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Review

Sry and the hesitant beginnings of male development

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Abstract

In mammals, *Sry* (*sex-determining region Y gene*) is the master regulator of male sex determination. The discovery of *Sry* in 1990 was expected to provide the key to unravelling the network of gene regulation underlying testis development. Intriguingly, no target gene of SRY protein has yet been discovered, and the mechanisms by which it mediates its developmental functions are still elusive. What is clear is that instead of the robust gene one might expect as the pillar of male sexual development, *Sry* function hangs by a thin thread, a situation that has profound biological, medical and evolutionary implications.

Keywords: *Sry*; Sex determination; Molecular mechanism; Evolution; Testis development; Brain gender

Introduction

Sex determination – the process by which one of two alternative pathways of development is engaged in the embryo – is essential for sexual reproduction and hence the survival of almost all metazoan species. Despite this, an immense variety of sex determination mechanisms is used in the animal kingdom (reviewed by Morrish and Sinclair, 2002; Crews, 2003; Matsuda, 2005), indicating a high degree of evolutionary plasticity of the sex determination pathway. While this undoubtedly reflects the different biological and environmental idiosyncrasies of the different species involved, one thing is clear: nature continues to tinker with sex determination even though most other developmental mechanisms have arrived at a more stable solution.

Sex determination is a binary switch mechanism that equates, in simple terms, to the molecular event that locks the embryonic gonads into their fate as testes or ovaries. Sexual differentiation, on the other hand, comprises the subsequent events required for correct gonadal development, and genesis of secondary characteristics that embody the male or female sexual phenotype. Even though sex-determining mechanisms vary a great deal, gonadal development, gonadal function, genital development, gamete production, genital form and function and other fundamental sexual characteristics follow more similar themes in disparate taxa. What is it about sex determination that is so vulnerable to evolutionary change? And how is it that diverse molecular switch mechanisms used in different taxa converge on developmental pathways of male or female development that themselves seem well conserved?

The discovery of *Sry*, the mammalian Y-chromosomal sex-determining gene, promised to answer these and many other questions relating to the genetics and developmental biology of sex determination (Sinclair et al., 1990; Gubbay et al., 1990). The simple transgenesis experiment of adding *Sry* function to an XX mouse to induce male phenotype confirmed the master switch role of this gene (Koopman et al., 1991). But since then, little else about this gene has proven to be simple or straightforward. The fact that *Sry* resides on the Y chromosome makes it vulnerable to degradation. As a result, it is minimally conserved and shows some functional flaws, surprising indeed for a gene on which survival and propagation of mammalian species so keenly depends.

We review here the molecular genetics and developmental biology of *Sry* and its role in mammalian sex determination. Although some pieces of the sex-determination jigsaw have been pieced together over the last 15 years (Fig. 1), basic issues of molecular mode of action and exact cellular roles of *Sry* in the early developing gonads remain obscure (Koopman et al.,

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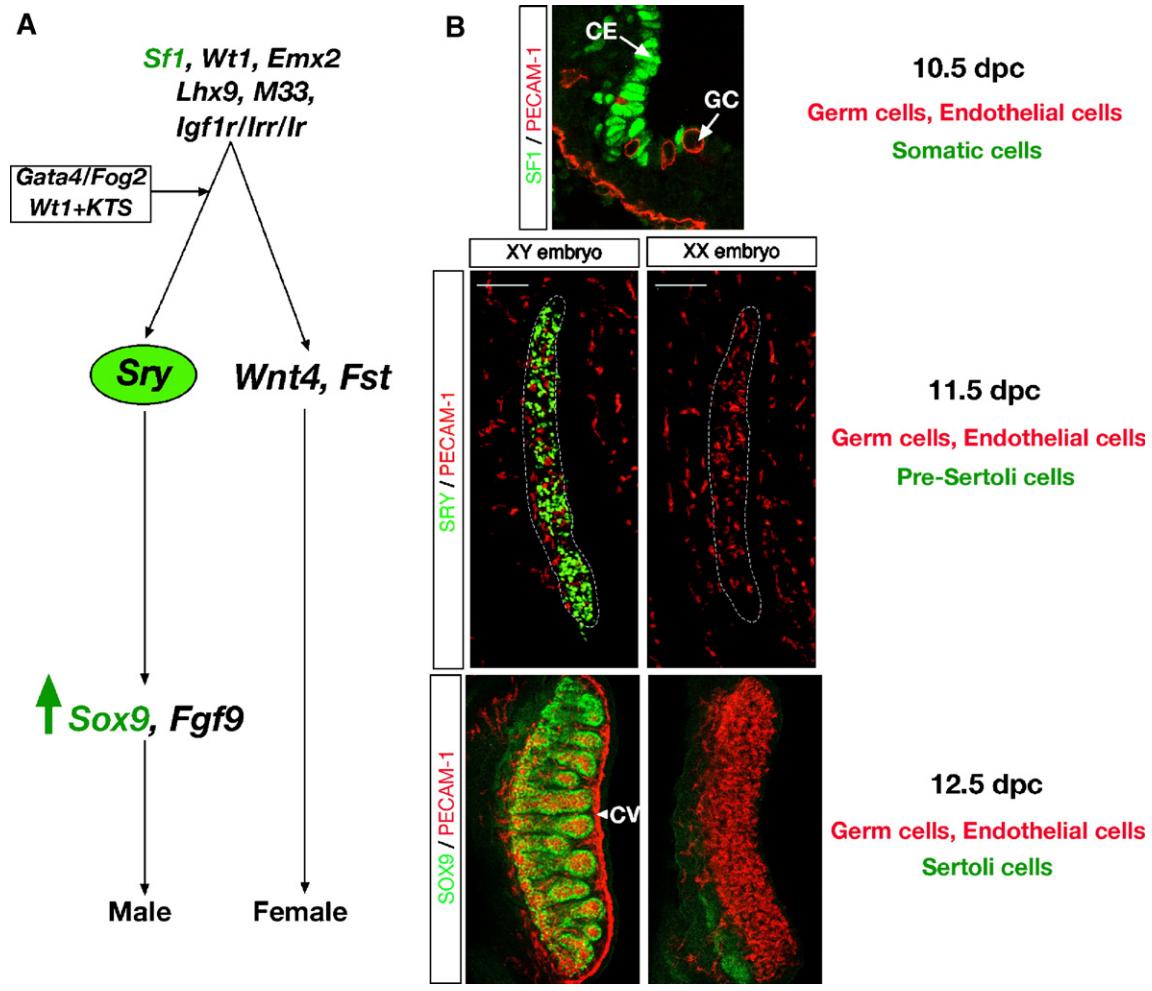

Fig. 1. Schematic representation of sex determination pathway in mammals. (A) Gene activities known to occur from 10.5 days *post coitum* (dpc) to 12.5 dpc, the critical period of sex determination. (B) Confocal gonadal images of gonad sections in the same period, immunostained with specific cellular markers. At 10.5 dpc both male and female gonads are seen as a thickening of the coelomic epithelium (CE), here shown as SF1-positive cells. From 10.5 to 11.5 dpc, several genes contribute to the development of the bipotential gonad, a stage marked by the migration of germ cells (GC) and proliferation of somatic cell lineages in both sexes. At this stage, Gata4/Fog2 and WT1+KTS are implicated in activation of *Sry* expression in the XY gonad. At 11.5 dpc, the morphology is the same for both male (left) and female (right) gonads, but male-specific markers such as *Sry*, and its downstream gene *Sox9* are already expressed. After the upregulation of *Sox9*, the morphology of the male gonad completely changes, as can be seen at 12.5 dpc by the presence of testis cords and the coelomic vessel (CV). In the absence of *Sry*, the female pathway takes place, involving *Wnt4* and *Fst* genes.

2001; Brennan and Capel, 2004). We show that *Sry* is a gene with intriguing quirks and weaknesses that likely explain its limited use as a sex determinant in the animal kingdom.

Regulation of Sry expression

Most of the functional information regarding *Sry* has been obtained using the mouse as a model system. In the mouse embryo, *Sry* exhibits a tightly-controlled and limited spatio-temporal profile of expression in the precursors of Sertoli cells of the XY gonad (Albrecht and Eicher, 2001; Sekido et al., 2004; Wilhelm et al., 2005). Early studies revealed that *Sry* is first expressed around 10.5 days *post coitum* (dpc), shortly after the emergence of the genital ridges, reaches peak levels of expression at 11.5 dpc, and is extinguished shortly after 12.5 dpc in mouse (Koopman et al., 1990; Hacker et al., 1995; Jeske et al., 1995). *Sry* mRNA is detectable only using sensitive methods such as reverse transcriptase-PCR and RNase protection, and appears to be expressed at lower levels than mRNAs of the related genes *Sox1*, −2 and −3 (Koopman et al., 1990; Hacker et al., 1995; Collignon et al., 1996).

Deeper analyses using *in situ* hybridization, transgenic reporter expression and immunofluorescence revealed that *Sry* mRNA and SRY protein display a dynamic expression pattern similar to a wave that emanates from the central longitudinal region of the genital ridges, then extends to rostral and caudal poles, and extinguishes in the order central–rostral–caudal (Albrecht and Eicher, 2001; Bullejos and Koopman, 2001; Sekido et al., 2004; Wilhelm et al., 2005). Mouse SRY protein is robustly expressed at 11.5 dpc (Wilhelm et al., 2005; Taketo et al., 2005), despite the low level of mRNA expression. Individual cells are exposed to SRY activity for a period estimated at 8 h or less (Sekido et al., 2004; Wilhelm et al., 2005). SRY clearly throws a molecular switch to engage a male-