase (PAF-AH)
(2002) *J Biochem*, 131, pp. 635-640.
- Raheem, S.G.
Investigating platelet-activating factor as a potent proinflammatory mediator in coronary atherosclerotic patients
(2021) *Cell Mol Biol (Noisy-le-grand)*, 67, pp. 1-4.
- Zhang, X., Yuan, C.L., Zhang, H.Z., Huang, R.X.
Age-related increase of plasma platelet-activating factor concentrations in Chinese
(2003) *Clin Chim Acta*, 337, pp. 157-162.
- Mazereeuw, G., Herrmann, N., Xu, H., Blanchard, A.P., Figeys, D., Oh, P.I., Bennett, S.A., Lanctôt, K.L.

Platelet activating factors are associated with depressive symptoms in coronary artery disease patients: a hypothesis-generating study
(2015) *Neuropsychiatr Dis Treat*, 11, pp. 2309-2314.

- Liu, P.-Y., Li, Y.-H., Wu, H.-L., Chao, T.-H., Tsai, L.-M., Lin, L.-J., Shi, G.-Y., Chen, J.-H. **Platelet-activating factor-acetylhydrolase A379V (exon 11) gene polymorphism is an independent and functional risk factor for premature myocardial infarction** (2006) *J Thromb Haemost*, 4, pp. 1023-1028.
- Denizot, Y., Aupetit, C., Bridoux, F., Alphonse, J.C., Cogné, M., Aldigier, J.C. **Deregulated platelet-activating factor levels and acetylhydrolase activity in patients with idiopathic IgA nephropathy** (2000) *Nephrol Dial Transplant*, 15, pp. 1344-1347.
- Yoon, H.-J., Kim, H., Kim, H.L., Lee, S.G., Zheng, S.-H., Shin, J.H., Lim, C.S., Kim, Y.S. **Interdependent effect of angiotensin-converting enzyme and platelet-activating factor acetylhydrolase gene polymorphisms on the progression of immunoglobulin A nephropathy** (2002) *Clin Genet*, 62, pp. 128-134.
- Xu, H., Iijima, K., Shirakawa, T., Shiozawa, S., Miwa, M., Yamaoka, K., Kawamura, N., Yoshikawa, N. **Platelet-activating factor acetylhydrolase gene mutation in Japanese children with Escherichia coli O157-associated hemolytic uremic syndrome** (2000) *Am J Kidney Dis*, 36, pp. 42-46.
- Kurano, M., Darestani, S.G., Shinnakasu, A., Yamamoto, K., Duchi, Y., Uemura, K., Ikeda, Y., Nishio, Y. **mRNA expression of platelet activating factor receptor (PAFR) in peripheral blood mononuclear cells is associated with albuminuria and vascular dysfunction in patients with type 2 diabetes** (2018) *Diabetes Res Clin Pract*, 136, pp. 124-133.
- Zhang, X., Yuan, C.-L., Zhang, H.-Z., Xu, J., Wu, J., Chen, B.-L. **Analysis of 994(G--> T) mutation in the plasma platelet-activating factor acetylhydrolase gene in the patients with cerebral infarction** (2005) *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, 22, pp. 450-452.
- Zhu, J., Brackett, N.L., Aballa, T.C., Lynne, C.M., Witt, M.A., Kort, H.I., Roudebush, W.E. **High seminal platelet-activating factor acetylhydrolase activity in men with spinal cord injury** (2006) *J Androl*, 27, pp. 429-433.
- Kihara, Y., Yanagida, K., Masago, K., Kita, Y., Hishikawa, D., Shindou, H., Ishii, S., Shimizu, T. **Platelet-activating factor production in the spinal cord of experimental allergic encephalomyelitis mice via the group IVA cytosolic phospholipase A2-lyso-PAFAT axis** (2008) *J Immunol*, 181, pp. 5008-5014.
- Messadi, A., Fekih-Mrissa, N., Zaouali, J., Layouni, S., Nsiri, B., Yedea, M., Raies, A., Gritli, N. **Implication of platelet-activating factor receptor A224D mutation in susceptibility to relapsing-remitting multiple sclerosis: a Tunisian population study** (2012) *Pathol Biol (Paris)*, 60, pp. 185-189.
- Moon, T.C., Kim, M.S., Lee, S.J., Lee, T.Y., Kwon, S.H., Baek, S.H., Chang, H.W. **Detection and characterization of 45 kDa platelet activating factor acetylhydrolase in cerebrospinal fluid of children with meningitis** (2003) *Arch Pharm Res*, 26, pp. 554-558.

- Dorninger, F., Moser, A.B., Kou, J., Wiesinger, C., Forss-Petter, S., Gleiss, A., Hinterberger, M., Berger, J.
Alterations in the plasma levels of specific choline phospholipids in Alzheimer's disease mimic accelerated aging
(2018) *J Alzheimers Dis*, 62, pp. 841-854.
- Liu, J., Jiao, L., Zhong, X., Yao, W., Du, K., Lu, S., Wu, Y., Liu, M.
Platelet activating factor receptor exaggerates microglia-mediated microenvironment by IL10-STAT3 signaling: a novel potential biomarker and target for diagnosis and treatment of Alzheimer's disease
(2022) *Front Aging Neurosci*, 14, p. 856628.
- Kim, B.K., Shin, E.-J., Kim, H.-C., Chung, Y.H., Dang, D.-K., Jung, B.-D., Park, D.-H., Jeong, J.H.
Platelet-activating factor receptor knockout mice are protected from MPTP-induced dopaminergic degeneration
(2013) *Neurochem Int*, 63, pp. 121-132.
- Denizot, Y., De Armas, R., Caire, F., Pommeuy, I., Truffinet, V., Labrousse, F.
Platelet-activating factor and human meningiomas
(2006) *Neuropathol Appl Neurobiol*, 32, pp. 674-678.
- Souza, J.L., Martins-Cardoso, K., Guimarães, I.S., de Melo, A.C., Lopes, A.H., Monteiro, R.Q., Almeida, V.H.
Interplay between EGFR and the platelet-activating factor/PAF receptor signaling axis mediates aggressive behavior of cervical cancer
(2020) *Front Oncol*, 10, p. 557280.
- Shi, K., Wang, Q., Su, Y., Xuan, X., Liu, Y., Chen, W., Qian, Y., Lash, G.E.
Identification and functional analyses of differentially expressed metabolites in early stage endometrial carcinoma
(2018) *Cancer Sci*, 109, pp. 1032-1043.
- Liao, Y., Badmann, S., Kaltofen, T., Mayr, D., Schmoeckel, E., Deuster, E., Mannewitz, M., Czogalla, B.
Platelet-activating factor acetylhydrolase expression in BRCA1 mutant ovarian cancer as a protective factor and potential negative regulator of the Wnt signaling pathway
(2021) *Biomedicines*, 9, p. 706.
- Tang, S., Ni, J., Chen, B., Sun, F., Huang, J., Ni, S., Tang, Z.
PAFAH1B3 predicts poor prognosis and promotes progression in lung adenocarcinoma
(2022) *BMC Cancer*, 22, p. 525.
- Jiang, W., Quan, R., Bhandari, A., Hirachan, S., Chen, C., Lv, S., Zheng, C.
PAFAH1B3 regulates papillary thyroid carcinoma cell proliferation and metastasis by affecting the EMT
(2023) *Curr Med Chem*, 31, pp. 1152-1164.
- Upton, J.E.M., Hoang, J.A., Leon-Ponte, M., Finkelstein, Y., Du, Y.J., Adeli, K., Eiwegger, T., Vadas, P.
Platelet-activating factor acetylhydrolase is a biomarker of severe anaphylaxis in children
(2022) *Allergy*, 77, pp. 2665-2676.
- Piwowarek, K., Rzeszotarska, A., Korsak, J., Juszkiewicz, A., Chciałowski, A., Kruszewski, J.
Clinical significance of plasma PAF acetylhydrolase activity measurements as a biomarker of anaphylaxis: cross-sectional study
(2021) *PLoS One*, 16.

- Vadas, P., Perelman, B., Liss, G.
Platelet-activating factor, histamine, and tryptase levels in human anaphylaxis
(2013) *J Allergy Clin Immunol*, 131, pp. 144-149.
- Stafforini, D.M., Numao, T., Tsodikov, A., Vaitkus, D., Fukuda, T., Watanabe, N., Fueki, N., Prescott, S.M.
Deficiency of platelet-activating factor acetylhydrolase is a severity factor for asthma
(1999) *J Clin Invest*, 103, pp. 989-997.
- Tsukioka, K., Matsuzaki, M., Nakamata, M., Kayahara, H., Nakagawa, T.
Increased plasma level of platelet-activating factor (PAF) and decreased serum PAF acetylhydrolase (PAFAH) activity in adults with bronchial asthma
(1996) *J Investig Allergol Clin Immunol*, 6, pp. 22-29.
- Jang, H., Kim, E.G., Kim, M., Kim, S.Y., Kim, Y.H., Sohn, M.H., Kim, K.W.
Metabolomic profiling revealed altered lipid metabolite levels in childhood food allergy
(2022) *J Allergy Clin Immunol*, 149, pp. 1722-1731.e9.
- Gomes, R.N., Bozza, F.A., Amâncio, R.T., Japiassú, A.M., Vianna, R.C., Larangeira, A.P., Gouvêa, J.M., Castro-Faria-Neto, H.C.
Exogenous platelet-activating factor acetylhydrolase reduces mortality in mice with systemic inflammatory response syndrome and sepsis
(2006) *Shock*, 26, pp. 41-49.
- Yang, J., Xu, J., Chen, X., Zhang, Y., Jiang, X., Guo, X., Zhao, G.
Decrease of plasma platelet-activating factor acetylhydrolase activity in lipopolysaccharide induced Mongolian gerbil sepsis model
(2010) *PLoS One*, 5.
- Lordan, R., Tsoupras, A., Zabetakis, I.
Platelet activation and prothrombotic mediators at the nexus of inflammation and atherosclerosis: potential role of antiplatelet agents
(2021) *Blood Rev*, 45.
- Hamel-Côté, G., Lapointe, F., Gendron, D., Rola-Pleszczynski, M., Stankova, J.
Regulation of platelet-activating factor-induced interleukin-8 expression by protein tyrosine phosphatase 1B
(2019) *Cell Commun Signal*, 17, p. 21.
- Hamel-Côté, G., Lapointe, F., Véronneau, S., Mayhue, M., Rola-Pleszczynski, M., Stankova, J.
Regulation of platelet-activating factor-mediated interleukin-6 promoter activation by the 48 kDa but not the 45 kDa isoform of protein tyrosine phosphatase non-receptor type 2
(2019) *Cell Biosci*, 9, p. 51.
- Proudfoot, J.M., Croft, K.D., Pudsey, I.B., Beilin, L.J.
Angiotensin II type 1 receptor antagonists inhibit basal as well as low-density lipoprotein and platelet-activating factor-stimulated human monocyte chemoattractant protein-1
(2003) *J Pharmacol Exp Ther*, 305, pp. 846-853.
- Pégorier, S., Stengel, D., Durand, H., Croset, M., Ninio, E.
Oxidized phospholipid: POVPC binds to platelet-activating-factor receptor on human macrophages. Implications in atherosclerosis
(2006) *Atherosclerosis*, 188, pp. 433-443.

- Gui, Y., Zheng, H., Cao, R.Y.
Foam cells in atherosclerosis: novel insights into its origins, consequences, and molecular mechanisms
(2022) *Front Cardiovasc Med*, 9, p. 845942.
- Rios, F.J., Gidlund, M., Jancar, S.
Pivotal role for platelet-activating factor receptor in CD36 expression and oxLDL uptake by human monocytes/macrophages
(2011) *Cell Physiol Biochem*, 27, pp. 363-372.
- Nemcsik, J., Kordás, K., Egresits, J., László, F., László, F.A., Pávó, I., Morschl, E.
Synergistic interaction of endogenous platelet-activating factor and vasopressin in generating angina in rats
(2004) *Eur J Pharmacol*, 498, pp. 195-202.
- Penna, C., Bassino, E., Alloatti, G.
Platelet activating factor: the good and the bad in the ischemic/reperfused heart
(2011) *Exp Biol Med (Maywood)*, 236, pp. 390-401.
- Fragopoulou, E., Iatrou, C., Antonopoulou, S., Ruan, X.Z., Fernando, R.L., Powis, S.H., Moorhead, J.F., Varghese, Z.
Platelet-activating factor (PAF) increase intracellular lipid accumulation by increasing both LDL and scavenger receptors in human mesangial cells
(2006) *J Lab Clin Med*, 147, pp. 281-289.
- Doi, K., Okamoto, K., Negishi, K., Suzuki, Y., Nakao, A., Fujita, T., Toda, A., Noiri, E.
Attenuation of folic acid-induced renal inflammatory injury in platelet-activating factor receptor-deficient mice
(2006) *Am J Pathol*, 168, pp. 1413-1424.
- Correa-Costa, M., Andrade-Oliveira, V., Braga, T.T., Castoldi, A., Aguiar, C.F., Origassa, C.S., Rodas, A.C., Câmara, N.O.
Activation of platelet-activating factor receptor exacerbates renal inflammation and promotes fibrosis
(2014) *Lab Invest*, 94, pp. 455-466.
- Coppo, R., Fonsato, V., Balegno, S., Ricotti, E., Loiacono, E., Camilla, R., Peruzzi, L., Camussi, G.
Aberrantly glycosylated IgA1 induces mesangial cells to produce platelet-activating factor that mediates nephrin loss in cultured podocytes
(2010) *Kidney Int*, 77, pp. 417-427.
- Zhou, S.-X., Huo, D.-M., He, X.-Y., Yu, P., Xiao, Y.-H., Ou, C.-L., Jiang, R.-M., Li, H.
High glucose/lysophosphatidylcholine levels stimulate extracellular matrix deposition in diabetic nephropathy via platelet-activating factor receptor
(2018) *Mol Med Rep*, 17, pp. 2366-2372.
- Hafez, H.M., Abdel-Hakeem, E.A., Hassanein, H.
Rupatadine, a dual antagonist of histamine and platelet-activating factor (PAF), attenuates experimentally induced diabetic nephropathy in rats
(2020) *Naunyn Schmiedebergs Arch Pharmacol*, 393, pp. 1487-1500.
- Toscano, E.C., Silva, B.C., Victoria, E.C., Cardoso, A.C., Miranda, A.S., Sugimoto, M.A., Sousa, L.P., Rachid, M.A.
Platelet-activating factor receptor (PAFR) plays a crucial role in experimental global cerebral ischemia and reperfusion
(2016) *Brain Res Bull*, 124, pp. 55-61.
- Wu, Y., Wang, L., Dai, C., Ma, G., Zhang, Y., Zhang, X., Wu, Z.
Neuroprotection by platelet-activating factor acetylhydrolase in a mouse model of

transient cerebral ischemia(2014) *Neurosci Lett*, 558, pp. 26-30.

- Hostettler, M.E., Carlson, S.L.

PAF antagonist treatment reduces pro-inflammatory cytokine mRNA after spinal cord injury(2002) *Neuroreport*, 13, pp. 21-24.

- Okubo, M., Yamanaka, H., Kobayashi, K., Kanda, H., Dai, Y., Noguchi, K.

Up-regulation of platelet-activating factor synthases and its receptor in spinal cord contribute to development of neuropathic pain following peripheral nerve injury(2012) *Mol Pain*, 8, p. 8.

- Wang, Y., Gao, Z., Zhang, Y., Feng, S.Q., Liu, Y., Shields, L.B.E., Zhao, Y.Z., Cai, J.

Attenuated reactive gliosis and enhanced functional recovery following spinal cord injury in null mutant mice of platelet-activating factor receptor(2016) *Mol Neurobiol*, 53, pp. 3448-3461.

- Midgley, A., Barakat, D., Braitch, M., Nichols, C., Nebozhyn, M., Edwards, L.J., Fox, S.C., Constantinescu, C.S.

PAF-R on activated T cells: role in the IL-23/Th17 pathway and relevance to multiple sclerosis(2021) *Immunobiology*, 226, p. 152023.

- Tian, Z., Chu, T., Shields, L.B.E., Zhu, Q., Zhang, Y.P., Kong, M., Barnes, G.N., Cai, J.

Platelet-activating factor deteriorates lysophosphatidylcholine-induced demyelination via its receptor-dependent and -independent effects(2020) *Mol Neurobiol*, 57, pp. 4069-4081.

- Rodrigues, D.H., Lacerda-Queiroz, N., de Miranda, A.S., Fagundes, C.T., Campos, R.D., Arantes, R.E., Vilela Mde, C., Teixeira, A.L.

Absence of PAF receptor alters cellular infiltrate but not rolling and adhesion of leukocytes in experimental autoimmune encephalomyelitis(2011) *Brain Res*, 1385, pp. 298-306.

- Kihara, Y., Ishii, S., Kita, Y., Toda, A., Shimada, A., Shimizu, T.

Dual phase regulation of experimental allergic encephalomyelitis by platelet-activating factor(2005) *J Exp Med*, 202, pp. 853-863.

- Vilela, M.C., Lima, G.K., Rodrigues, D.H., Lacerda-Queiroz, N., Pedroso, V.S., de Miranda, A.S., Rachid, M.A., Teixeira, A.L.

Platelet activating factor (PAF) receptor deletion or antagonism attenuates severe HSV-1 meningoencephalitis(2016) *J Neuroimmune Pharmacol*, 11, pp. 613-621.

- Simmons, C., Ingham, V., Williams, A., Bate, C.

Platelet-activating factor antagonists enhance intracellular degradation of amyloid- β 42 in neurons via regulation of cholesterol ester hydrolases(2014) *Alzheimers Res Ther*, 6, p. 15.

- Anandi, V.L., Ashiq, K.A., Nitheesh, K., Lahiri, M.

Platelet-activating factor promotes motility in breast cancer cells and disrupts non-transformed breast acinar structures(2016) *Oncol Rep*, 35, pp. 179-188.

- Chakravarty, V., Anandi, L., Ashiq, K.A., Abhijith, K., Umesh, R., Lahiri, M.

Prolonged exposure to platelet activating factor transforms breast epithelial cells(2021) *Front Genet*, 12, p. 634938.

- Kispert, S., Marentette, J., McHowat, J.
Cigarette smoking promotes bladder cancer via increased platelet-activating factor
(2019) *Physiol Rep*, 7.
- Kispert, S.E., Marentette, J.O., McHowat, J.
Enhanced breast cancer cell adherence to the lung endothelium via PAF acetylhydrolase inhibition: a potential mechanism for enhanced metastasis in smokers
(2014) *Am J Physiol Cell Physiol*, 307, pp. C951-C956.
- Travers, J.B.
Platelet-activating factor as an effector for environmental stressors
(2020) *Handb Exp Pharmacol*, 259, pp. 185-203.
- Gao, T., Zhao, R., Yao, L., Xu, C., Cong, Q., Jiang, W.
Platelet-activating factor induces the stemness of ovarian cancer cells via the PAF/PAFR signaling pathway
(2020) *Am J Transl Res*, 12, pp. 7249-7261.
- Kono, N., Arai, H.
Platelet-activating factor acetylhydrolases: an overview and update
(2019) *Biochim Biophys Acta Mol Cell Biol Lipids*, 1864, pp. 922-931.
- Yuan, Y., Jiang, X., Tang, L., Wang, J., Duan, L.
Comprehensive analysis of the prognostic and immunological role of PAFAH1B in pan-cancer
(2021) *Front Mol Biosci*, 8, p. 799497.
- Romer, E., Thyagarajan, A., Krishnamurthy, S., Rapp, C.M., Liu, L., Fahy, K., Awoyemi, A., Sahu, R.P.
Systemic platelet-activating factor-receptor agonism enhances non-melanoma skin cancer growth
(2018) *Int J Mol Sci*, 19, p. 3109.
- Duitman, J., Hartl, L., Roelofs, J.T.H., Bijlsma, M.F., Spek, C.A.
Non-tumor CCAAT/enhancer-binding protein delta potentiates tumor cell extravasation and pancreatic cancer metastasis formation
(2021) *Biomolecules*, 11, p. 1079.
- da Silva Junior, I.A., Stone, S.C., Rossetti, R.M., Jancar, S., Lepique, A.P.
Modulation of tumor-associated macrophages (TAM) phenotype by platelet-activating factor (PAF) receptor
(2017) *J Immunol Res*, 2017.
- Kajiwara, N., Sasaki, T., Bradding, P., Cruse, G., Sagara, H., Ohmori, K., Saito, H., Okayama, Y.
Activation of human mast cells through the platelet-activating factor receptor
(2010) *J Allergy Clin Immunol*, 125, pp. 1137-1145.
- Dyer, K.D., Percopo, C.M., Xie, Z., Yang, Z., Kim, J.D., Davoine, F., Lacy, P., Rosenberg, H.F.
Mouse and human eosinophils degranulate in response to platelet-activating factor (PAF) and lysoPAF via a PAF-receptor-independent mechanism: evidence for a novel receptor
(2010) *J Immunol*, 184, pp. 6327-6334.
- Reber, L.L., Marichal, T., Mukai, K., Kita, Y., Tokuoka, S.M., Roers, A., Hartmann, K., Galli, S.J.
Selective ablation of mast cells or basophils reduces peanut-induced anaphylaxis in mice
(2013) *J Allergy Clin Immunol*, 132, pp. 881-888.

- Jönsson, F., Mancardi, D.A., Kita, Y., Karasuyama, H., Iannascoli, B., Van Rooijen, N., Shimizu, T., Bruhns, P.
Mouse and human neutrophils induce anaphylaxis
(2011) *J Clin Invest*, 121, pp. 1484-1496.
- Triggiani, M., Patella, V., Staiano, R.I., Granata, F., Marone, G.
Allergy and the cardiovascular system
(2008) *Clin Exp Immunol*, 1, pp. 7-11.
- Gabrijelcic, J., Acuña, A., Profita, M., Paternò, A., Chung, K.F., Vignola, A.M., Rodríguez-Roisin, R.
Neutrophil airway influx by platelet-activating factor in asthma: role of adhesion molecules and LTB4 expression
(2003) *Eur Respir J*, 22, pp. 290-297.
- Guo, X., Zheng, M., Pan, R., Zang, B., Gao, J., Ma, H., Jin, M.
Hydroxysafflor yellow A (HSYA) targets the platelet-activating factor (PAF) receptor and inhibits human bronchial smooth muscle activation induced by PAF
(2019) *Food Funct*, 10, pp. 4661-4673.
- Henderson, W.R., Jr., Lu, J., Poole, K.M., Dietsch, G.N., Chi, E.Y.
Recombinant human platelet-activating factor-acetylhydrolase inhibits airway inflammation and hyperreactivity in mouse asthma model
(2000) *J Immunol*, 164, pp. 3360-3367.
- Batista, N.V., Fonseca, R.C., Perez, D., Pereira, R.V., de Lima Alves, J., Pinho, V., Faria, A.M., Cara, D.C.
Lack of platelet-activating factor receptor attenuates experimental food allergy but not its metabolic alterations regarding adipokine levels
(2016) *Biomed Res Int*, 2016, p. 8601359.
- Moreno, S.E., Alves-Filho, J.C., Rios-Santos, F., Silva, J.S., Ferreira, S.H., Cunha, F.Q., Teixeira, M.M.
Signaling via platelet-activating factor receptors accounts for the impairment of neutrophil migration in polymicrobial sepsis
(2006) *J Immunol*, 177, pp. 1264-1271.
- Hug, S., Bernhard, S., Stratmann, A.E.P., Erber, M., Wohlgemuth, L., Knapp, C.L., Bauer, J.M., Messerer, D.A.C.
Activation of neutrophil granulocytes by platelet-activating factor is impaired during experimental sepsis
(2021) *Front Immunol*, 12.
- Teixeira-da-Cunha, M.G., Gomes, R.N., Roehrs, N., Bozza, F.A., Prescott, S.M., Stafforini, D., Zimmerman, G.A., Castro-Faria-Neto, H.C.
Bacterial clearance is improved in septic mice by platelet-activating factor-acetylhydrolase (PAF-AH) administration
(2013) *PLoS One*, 8.
- Alvi, S.A., Brown, N.L., Bennett, P.R., Elder, M.G., Sullivan, M.H.
Corticotrophin-releasing hormone and platelet-activating factor induce transcription of the type-2 cyclo-oxygenase gene in human fetal membranes
(1999) *Mol Hum Reprod*, 5, pp. 476-480.
- Gu, Y., Burlison, S.A., Wang, Y.
PAF levels and PAF-AH activities in placentas from normal and preeclamptic pregnancies
(2006) *Placenta*, 27, pp. 744-749.

- Narahara, H., Kawano, Y., Nasu, K., Yoshimatsu, J., Johnston, J.M., Miyakawa, I.
Platelet-activating factor inhibits the secretion of platelet-activating factor-acetylhydrolase by human decidual macrophages
(2003) *J Clin Endocrinol Metab*, 88, pp. 6029-6033.
- Narahara, H., Johnston, J.M.
Effects of endotoxins and cytokines on the secretion of platelet-activating factor-acetylhydrolase by human decidual macrophages
(1993) *Am J Obstet Gynecol*, 169, pp. 531-537.
- Narahara, H., Johnston, J.M.
Smoking and preterm labor: effect of a cigarette smoke extract on the secretion of platelet-activating factor-acetylhydrolase by human decidual macrophages
(1993) *Am J Obstet Gynecol*, 169, pp. 1321-1326.
- Hellman, K.M., Yu, P.Y., Oladosu, F.A., Segel, C., Han, A., Prasad, P.V., Jilling, T., Tu, F.F.
The effects of platelet-activating factor on uterine contractility, perfusion, hypoxia, and pain in mice
(2018) *Reprod Sci*, 25, pp. 384-394.
- Sugano, T., Nasu, K., Narahara, H., Kawano, Y., Nishida, Y., Miyakawa, I.
Platelet-activating factor induces an imbalance between matrix metalloproteinase-1 and tissue inhibitor of metalloproteinases-1 expression in human uterine cervical fibroblasts
(2000) *Biol Reprod*, 62, pp. 540-546.
- Sugano, T., Narahara, H., Nasu, K., Arima, K., Fujisawa, K., Miyakawa, I.
Effects of platelet-activating factor on cytokine production by human uterine cervical fibroblasts
(2001) *Mol Hum Reprod*, 7, pp. 475-481.
- Stjernholm-Vladic, Y., Stygar, D., Mansson, C., Masironi, B., Akerberg, S., Wang, H., Ekman-Ordeberg, G., Sahlin, L.
Factors involved in the inflammatory events of cervical ripening in humans
(2004) *Reprod Biol Endocrinol*, 2, p. 74.
- Wahid, H.H., Mustapha Rounal, P.F.D., Bahez, A., Mustafa Mahmud, M.I.A., Kamarudin, N., Selvakumaran, A.R., Ahmad Mustafa, A.M., Ismail, H.
A review of group B Streptococcus (GBS) vaginal colonization and ascending intrauterine infection: interaction between host immune responses and GBS virulence factors
(2022) *Acta Sci Malaysia*, 6, pp. 17-22.
- Henn, V., Slupsky, J.R., Gräfe, M., Anagnostopoulos, I., Förster, R., Müller-Berghaus, G., Kroczeck, R.A.
CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells
(1998) *Nature*, 391, pp. 591-594.
- Henn, V., Steinbach, S., Büchner, K., Presek, P., Kroczeck, R.A.
The inflammatory action of CD40 ligand (CD154) expressed on activated human platelets is temporally limited by coexpressed CD40
(2001) *Blood*, 98, pp. 1047-1054.
- Erez, O., Romero, R., Hoppensteadt, D., Fareed, J., Chaiworapongsa, T., Kusanovic, J.P., Mazaki-Tovi, S., Hassan, S.
Premature labor: a state of platelet activation?
(2008) *J Perinat Med*, 36, pp. 377-387.
- Saleh, A.A., Gerbasi, F.R., Mammen, E.F., Farag, A.
Increased platelet activation in preterm labor

(1992) *Thromb Res*, 65, pp. 475-477.

- Agrawal, V., Jaiswal, M.K., Ilievski, V., Beaman, K.D., Jillings, T., Hirsch, E.
Platelet-activating factor: a role in preterm delivery and an essential interaction with Toll-like receptor signaling in mice
(2014) *Biol Reprod*, 91, p. 119.
- Thaete, L.G., Neerhof, M.G., Jillings, T., Caplan, M.S.
Infusion of exogenous platelet-activating factor produces intrauterine growth restriction in the rat
(2003) *J Soc Gynecol Investig*, 10, pp. 145-150.
- Neerhof, M.G., Khan, S., Synowiec, S., Qu, X.W., Thaete, L.G.
The significance of endothelin in platelet-activating factor-induced fetal growth restriction
(2012) *Reprod Sci*, 19, pp. 1175-1180.
- Maul, H., Shi, L., Marx, S.G., Garfield, R.E., Saade, G.R.
Platelet-activating factor antagonist WEB-2170 inhibits lipopolysaccharide-induced, but not antiprogestin-induced, preterm cervical ripening in timed-pregnant rats
(2003) *Am J Obstet Gynecol*, 189, pp. 963-967.

Correspondence Address

Wahid H.H.; Department of Basic Medical Sciences, Jalan Sultan Ahmad Shah, Bandar Indera Mahkota, Malaysia; email: hananwahid@iium.edu.my

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