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The Emerging Role of Platelet-Activating Factor on the Regulation of Embryonic Ploidy *via* Apoptosis

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ABSTRACT

Sea Urchins have been one of the principal animals of choice to study the mechanism's regarding fertilization and embryo development. A key influencer of events during embryo development is apoptosis, which can assist in modifying chromosome normality. Platelet-activating factor (PAF), a potent phospholipid, is produced by spermatozoa and early embryos and is required for fertilization and development. PAF has profound effects on fertilization and early embryo development including, but not limited to, apoptosis. This review will look at the significant relationship between PAF and apoptosis during early embryo development with emphasis in the sea urchin and to suggest next steps for study.

KEYWORDS: Platelet-activating factor; Apoptosis: Embryogenesis

ABBREVIATIONS: PAF: Platelet-Activating Factor; IVF: *In Vitro* Fertilization

INTRODUCTION

In 1972, Benveniste et al. [1] used the term Platelet Activating Factor (PAF) to describe a substance that leukocytes released upon stimulation that led to platelet aggregation as well as histamine release in rabbits [2]. While the efforts leading to PAF's discovery were aimed at elucidating the mechanism behind leukocyte-dependent histamine release, it is now known that PAF plays a critical role in a diverse set of biological pathways.

At the time, PAF was thought to solely function as a lipid mediator, which initiates movement of leukocytes to begin an immune reaction [3]. Further structural research, however, revealed that PAF is a phospholipid that uniquely was able to function in signaling, specifically in a juxtacrine, paracrine, autocrine, and endocrine manner [2]. Consequently, throughout the years research has shown that PAF mediates a variety of cellular interactions beyond inflammation, such as long-term potentiation, apoptosis, and reproduction [4-6]. It is also implicated in a host of disease states that begin at the cellular level such as cancer, cardiovascular disease, and renal disease [7-9].

Of growing interest, however, is PAF's relevance in early preimplantation embryo development and subsequent implantation, and consequently, embryo viability and a successful pregnancy. Embryos produce high levels of PAF, and the amount of embryo derived PAF increases at variable rates throughout development, suggesting a critical role in embryogenesis [10]. This review revisits research establishing PAF's role during embryo development as well as explores the emerging studies establishing a connection between PAF and apoptosis pathways as a means to promote development and implement implantation.

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DISCUSSION

Mammalian PAF Studies

Our understanding of PAF's role in embryo development has been expanded over the years. Preimplantation stage embryos in a variety of species (human, mouse, sheep, rabbit and pig) produce and release PAF [11-14]. The importance of PAF's role in embryonic development was documented when it was shown that PAF-antibodies inhibited embryonic development [15] and that PAF-antagonists inhibited implantation [16-17] providing further evidence on the presence and requirement of embryo-derived PAF during the pre-, peri- and implantation periods. Roberts et al. [18] showed that mouse preimplantation embryos in the presence of exogenous PAF have enhanced developmental rates higher implantation rates upon transfer to synchronized recipients [19] and larger litter sizes [20]. It was hypothesized that these results may be due to embryo-derived PAF stimulation of embryonic metabolism [21]. Additionally, investigations provided evidence that PAF directly influences the oxidative metabolism of glucose and lactate in the mouse preimplantation embryo [22]. Further evidence was provided that showed enhanced embryo development occurred in rabbit oocytes that were fertilized in vitro with PAF treated spermatozoa [23].

PAF Mechanism Studies

PAF released from the embryo can cause changes in maternal physiology. These changes include, but are not limited to platelet activation, changes in oviductal, endometrial and maternal immune function, and has even been shown to act as an autocrine molecule that acts as a survival factor for the early embryo [24]. Embryo survivability was limited in an experiment that blocked PAF's autocrine action [24]. This could be because embryonic-PAF acts as an autocrine stimulator of embryo development [25]. The action(s) of this embryo derived PAF on development were demonstrated by an experiment that used PAF-antibodies or PAF-antagonists that acted to block the frequency of complete embryonic development [26].

In humans, PAF has been shown to act through paracrine pathways to control embryo transport through the oviduct [27]. PAF production by human embryos has been correlated with pregnancy potential, the ability for the embryos to successfully implant [28,29]. In vitro, supplementation of culture media with PAF has shown to improve embryo development, although this mechanism is not well understood [24]. This has led to further research on the mechanisms of action of PAF because of the advances it could provide to women with fertility problems. Treatment of mouse embryos resulted in a significant improvement of delivery rates and birth weights [30]. Improved rabbit blastocyst development after in vitro fertilization with PAF treated spermatozoa has also been reported [23]. In other cell types, PAF receptor and its believed mechanism of action has been reported as a receptor-mediated process. PAF's action in the embryo is also a receptor-mediated since different PAF-antagonists competitively inhibit its action [26].

Sea Urchins Model to Study PAF Molecular Mechanisms

Sea Urchins have been one of the animals of choice to study the PAF mechanism regarding fertilization and development. Sea urchins are a class of marine invertebrates that possess many genetic similarities to humans [31]. They are estimated to have over 23,000 genes similar to vertebrae's and have long been used as models in developmental biology studies [31,32]. Recently, sea urchins have been used more frequently to study the PAF molecule and its role in embryo development due to the ease of using in the lab and the speed at which fertilization is completed [33]. It is important to understand the PAF molecular mechanisms that modulate fertilization and development in order to potentially enhance in vitro fertilization (IVF) remain outcomes.

Using the Sea urchins as a model, PAF was shown to be a molecule that increases sperm motility and fertilizing capability [32]. The collective data provides further evidence that PAF's effect on development is receptor-mediated and may involve the inositol triphosphate system. PAF binding to its receptor on the embryo results in increased intracellular calcium levels which enhance sperm capacitation and cell motility leading to increased fertilization [34]. This helped establish the mechanism by which PAF affects fertility, but not development. It was shown that exogenous PAF induced advanced stages of embryo development [33]. However, the mechanism is still not fully understood. One such hypothesis is the relationship between PAF and apoptosis in embryos and figuring out the mechanism associated with this process could lead to a valuable breakthrough in IVF fertility rates [35].

Apoptosis and Embryogenesis

Even though PAF works through a range of pathways to induce different outcomes during embryonic development, it is postulated that PAF promotes implantation. In other cell systems, apoptosis appears to be one mechanism by which PAF functions, either through activation or inhibition of apoptosis.

For example, in exploring the nervous system in mice, deleting the PAF receptor led to high levels of circulating PAF which triggered caspase 3/7 activity and neuronal death [36]. In this system, PAF's receptor may prevent apoptosis. In addition, when both rabbit and human corneal cells were exposed to ultraviolet radiation, PAF, cytochrome C, and caspase levels increased only in ultraviolet damaged cells. When PAF was exogenously delivered to corneal cells, they also underwent apoptosis [37].

To study apoptosis in embryogenesis, however, sea urchin experiments provide insight on the influence of PAF. Apoptosis may not occur during cleavage phase [38-40]. Low rates of apoptosis have been observed during the blastula and gastrula phase [38]. This timing when programmed cell death occurs is not altered even in the presence of chemical insults [38]. Prior studies sought to apply a variety of chemicals (for example, staurosporine, etopside and emetine) to induce apoptosis on the sea urchin and monitor the consequences. Inappropriately turning on apoptosis in the sea urchin through genetically removing cell cycle checkpoint genes showed that once the embryo entered the gastrula they were no longer viable.

When researchers exogenously exposed sea urchin embryos to PAF, however, those embryos exhibited lower levels of caspase-3 and significantly more developed to the late-stage gastrula phase than the controls [35]. PAF-treated embryos were found to cleave caspase-3, suggesting that PAF may modulate apoptotic activity in the developing embryo through the intrinsic pathway.

While studies provide a correlation between PAF and apoptosis, and even the intrinsic pathway of apoptosis, in a developing embryo, few studies exist to date that look at how PAF, and

furthermore, fluctuations in PAF, impact embryo viability as well as the mechanism that takes place.

CONCLUSION

Future work should aim at clarifying the mechanism that PAF uses to potentially regulate apoptosis. With the knowledge that PAF has a direct relationship with caspase-3 levels, further studies should focus on how caspase-3 mediated activation of the apoptotic process affects early development.

This research can help us understand the basics on the role of apoptosis with the potential to increase the percentage of successful IVF procedures. Using sea urchins is a viable research model going forward due to the similarity to humans, and the cost/time they take to use. There has been growing interest in using PAF as a therapeutic target; however, there have been few studies on the risk/benefits of using PAF to influence IVF success rate.

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