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Review

Regulators in the apoptotic pathway during spermatogenesis: Killers or guards?

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ABSTRACT

Apoptosis occurs at any time in the ontogeny of the testis, especially during the first wave of spermatogenesis. However, the exact mechanisms by which homeostasis of apoptosis and survival in GCs and mature sperm are orchestrated remain unclear. Three pathways during the process of apoptosis in mammals are discussed extensively. The three pathways are extrinsic pathway, mitochondrial pathway and endoplasmic reticulum pathway. Based on that, many factors, such as growth factors (SCF, FGF, TGF), hormones (FSH, LH, E2, MIS), partial oxygen pressure, and testis specific genes are involved in apoptosis and survival process. The pathways of apoptosis adopted by the GCs and sperm depend on the types of stimuli they receive. Diverse pathways are initiated in heat-stress induced apoptosis of GCs and the destiny of GCs suppressed by hyperglycemia is mainly regulated by a rheostat of total oxidants and anti-oxidants which leading to intrinsic pathway. In this review, we provide an overview of three classic pathways and important factors involved in the process of germ cell apoptosis and survival, and discuss the recent advances made in understanding of the molecular mechanisms of spermatogenic cells and sperm response to stress-inducers, such as heat stress and hyperglycemia. All the findings may provide clues to the control of male fertility or treating germ cell tumors and other testis associated pathological conditions, at the same time, a novel idea may result in devising much safer contraception with high efficiency.

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Abbreviations: GCs, germ cells; FasL, Fas ligand; SCF, stem cell factor; FGF, fibroblast growth factor; TGF, transforming growth factor; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estrogen; MIS, Müllerian inhibiting substance; SCs, Sertoli cells; GnRH, gonadotropin-releasing hormone; T, testosterone; Bcl-2, B-cell lymphoma 2; TNF, tumor necrosis factor; FADD, Fas associated death domain; TRAIL, TNF-related to apoptosis-inducing ligand; DISC, death-inducing signaling complex; cytC, cytochrome c; FLIPs, FLICE-like inhibitory protein; IGFBP, insulin-like growth factor binding protein; PGCs, primordial germ cells; MAPK, mitogen-activated protein kinase; NOS, nitric oxide synthase; ER, endoplasmic reticulum; UPR, unfolded protein response; IRE1, Inositol-requiring protein-1; PERK, protein kinase RNA(PKR)-like ER kinase; ATF6, activating transcription factor 6; CHOP, CEBP-homologous protein; KL, kit ligand; RA, retinoic acid; PI3K, phosphoinositide 3-kinase; ERK, extracellular signal-regulated kinase; PRL, prolactin; AP-1, activator protein-1; mAC, membrane adenylyl cyclase; cAMP, cyclic AMP; PKA, protein kinase A; CREB, cAMP response element-binding protein; CFTR, cystic fibrosis transmembrane conductance regulator; ERE, estrogen response element; GPR-30, Go protein-coupled receptor-30; JNK, c-jun N-terminal kinase; RARA, Retinoic acid receptor A protein; 4-HNE, 4-hydroxynonenal; ROS, reactive oxygen species; PARP, Poly (ADP-ribose) polymerase; *Fank1*, fibronectin type III and ankyrin repeat domains 1; *RHBDD1*, rhomboid domain containing 1; *Spata17*, anti-spermatogenesis-associated 17; HSF, heat shock factor.

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1. Introduction

With the development of testis, dysfunctional GCs (germ cells) need to be efficiently removed, which ensure that genetic abnormalities never pass onto offspring. On the other hand, this process may maintain tissue homeostasis of different cell types. A well-organized cell population is vital for successful spermatogenesis and male fertility (Bonde et al., 1998; Ng et al., 2004). SCs (Sertoli cells) and GCs exist in a good proportions during normal spermatogenesis in testis because each SC can only sustain about 30–50 GCs (Richburg, 2000; Orth et al., 1988). Different cell prospects aim to balance somatic cells and GCs, eliminate redundant cells, get rid of the impaired cells to make sure that the intact and accurate inheritance could be passed on to offspring. Problems with male fertility have increased during recent years, the fact that up to 75% of GCs from various stages undergo apoptosis in the testis causes growing interest in the mechanisms of germ cell death (Huckins and Oakberg, 1978). The disruption of the balance between cell survival and apoptosis have been demonstrated to adversely affect spermatogenesis caused by pathological conditions and/or environmental factors, which can lead to azoospermia with low ejaculated sperm, asthenozoospermia, hematospermia, and so on (Almeida et al., 2013). (See Tables 1 and 2.)

Testis produces sperm, hormones, and testis developmental factors. All these are indispensible for male fertility. Sperm output relies upon the coordinated proliferation, differentiation and survival of each progressively maturing germ cell type during mammalian spermatogenesis. There are three distinct phases of spermatogenesis: the mitotic phase in which undifferentiated spermatogonia undergo rapid proliferation; the meiotic phase in which spermatocytes proceed through two cell divisions to give rise to haploid spermatids; and the spermiogenesis phase in which spermatids undergo a complex process of morphological and functional differentiation resulting in the production of mature spermatozoa. There are so many orchestrated event involved in the process of spermatogenesis that the detailed control mechanism for sperm output remain elusive, though spectacular progress was made about the intricate mammalian spermatogenesis and sperm quality control mechanism during last two decades. During the process of spermatogenesis, abnormal expression of molecules regulating the apoptotic process or apoptosis is eliminated, which will result in an abnormal number of GCs accumulation in the seminiferous tubules and infertility. The dynamic balance between apoptosis and survival exists in many human diseases, it plays a major role during normal development and homeostasis. The hypothalamus pituitary-gonad axis plays a key role in regulating the testis function and affect GCs. There are many important hormones such as GnRH (gonadotropin-releasing hormone), FSH (follicle stimulating hormone), LH (luteinizing hormone), T (testosterone) and so on.

Apoptosis, also called programmed cell death, is an evolutionarily conserved cell death process. In adult mammals, including human beings, germ cell apoptosis is conspicuous during normal spermatogenesis, especially the first wave of spermatogenesis (Jahnukainen et al., 2004). The well-studied apoptosis is a good choice to control germ cell number and eliminate defective GCs during testicular development and spermatogenesis (Shaha et al., 2010). The mechanisms of apoptosis have been illuminated by previous studies about the Bcl-2 (B-cell lymphoma 2) protein family (Sinha Hikim and Swerdloff, 1999; Russell et al., 2002). It is generally believed that the ratio of pro-apoptotic to anti-apoptotic Bcl-2 family proteins is the critical determinant of cell fate, with an excess of Bcl-2 resulting in cell survival but an excess of Bax resulting in cell death (Adams and Cory, 1998). Two major pathways, the mitochondrial pathway and the cell death receptor pathway are involved in the process of apoptosis in mammals. The mitochondrial pathway of apoptosis involves many members of Bcl-2 group of proteins in different process. The cell death receptor pathway involves members of the TNF (tumor necrosis factor) receptor superfamily. Recently, another novel pathway caused by UPR (unfolded protein response) in response to ER (endoplasmic reticulum) stress is also critical to germ cell elimination. Apoptosis is mediated by signals derived from the SCs with which each germ cell is closely associated, as well as by signals originating outside the testis. The pathway of apoptosis adopted by the GCs and mature sperm depends on the types of stimuli they receive. In contrast, the pathway of germ cell and mature sperm survival is anti-apoptosis, but the mechanism is not fully understood. Recently, many finding about germ cell survival provide a lot of information to understand the pathways. We try to summarize the recent advances achieved in the field of the mechanisms of sperm survival that may open new avenues in the understanding of the internal relation and significance of germ cell survival during normal and abnormal states of spermatogenesis, and we also try to provide clues to the control of male fertility or treating germ cell tumors and other testis associated pathological conditions.

2. Signaling pathways of testicular cell apoptosis and survival

In view of the significance of apoptosis, a deep knowledge of the molecular components of existing programs in varies conditions is a fundamental step to master the balance mechanism between survival and apoptosis. The complicated mechanisms determining male GCs survival