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Androgen insensitivity syndrome

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Androgen insensitivity syndrome (AIS) results from androgen receptor dysfunction and is a common cause of disorder of sex development. The AIS phenotype largely depends on the degree of residual androgen receptor (AR) activity. This review describes the molecular action of androgens and the range of androgen receptor gene mutations, essential knowledge to understand the pathogenesis of the complete and partial forms of this syndrome. A multidisciplinary approach is recommended for clinical management from infancy through to adulthood. Hormone replacement therapy is needed following gonadectomy. Patients who choose to retain the gonads are at risk of developing germ cell tumors for which sensitive circulating tumor markers may soon become available. Whilst the contribution of AR dysfunction to complete AIS is well understood, the involvement of the AR and associated proteins as contributors to partial AIS is an area of active research. Disorders of sex development such as AIS which are related to AR dysfunction offer a breadth of manifestations for the clinician to manage and opportunities for further research on the mechanism of androgen action.

Abbreviations: AIS, androgen insensitivity syndrome; AR, androgen receptor; DBD, DNA binding domain; LBD, ligand binding domain; AREs, androgen response elements; CAIS, complete androgen insensitivity syndrome; PAIS, partial androgen insensitivity syndrome; MAIS, mild androgen insensitivity syndrome; DSD, disorder of sex development; DHT, dihydrotestosterone; BF3, binding function 3; AF2, activation function 2; EMS, external musculinisation score; LH, lutenising hormone; FSH, follicle-stimulating hormone; PKA, protein kinase A; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; HRT, hormone replacement therapy; BMD, bone mineral density.

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Introduction

Androgen insensitivity syndrome (AIS) represents the paradigm of a clinical disorder resulting from androgen receptor (AR) dysfunction leading to hormone resistance. This is dramatically illustrated by the complete form of the syndrome (CAIS) characterised by XY sex reversal and a female phenotype despite serum concentrations of testosterone often exceeding the normal adult male range. The X-linked *AR* gene appears to be universally resistant to activation by androgen ligand in CAIS as illustrated by normal female gender identity in women with CAIS. However the phenotypic diversity related to AR dysfunction in AIS is greater when residual AR function in response to androgen remains. Thus the partial form of AIS (PAIS) can present a conundrum for the clinician to resolve, including issues as fundamental as knowing what sex to assign an infant at birth. Consequently, knowledge about the molecular mechanism of androgen action and how the range and type of mutations distributed throughout the AR gene affect phenotype is essential for the clinician to establish a diagnosis and to manage AIS from infancy through to adulthood.

Molecular aspects of the androgen receptor

The AR is a member of the ligand dependent transcription factor super-family of nuclear receptors [1]. The AR shares conserved structural similarities with other members of the nuclear receptor family, including a central DNA binding domain (DBD) and C-terminal ligand binding domain (LBD) (Fig. 1A). The AR uniquely contains an extended N-terminal domain which includes polymorphic poly-glutamine (CAG) and poly-glycine (GGN) repeats which are known to influence AR activity [2,3]. In clinical studies, the CAG repeat length has an association with genital abnormalities [3], a positive correlation with serum testosterone concentrations but not with male infertility [4]. A shorter CAG repeat polymorphism may increase the risk of prostate cancer [5]. As described subsequently, the physical interaction of the AR N- and C-terminal domains plays a crucial role in effecting androgen regulated transcription of target genes. The AR DBD can preferentially distinguish androgen response elements (AREs) composed of an inverted repeat of DNA sequences related to 5′-AGAACA-3′ [6]. However, the recent completion of several studies exploiting the powerful and unbiased ChIPseq technique (genomewide chromatin immunoprecipitation assays coupled with next generation sequencing) has revealed the complexity of AR-chromatin interactions [7–13]. In the presence of the primary physiological androgens, testosterone and dihydrotestosterone (DHT) (Fig. 1B), the AR recruits multiple, enzymatically diverse epigenetic coregulators [14] which cooperate in the activation of transcription of androgen regulated genes (Figs. 1D and 2A). Molecular analysis of the androgen [15,16] estrogen (ERα) [17,18], and retinoic acid (RAR) [19] LBD domains revealed the crucial roles of agonist induced changes in LBD organisation which enable coactivator recruitment and established the importance of the coactivator LxxLL motif in mediating these interactions [15,17,18,20] (Fig. 1C). The AR also exhibits a selective preference for the ARA70, ARA55 and ARA54 coregulators which contain FxxLF motifs [21] related to AR N-terminal ^{23}FQNLF^{27} and ^{435}WHTLF^{439} sequences which participate in the AR N–C terminal interactions [22–24]. Together with recent advances in understanding of the functional interplay between the AR, epigenetic coregulators [25], pioneer [26,27] and other transcription factors [28], the mechanisms whereby the AR can regulate tissue specific transcriptional profiles are now better understood. This knowledge of the transcriptional events orchestrated by the AR are complimented by insights garnered from conditional *AR* knockout mice [29–34] which have revealed the role of AR signaling in diverse physiological processes [35]. Collectively these approaches are informative in understanding androgen signaling in the context of disorders of sex development associated with androgen resistance.

AR mutations are the best understood molecular cause of complete (CAIS) and partial (PAIS) androgen insensitivity syndrome [36,37]. While the vast majority of CAIS cases (90–95%) are attributable to *AR* mutations, less than a third of cases with a phenotype consistent with PAIS are associated with *AR* mutations. This suggests that while the AR is essential for masculinisation, multiple other components of the AR complex and signaling network are required for complete virilisation. For this reason AR associated coactivators have been considered candidate factors to explain androgen resistance in the presence of a normal AR [38]. Consistent with this, the clinical and mechanistic evidence

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