Best Practice & Research Clinical Endocrinology & Metabolism 24 (2010) 163–186

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Control of sex development

Anna Biason-Lauber, MD, Assistant Professor of Pediatric Endocrinology *

Division of Endocrinology/Diabetology, University Children's Hospital, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland

Keywords:
sex development
sex determination
sex differentiation
ovary
testis
disorders of sex development (DSD)
bipotential state

The process of sexual differentiation is central for reproduction of almost all metazoan, and therefore, for maintenance of practically all multicellular organisms. In sex development, we can distinguish two different processes, sex determination, that is the developmental decision that directs the undifferentiated embryo into a sexually dimorphic individual. In mammals, sex determination equals gonadal development. The second process known as sex differentiation takes place once the sex determination decision has been made through factors produced by the gonads that determine the development of the phenotypic sex. Most of the knowledge on the factors involved in sexual development came from animal models and from studies of cases in whom the genetic or the gonadal sex does not match the phenotypical sex, that is, patients affected by disorders of sex development (DSDs).Generally speaking, factors influencing sex determination are transcriptional regulators, whereas factors important for sex differentiation are secreted hormones and their receptors.

This review focusses on these factors and whenever possible, references regarding the 'prismatic' clinical cases are given.

*Abbreviations: DSD, Disorders of sex development; Pax2, Paired Homeobox 2; Emx2, Empty spiracle homolog 2; Lhx9, Lim Homeobox protein 9; WT1, Wilms Tumour 1; GATA4, GATA-binding protein 4; SRY, Sex determining Region Y; SOX9, SRY- box 9; SF1/NR5A1, Steroidogenic Factor 1/Nuclear Receptor subfamily 5, group A, member 1; DAX1, Dosage sensitive sex reversal, Adrenal hypoplasia congenital critical region on the X chromosome gene 1; DMRT1, Doublesex and MAB3-Related Transcription factor 1; DHH, Desert Hedgehog; ATRX, Alpha Thalassemia, mental Retardation syndrome, X-linked; CBX2, Chromobox homolog 2; TSPYL1, Testis-specific protein Y-like-1; MAMLD1, Mastermind-Like Domain-Containing Protein 1; PGD2S, **P**rostaglandin D2 synthase; RSPO1, Root-plate specific Spondin 1; WNT4/FST, Wingless Type MMTV intergration site family, member 4/Follicostatin; FOXL2, Forkhead transcription factor; AMH/AMHR = MIS, Anti-Müllerian Hormone/Receptor = Müllerian Inhibiting Substance; HOXA, Homeobox A; Lim1/LHX1, Lim Homeobox protein 1; LH/CG, Luteinising Hormone/Corionic Gonadotropin; POF, Premature ovarian failure; ODG, Ovarian dysgenesis; FMR1, Fragile X Mental Retardation 1; DIAPH2, Diaphanous (dia) homolog 2; GDF9, Growth Differentiation Factor 9; BMP15, Bone Morphogenic Protein 15; NOBOX, Newborn Ovary Homeobox; FIGLA, Factor in Germ Line Alpha.*

* Tel.: + 41 44 266 7623; Fax:+ 41 44 266 7169.
E-mail address: Anna.Lauber@kispi.uzh.ch

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doi:10.1016/j.beem.2009.12.002

Physiology of sex development

In sex development, we can distinguish two different processes, 'sex determination', that is, the developmental decision that directs the undifferentiated embryo into a sexually dimorphic individual and 'sex differentiation' that takes place once the sex determination decision has been made through factors produced by the gonads that determine the development of the phenotypic sex. At the beginning of gestation (1st and 2nd week), embryos of the two sexes differ only by their karyotypes. Starting at week 3, specific genes lead to the differentiation of the gonads, which in turn, produce hormones inducing anatomical and psychological differences, leading to behavioural differences that are ultimately influenced by the social environment. As very nicely put by Sekido and Lovell-Badge: "Overall, sex determination is a story of opposing forces and crucial alliances but, although the winning team takes all, its rule can be surprisingly tenuous."[1]

The main steps of intrauterine sex differentiation are depicted in Fig. 1. At gestational weeks 6–7, the paramesonephric duct (Müllerian duct) develops next to the mesonephric duct. If testes develop and secrete testosterone, the mesonephric (Wolffian) duct increases in size and differentiates into epididymis, vas deferens and prostate. A glycoprotein secreted from the testicular Sertoli cells known as anti-Müllerian hormone (AMH) or Müllerian inhibiting substance (MIS) results in Müllerian duct regression. If testes do not develop, the mesonephric duct does not grow and eventually degenerates, whereas the paramesonephric duct proliferates and the fallopian tube, uterus and the upper third of the vagina develop (Fig. 2).

In mammals, including humans, the differentiation of the gonads is the turning point of this whole process. The classical textbook theory says that in the presence of the sex-determining region on the Y chromosome (SRY), the 'default' ovarian pathway of sex determination will be inhibited and therefore, testes will be formed. In the XX individual, due to the absence of SRY, no inhibition of the 'default' programme will take place and ovaries will develop. Ovarian-determining factors might help the process of differentiation. However, these factors are yet to be determined. The second model called the 'Z-factor theory' was proposed to explain the cases where XX individuals develop testes in the absence of SRY. According to this theory, the XX gonad expresses a factor that has both anti-testis and pro-ovary functions. SRY in XY individuals acts as an inhibitor of the Z-factor to lift the block on the male pathway. In this case, the bipotential gonad will differentiate into a testis.[2] The Z-factor remains unknown.

It is important to notice that most of the knowledge on the factors involved in sexual development came from studies of cases in whom the genetic or the gonadal sex does not match the phenotypical sex, that is, patients affected by defects of sex development[3] and from animal models. This review focusses on these factors and whenever possible, references on the 'prismatic' clinical cases are given.

Fig. 3 and Table 1 summarise the role of such factors and the effects of their mutations in mice and men.

Factors involved in sex determination

Indifferentiated state (bipotential)

Pax2

Pax-2 is a transcriptional regulator of the paired-box family and is widely expressed during the development of both ductal and mesenchymal components of the urogenital system. Pax-2 homozygous mutant newborn mice lack kidneys, ureters and genital tracts. These defects might be attributed to dysgenesis of both ductal and mesenchymal components of the developing urogenital system.[4]

In humans, genetic defects in PAX2 are identified in renal-coloboma syndrome, without genitourinary abnormalities.

Emx2

The homeobox gene Emx2 is a mouse homologue of a Drosophila head gap gene empty spiracles (ems) and is essential for the development of dorsal telencephalon.[5] At the same time, Emx2 is