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Review

Regulation of the germ stem cell niche as the foundation for adult spermatogenesis: A role for miRNAs?

Sander van den Driesche*, Richard M. Sharpe, Philippa T.K. Saunders, Rod T. Mitchell

MRC Centre for Reproductive Health, The Queen's Medical Research Institute, The University of Edinburgh, 47 Little France Crescent, Edinburgh EH16 4TJ, UK

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ABSTRACT

Within the testis the spermatogonial stem cells reside in a unique microenvironment, or 'niche', which includes the surrounding somatic cells. The regulation of the balance between self-renewal and differentiation of spermatogonial stem cells determines the lifelong supply of spermatozoa by maintaining a population of undifferentiated spermatogonial stem cells and ensuring that adequate numbers of spermatogonia undergo spermatogenesis. Mouse models have been instrumental in determining a large number of factors involved in regulating the spermatogonial stem cell self-renewal and/or differentiation. However, the precise mechanisms controlling regulation of the germ cell niche remain to be elucidated. Recently the discovery of microRNAs, which regulate gene expression at the post-transcriptional level, has provided new insight into testis biology, spermatogenesis and germ stem cell regulation. In this review we summarize the main factors involved in the regulation of the germ stem cell niche and describe the role of microRNA signaling in this regulation.

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Contents

1. Introduction

Fertility in postpubertal males depends on the continued production of spermatozoa in the testis *via* the process of spermatogenesis. Spermatogenesis involves a delicate balance between self-renewal and differentiation of spermatogonial stem cells (SSC) to ensure an endless production of mature spermatozoa [1]. In keeping with other stem cell systems, the SSCs reside in a unique microenvironment or 'niche', which is composed of the stem cell and the surrounding somatic cells. The germ stem cell niche is composed of the growth factor environment that is provided by various somatic support cell populations in the testis [2,3]. In the adult testis, it has been shown that Sertoli cells, peritubular myoid cells, Leydig cells and the surrounding vasculature are all important components of the germ stem cell niche [3–5].

During fetal/early postnatal life the germ cells undergo a crucial period of development from gonocyte to spermatogonium, and it is thought that establishment of a suitable germ cell niche is a prerequisite for this to occur. This is important to ensure the establishment of a supply of SSCs for future fertility, but also because failure of these cells to undergo differentiation in humans results in pre-neoplastic change into carcinoma *in situ* (CIS) cells which will ultimately lead to a testicular germ cell cancer (TGCC) in adulthood [6,7]. In the postnatal period, active SSC self-renewal takes

* Corresponding author. Tel.: +44 0131 242 619; fax: +44 0131 242 6231.
E-mail address: s.vandendriesche@ed.ac.uk (S. van den Driesche).

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place to establish the male germline, whereas in adulthood SSC self-renewal only occurs at certain times during specific stages of the seminiferous epithelial cycle when subpopulations of spermatogonia undergo the transition into differentiating spermatogonia [3]. However, increase in SSC self-renewal has also been observed after testicular damage such as after chemotherapy [8].

Most data on the mammalian germ stem cell niche derives from mouse studies and there is still little known about the biology/regulation of the human germ stem cell niche, specifically regarding the maintenance and regulation of SSC self-renewal and differentiation. This ignorance is due partly to the absence of techniques for identifying and isolating pure populations of human SSCs for *in vitro* study [9]. However, transplantation of testis cells from humans into immunodeficient mice results in limited replication and maintenance of spermatogonia in the recipient seminiferous tubules [10,11], suggesting a degree of conservation of the mechanisms for self-renewal and SSC survival between human and mouse. Furthermore, prepubertal human and mouse spermatogonia have remarkable conservation of their gene expression, especially in the genes involved in SSC self-renewal [9]. Despite these similarities there also exist a number of significant differences. In the human testis there are no mitoses of differentiating spermatogonia, which contrasts with the 6 rounds of mitotic divisions in the rodent testis [12]. In addition, transplantation studies have demonstrated that human SSCs are unable to differentiate following incorporation into the SSC niche in the mouse testis [10]. This suggests that the mechanisms regulating spermatogenic differentiation in the rodent and human are different. Recently, the importance of microRNA (miRNA) signaling for spermatogenesis and testicular function has been demonstrated using Sertoli- or germ cell-specific knockout of key enzymes in the miRNA biosynthesis pathway [13]. Hence, miRNA signaling in testicular somatic and germ cells may comprise another level of regulation of the germ stem cell niche.

In this review we describe the main factors involved in regulation of the germ stem cell niche based on studies performed in rodents. We also summarize how conditional deletions of components of the miRNA biogenesis pathway in either Sertoli or germ cells affect the germ stem cell niche and the consequences for adult spermatogenesis. More importantly, we discuss recent findings of miRNA involvement in the regulation and/or modulation of the germ stem cell niche, suggesting that miRNA may be a new mechanism regulating the correct timing of spermatogonial differentiation and perhaps thus of spermatogenic output in adult life. Because miRNAs work as translational repressors, their expression in the germ stem cell niche could be viewed as part of a 'restraint mechanism', whereby the SSCs are prevented from differentiating into spermatogonia/meiotic germ cells too early. Especially in humans, where there is a long childhood period this is important as germ cells entering meiosis before the pubertal period will undergo apoptosis as there is no sustainable support [14]. Therefore, maintaining SSC and early spermatogonia in a quiescent, non-differentiating state is a crucial necessity and, because of the way that they work, miRNAs could play a big part in controlling differentiation mechanisms, including the niche, to ensure this process occurs correctly.

2. The germ stem cell niche

Sertoli cells are the "nurse" cells in the testis, supporting germ cell survival and spermatogenesis [1]. Sertoli cells control the germ stem cell niche either by direct contact with SCCs through membrane intercellular communications or indirectly by the production of paracrine signals such as growth factors and cytokines [15] (Fig. 1). An important factor that Sertoli cells produce is glial cell line-derived neurotropic factor (GDNF), which signals through the GDNF-family receptor α1 (GFRα1) and the Ret receptor tyrosine-kinase [16–20]. Deletion of GDNF in mice interferes with SSC self-renewal and causes premature differentiation of SCC leading to testes devoid of germ cells, resembling a Sertoli-cell only phenotype [17]. Conversely, overexpression of GDNF in mouse testes results in a block of spermatogonial differentiation as a result of over-stimulated self-renewal of SSCs [17,20]. GDNF signaling is essential for the maintenance of NANOS2 (an RNA-binding factor) expression in SSCs, which is important

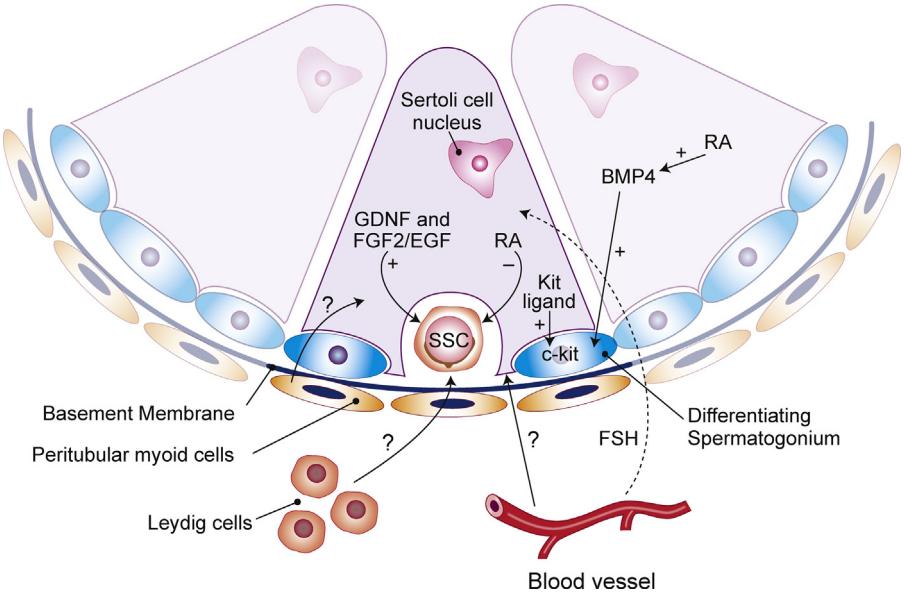

Fig. 1. Schematic diagram of the germ stem cell niche in the mammalian testis. The spermatogonial stem cell (SSC) is supported by the Sertoli cell within the seminiferous tubule. Sertoli cell produced factors such as GDNF in combination with FGF2 and EGF promote SSC self-renewal, whereas retinoic acid (RA) induces spermatogonial differentiation. Upon differentiation, spermatogonia start expressing c-kit, which is the receptor for Sertoli cell derived kit ligand. RA also induces BMP4 production which is also implicated in spermatogonial differentiation. It has been suggested that peritubular myoid cells, Leydig cells and the vasculature all somehow regulate the germ stem cell niche, but the exact mechanisms are still unknown. Follicle stimulating hormone (FSH) enters the testis through the bloodstream and induces Sertoli cell expressed GDNF, which may be one mechanism *via* which pubertal onset of spermatogenesis can be regulated centrally. For more detailed reviews on the germ stem cell see [2,3].

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