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Literature Review

Chronic Inflammation and Gut Microbiota at A Glance: Insights into Fertility Barriers

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Abstract

The acrosome reaction (AR) is a crucial step in fertilization, enabling sperm to penetrate the oocyte's protective layers, but various elements can hinder AR. Fertilization is a fundamental process in mammalian reproduction, involving the fusion of a sperm with oocyte. To achieve this, sperm must undergo capacitation, a series of biochemical changes that prepare them for fertilization. Once capacitated, sperm can penetrate the protective layers of the oocyte, after capacitation, sperm bind to receptors on the zona pellucida (ZP), a protective layer surrounding the egg. This binding triggers the acrosome reaction (AR), releasing enzymes that help the sperm penetrate the protective layers. Once the sperm has penetrated, it fuses with the oocyte's plasma membrane, delivering its genetic material. Anti-sperm antibodies (ASA) can directly bind to sperm, hindering their function and ability to undergo AR. Chronic inflammation, often associated with conditions like diabetes and obesity, with chronic hyperglycemia producing advanced glycation end products (AGEs) can create a pro-inflammatory environment that negatively impacts sperm parameter and function. Additionally, gut microbiota (GM) dysbiosis has been linked to chronic inflammation and may contribute to infertility. Proper AR is essential for successful fertilization, but presence of ASA, GM dysbiosis, and chronic inflammation may hinder fertility. The evidence suggests improving inflammation by proper GM symbiosis may improve sperm parameter and fertility.

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1. Introduction

Fertilization requires sperm to successfully unite with oocyte[1]. One of the important steps is the acrosome reaction (AR), allowing the sperm to penetrate oocyte's protective layers. However, various factors can affect this process, leading to infertility. First is the presence of anti-sperm antibodies (ASA) which can hinder sperm function and fertilization. Additionally, chronic inflammation, often associated with metabolic disorders like diabetes and obesity, can create an adverse environment for sperm parameter and function. This review will briefly look into the mechanisms by which ASA, chronic inflammation, and gut microbiota dysbiosis can disrupt the acrosome reaction, ultimately affecting fertility.

2. Review

Fertilization is one of the major processes in mammalian reproduction, the unification of male spermatozoa and female oocyte that forms a zygote inheriting half genetic material from the father and the other half from the mother[1]. In order to achieve successful fertilization, a single sperm ought to penetrate the outer layers of the oocyte, which then fusing with the plasma membrane, aside from competing with other sperms[2]. After the sperm is released into the female reproductive tract, the sperm experience multiple biochemical changes what is known as capacitation. This allows the sperm to prepare for fertilization. During capacitation, the sperm membrane changes, and enzyme is released to allow degradation of oocyte outer layers. The sperm then adhere to receptors in zona pellucida (ZP) that will trigger acrosomal reaction (AR) that help sperms to enter the oocyte. Following this, the sperm then penetrate the corona radiata thus finally the sperm fuses with oocyte's plasma membrane and release its genetic material into the oocyte[3].

Acrosome

Spermatozoa has a distinct morphology, a head and a flagellum[1]. The flagellum provides the driving force for the sperm to reach the site for fertilization and the head contains father's genetic material[1]. To penetrate the protecting layers of the oocyte, the sperm must experience a morphological change of the acrosome as known as AR[4]. Acrosome, a cap-like structure located at the front of the sperm head that contains various hydrolytic enzymes that helps the sperm to penetrate the oocyte's outer layer. It is believed the acrosome originates from Golgi apparatus and develops during spermiogenesis. The acrosome contains hydrolytic enzymes, such as acrosin, which facilitate the penetration of the ZP and the fusion of sperm with the oocyte's membrane plasma[5]. The AR is one of the most important steps in fertilization, however there are factors that influence this process, such as immune system in the body may modulate or interfere with this process. For example, anti-sperm antibodies (ASA) can hinder sperm function, transport, capacitation, and AR potentially resulting in immunological infertility[6].

Acrosome Reaction

AR is the fundamental step in fertilization process in many species not limited to human. As mentioned previously, AR allows sperm to enter the oocyte through its protective layers, hence, sperm that does not undergo AR for any reason will not be able to fertilize the oocyte[4]. The start of AR is thought to be caused by substances found surrounding oocyte in female reproductive tract for example, follicular fluid, human cumulus oophorus, and human mural granulosa cells. On the other hand, ZP from the oocytes also binds to spermatozoa inducing AR facilitated by hormones. Progesterone and 17a-hydroxyprogesterone are also responsible in inducing AR. The human cumulus oophorus is observed to has a high level of progesterone exceeding 1 µg/ml and is sufficient to induce AR. Additionally, the follicular fluid found in the ovarian follicles also has a sufficient progesterone level to induce AR. Nevertheless, the induction of AR requires prior sperm capacitation[4]. There are various factors that can affect fertilization process and AR, one of them is immunological factors. Anti-sperm antibodies are one of those factors that responsible.

Anti Sperm Antibodies

It is known that sperm is considered foreign by both male and female immune systems. This implies that proteins and molecules inside sperm will trigger immune response if not tolerated, hence in both males and females exist immune tolerance, multiple means the body prevent unwanted immune responses toward sperm. ASA are naturally formed if the proteins are exposed to the immune system if there are any distortions in blood-testis barrier (BTB), producing autoantibodies that can directly adhere to the sperm[7,8]. Studies suggest that the presence of ASA may cause altered sperm quality, usually a negative effect[7,9]. ASA can cause agglutination, immobilization, altered capacitation and eventually hinder it from performing AR, in some cases the presence of ASA may induce premature AR, leaving sperm unable to penetrate the outer layers of the oocyte[10]. In men, ASA can be found locally in seminal fluid or systemically in blood or lymph. On the other hand, women with poor immune tolerance may develop sensitivity toward the sperm and eventually end in sperm elimination[11]. Although early study showed the prevalence of ASA in infertile men is quite high[12], later study showed otherwise low prevalence of ASA in infertile couples[13]. Despite all the inconsistency in regards of ASA and pregnancy rate, for over a decade, meta-analysis has shown that in the context of assisted reproductive technology (ART) such as IVF or ICSI, the presence of ASA is not related with pregnancy rate[14].

Chronic Inflammation

Immune response is an important function to protect the body from various harm. Nevertheless, immune system may also pose a threat to its own host, in this context are chronic inflammation and autoimmune diseases, inclusive of those that disturb the male reproductive system[15]. Chronic inflammation, unlike acute inflammation that lasts only for a short while, it can persist for years and mostly presents with low grade inflammation without any obvious symptoms[16]. One of the features of chronic inflammation is the presence of inflammatory cytokines and cells such as tumor necrosis factor (TNF) and interleukin (IL)-1,6, lymphocyte, macrophages, and plasma cells[17]. The increase of pro-inflammatory factors may induce cytokine-mediated anti-fertility effects where chronic inflammation may directly increase reactive oxygen species (ROS) and ultimately induce oxidative stress that affect negatively toward sperm parameters and fertility[18]. Acrosome, one of critical part in sperm that facilitate fertilization can be significantly impaired by the presence of chronic inflammation and it is thought the impairment is caused by oxidative stress which membrane fluidity is disturbed and negatively impacting its responsiveness that prevents the release of enzyme needed for AR[18]. Additionally, inflammation may alter calcium signaling that can cause the sperm to experience spontaneous AR or premature AR[4]. Another thing that tightly linked with chronic inflammation is advanced glycation end products (AGEs) which is the result of chronic hyperglycemia. Receptor for AGEs is found and directly correlated with poor sperm health, impairing acrosome structural integrity, elasticity, low motility, decreased mitochondrial function, DNA fragmentation, and higher apoptosis[19]. Both chronic hyperglycemia and chronic inflammation are often seen in conditions like obesity, metabolic syndrome, and diabetes[20–22].

Gut Microbiota

One emerging aspect from endocrinology is gut microbiota (GM), the microorganisms in the digestive tract may be a major factor in obesity, metabolic syndrome, diabetes, and to a certain extent even fertility [21,23]. The decrease in microbial diversity and number is called GM dysbiosis and is linked to energy metabolism, inflammation, and brain satiety centers[24,25]. Additionally, GM take parts in immune regulation and balance by maintaining the barrier in the intestinal wall, modulating T-cell differentiation, promoting anti-inflammatory cytokines, and inhibiting pro-inflammatory pathways[26,27]. GM dysbiosis thus may induce chronic low-grade inflammation and eventually promote more release of pro-inflammatory cytokines from adipose tissue and promote further lipogenesis creating a cycle[24]. With GM dysbiosis tightly related with chronic

inflammation, a randomized controlled trial was performed to explore the extent of GM showed that probiotic supplementation in infertile men result in increased sperm parameter, and reduction in both oxidative stress and inflammatory markers [23].

3. Summary

The acrosome is a critical structure in sperm that facilitates fertilization by releasing enzymes necessary to penetrate the oocyte's protective layers. Proper AR is essential for successful fertilization, however factors such as ASA and chronic inflammation can hinder this process. Chronic inflammation itself is linked to oxidative stress and conditions such as obesity and diabetes. Oxidative stress and AGEs disrupt acrosome function and sperm health. Emerging endocrine aspect of GM dysbiosis is associated with inflammation, may also affect fertility. Thus, reducing inflammation with proper GM symbiosis has shown potential in reducing inflammation, recovering sperm parameters, and improving fertility.

Author's Contribution

All authors have contributed to the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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