Exposure to the various environmental microbial pathogens is a constant threat to mammals. As a rapid mobilized first line defense, innate immunity is of critical importance for mammalian cells to maintain their normal activities. One of the key features of innate immune response is to distinguish non-self from self cues and thus initiates downstream defense responses including releasing cytokines, activation and recruitment of immune cells, etc. Identification of pathogenic cues relies on a special group of germline-encoded surface and intracellular proteins, called pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide binding domain, leucine-rich repeat (LRR)-containing [or nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)], RIG-I like receptors (RLRs), and the AIM2-like receptors (ALRs) (1). Recognition of foreign molecular cues will trigger a cascade of events resulted in activation of immune related genes and rapid releasement of associated cytokines.

However, foreign molecular cues are not always from environmental pathogens. A couple of unique situations in mammals exist where foreign cues are not a threat and innate immunity shall be repressed, such as fertilization and pregnancy. Dysregulation of innate immune regulation thus could have a significant impact on human fertility. In fact, nearly one-half of idiopathic infertility cases are believed to have a genetic cause (2) and many of the identified infertility associated genes are immune related (3). However, the underlining molecular mechanism for human infertility is still largely unknown.

NOD, LRR, and pyrin domain containing proteins (NLRPs) are members of NLRs protein family (4). Previous studies focused on their roles in apoptotic and inflammatory signaling pathways via the formation of an inflammasome and activation of caspases in innate immunity (5-7). However, more recent researches have revealed their roles in mammalian reproduction (Table 1).

In mouse, the first identified mammalian maternal effect gene in this family is \( NLRP5 \), which encodes mRNA required for successful development of a fertilized oocyte (14). Additionally, expression analysis of \( NLRP \) genes in the human and macaque monkeys (\( Macaca mulatta \)) has shown that most if not all \( NLRP \) genes are expressed specifically in primate gametes and early embryos, suggesting a general role of NLRPs in primate preimplantation development (18,26), as well as their involvement in innate immunity.

\( Nlrp14 \) gene is one of the key members in NLRP family. NLRP14 protein typically contains a NACHT domain, a NACHT-associated domain (NAD), a C-terminal LRR, and 14 N-terminal pyrin domain (PYD). It is also known as NALP14, NOD5, GC-LRR, Nalp-iota, PAN8, and CLR11.2. Expression of \( NLRP14 \) has been confirmed through an unbiased proteomics approach in oocytes (27). Its mRNA transcript level appeared to decrease with age, coinciding with reduced fertility (20). These evidences suggest that \( NLRP14 \) may play a role in female reproduction, although detailed mechanism remains to be explored.
Meanwhile, northern analysis of multiple tissues with a NLRP14 specific probe indicated that NLRP14 was exclusively expression in human adult testis (24) rather than ovary, which was also confirmed in mouse tissues (20,21). Immuno-histology analysis revealed that NLRP14 showed a clear signal in the cytoplasm of a dark spermatogonia, which is reserve as stem cell, mid and late pachytene spermatocytes and spermatids (24). Sertoli cells also showed some cytoplasmic staining for NLRP14 (24). It seems that NLRP14 has the roles in the most types of the male germ cell, particularly in the spermatogonia, or even in primordial germ cell.

Moreover, after a mutation screen of the NLRP14 gene in 157 men with azoospermia or severe oligozoospermia by direct sequencing, the researchers identified 25 sequence variants in total; 1 nonsense mutation, 14 missense

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<th>Table 1 Reproduction-related NLRPs</th>
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<td><strong>Gene</strong></td>
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NLRP, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain containing proteins.
mutation, 6 silent mutation and 4 intronic variants (24). One of these mutations was an early stop codon mutation (p.K108X), this A to T change in exon 2 introduced a stop codon at amino acid position 108, and it would lead to lack of the functional NACHT and LRR domains (24). Accordingly, NLRP14 seems to be very important for spermatogenesis, but the specific molecular mechanism is unknown yet.

Another important process in reproduction is fertilization. Fertilization is the fusion of gametes from parents to initiate the development of a new embryo. For oocytes, nucleic acids from sperms is a non-self signal that may trigger cytosolic PRRs and initiate innate immune response. Therefore, embryos must have a regulatory network in place to suppress innate immune activation to achieve successful fertilization. In a recent study by Abe et al., NLRP14 was identified as a key player in regulating innate immune response in oocyte and negatively regulates cytosolic nucleic acid sensing to promote fertilization (Figure 1) (25).

In this study, evidence was shown that NLRP14 could achieve the highest suppression of STING signaling mediated by cGAS, an important cytosolic DNA sensor (25). Additionally, loss- and gain-of-function experiments in 293T cell revealed that NLRP14 might interact with a kinase called TBK1 for ubiquitination and degradation to negatively regulates cytosolic sensing of DNA and RNA (25). Ectopic expression of the K180X allele of NLRP14, which has identified in sterile men with spermatogonia failure (24), resulted in reduced inhibition of TBK1-mediated signaling (25). This allele has an average frequency of 1.7% in the human population and a minor allele frequency of 3% in East Asian and admixed American populations (28), suggesting that the infertility which caused by this kind of mutation may have a wide range of impact.

Furthermore, The sub-clone version of this allele, just containing sequence for amino acid from 1 to 108, showed further enhancement of TBK1-mediated IFN- and NF-B activation (25). Another published data showed that the excess amount of type I IFN signaling disrupts seminiferous tubules in mice, leading to a loss of germ cells and infertility (29). These reports indicated that some NLRP14 mutations might cause spermatogenesis failure through inappropriate innate immune responses in testis.

In summary, NLRP14 seems to be very important for both female and male reproduction. This study was the first report towards understanding the function of NLRP14 in innate immune regulation and its role in human reproduction. Meanwhile, as many of these experiments were done in established non-germline cell lines, more efforts are warranted to explore the function of NLRP14 in vivo and whether it could have different interacting partners in male gametes and oocytes. Nevertheless, the
finding has set up a solid ground that there is a NOD between innate immunity and reproduction.

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None.

**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**References**


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