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Gene Section
Review

NR0B1 (nuclear receptor subfamily 0, group B, member 1)

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Abstract

Review on NR0B1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: AHC, AHCH, AHX, DAX-1, DAX1, DSS, GTD, HHG, NROB1, SRXY2

HGNC (Hugo): NR0B1

Location: Xp21.2

Note: Locus type: gene with protein product.

DAX-1 is an unusual orphan nuclear receptor playing a pivotal role in the development and function of steroidogenic tissues, being responsible for the human disease adrenal hypoplasia congenita (AHC). Moreover, it controls embryonic stem (ES) cell differentiation and is implicated in the pathogenesis of several types of cancers.

DNA/RNA

Note

A region of approximately 160 kb, whose duplication is responsible for male-to-female sex reversal, was identified on chromosome Xp21. The genetic disorder characterized by this duplication was indicated as Dosage-Sensitive Sex reversal (DSS) (Bardoni et al., 1994). This chromosomal region harbors the NR0B1 gene (Zanaria et al., 1994). Mutations in NR0B1 cause adrenal hypoplasia congenita (AHC), a congenital disease of the adrenal cortex, which is associated to hypogonadotropic hypogonadism (HHG) at puberty. The gene was initially designated DAX-1, which stands for **D**SS, **A**HC locus on the **X**-chromosome, gene **1** (Zanaria et al., 1994, Muscatelli et al., 1994). It encodes an orphan member of the nuclear receptor family and was later termed NR0B1 (nuclear receptor subfamily 0, group B, member 1) according to the standard nomenclature system for nuclear receptors.

Description

Size: 4.96 kb, 2 exons. mRNA: 1.9 kb.

DAX-1 has two exons separated by an intronic region. Most of the coding sequence is found in exon one (McCabe et al., 2001; Burris et al., 1996), which encodes the N-terminal domain and part of the C-terminal domain of the protein, whereas exon two encodes the remaining part of the C-terminal domain.

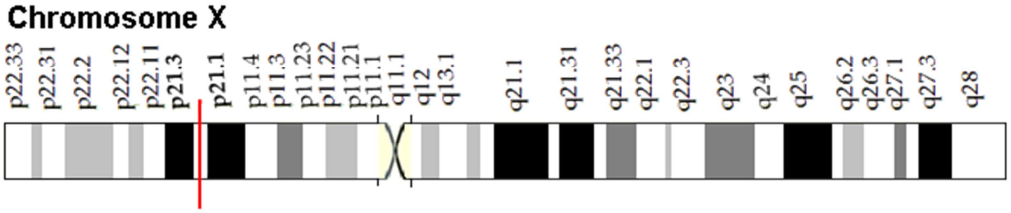

Figure 1. DAX-1 chromosomal localization. The DAX-1 gene maps on chromosome Xp21.3-p21.2 (adapted from GeneCards).

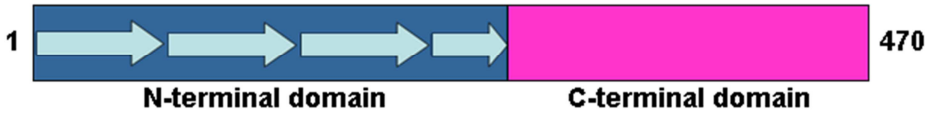

Figure 2. Schematic diagram of the DAX-1 protein. The DAX-1 protein (470 aa) harbors an N-terminal domain (blue box) and a C-terminal nuclear receptor ligand binding-like domain (pink box). The three repeats of about 70 aa in length and the fourth incomplete repeat in the N-terminal region are indicated by arrows.

Protein

Description

The C-terminal portion of DAX-1 has homology to the ligand-binding domain (LBD) of nuclear receptors, although no ligands have been described to bind to the protein, thus explaining its classification as an orphan receptor. All features constituting the nuclear receptor LBD fold are present in DAX-1 C-terminal domain, as shown by homology models based on the crystal structure of apo-retinoic X receptor-α, holo-retinoic acid receptor-α and thyroid hormone receptor α (Lalli et al., 1997; Zhang et al., 1998). A conserved ΦΦXEΦΦ motif has been identified in the C-terminal H12 helix, which in other nuclear receptors has been shown to be essential for ligand-dependent transcriptional activation (AF-2, activation function 2). A potent transcriptional silencing domain is present in the DAX-1 C-terminus (Lalli et al., 1997) and no ligands are known that can convert DAX-1 from a transcriptional repressor to an activator. Mutations causing AHC/hypogonadotropic hypogonadism (HHG) invariably disrupt the C-terminal domain of the protein, leading to the loss of the transcriptional repressor activity of the molecule (see Mutations below) (Zanaria et al., 1994; Muscatelli et al, 1994; Ito et al., 1997; Lalli et al., 1997). This is due to altered nuclear localization of DAX-1 AHC missense mutants induced by protein misfolding (see Mutations below) (Lehmann et al., 2002; Lehmann et al., 2003).

DAX-1 structure is unusual when compared with other members of the nuclear receptor family, as it lacks the canonical DNA-binding domain (DBD), the AF-1 transcriptional activation domain and the hinge region.

Instead, the N-terminus is constituted by three repeats of a unique cysteine-rich motif of about 70 aminoacids (aa) in length.

The number of repeats varies during evolution. Non-mammalian species display only one repeat (Smith et al., 2000; Western et al., 2000; Sugita et al., 2001, Wang et al., 2002).

Protein translation:

MAGENHQWQGSILYNMLMSAKQTRAAPEAP
ETRLVDQCWGCSCGDEPGVGREG
LLGGRNVALLYRCCFCGKDHPRQGSILYSML
TSAKQTYAAPKAPEATLGPCWGCSC
GSDPGVGRAGLPGGRPVALLYRCCFCGEDHP
RQGSILYSLLTSSKQTHVAPAAPEA
RPGGAWWDRSYFAQRPGGKEALPGGRATAL
LYRCCFCGEDHPQQGSTLYCVPTS
TNQAQAAPEERPRAPWWDTSSGALRPVALKS
PQVVCEAASAGLLKTLRFVKYLPC
FQVLPLDQQLVLVRNCWASLLMLELAQDRL
QFETVEVSEPSMLQKILTTRRRETGG
NEPLPVPTLQHHLAPPAEARKVPSASQVQAIK
CFLSKCWSLNISTKEYAYLKGTVLFN
PDVPGLQCVKYIQGLQWGTQQILSEHTRMTH
QGPHDRFIELNSTLFLLRFINANVIAE
LFFRPIIGTVSMDDMMLEMLCTKI

Sequence length: 470 aa. Molecular weight: 51,718 kDa.

An alternatively spliced isoform of DAX-1 has been described in human tissues (Ho et al., 2004; Hossain et al., 2004). The protein DAX-1A or DAX-1α contains the first 389 aa of DAX-1 followed by a novel 12-aa motif. It thus lacks the last 70 aa of the DAX1 C-terminal domain, which includes part of the transcriptional silencing domain and the AF-2 motif. However, the expression levels of this isoform are extremely low in steroidogenic tissues (Nakamura et al., 2009b).

Expression

DAX-1 is expressed in tissues involved in steroid hormone production and reproductive function, i.e. adrenal cortex, testicular Leydig and Sertoli cells, ovarian theca and granulosa cells, pituitary gonadotropes, ventromedial hypothalamic nucleus in the brain and some other brain areas (arcuate nuclei, amygdala, hippocampus, cerebral cortex) (Ikeda et al., 1996; Swain et al., 1996; Tamai et al., 1996; Ikeda et al., 2001). This expression pattern is strikingly overlapping with that of another nuclear receptor, steroidogenic factor 1 (SF-1; NR5A1), a master regulator of adrenocortical gonadal and gonadotrope development and function (reviewed in Parker and Schimmer, 1997; Lalli et al., 2013).

Localisation

Studies on cultured cells and the developing mouse pituitary show that DAX-1 is present both in the nucleus and the cytoplasm (Lalli et al., 2000; Lehmann et al., 2002; Holter et al., 2002; Kawajiri et al., 2003; Clipsham et al., 2004). Moreover, DAX-1 is able to homodimerize in both these subcellular compartments (Iyer et al., 2006) and associates with polyribosomes via mRNA,

functioning as a shuttling RNA binding protein (see Role in transcriptional regulation below) (Lalli et al., 2000).

Function

Role in transcriptional regulation

Starting from the studies which show that DAX-1 expression pattern overlaps with that of SF-1 (see Expression above), it was demonstrated that DAX-1 inhibits SF-1 - mediated transactivation and steroid hormone production (Ito et al., 1997; Zazopoulos et al., 1997). Indeed DAX-1 contains a powerful transcriptional repression domain in its C-terminus (see Protein; Description above) overlapping with its nuclear receptor LBD domain (Ito et al., 1997; Lalli et al., 1997), through which it acts as a negative regulator of SF-1-induced transactivation. DAX-1 binds to gene promoters regulated by SF-1 (e.g. StAR and Dax-1 promoters, Zazopoulos et al., 1997) or it directly interacts with SF-1 (via one of the LXXLL motifs in the DAX-1 N-terminus), thus repressing SF-1 transactivation (Suzuki et al., 2003). On the other hand, SF-1 enhances Dax-1 expression through binding to its promoter (Kawabe et al., 1999), probably establishing a negative feedback loop to limit SF-1 action in steroidogenic and reproductive tissues. DAX-1 inhibits the steroidogenic process at various levels. It acts both on the steroidogenic acute regulatory protein (StAR)-mediated rate-limiting step of cholesterol import into mitochondria, but also on the expression of CYP11A1 and 3-β-hydroxysteroid dehydrogenase (HSD3B2) (Zazopoulos et al., 1997; Lalli et al., 1998). The presence of cells expressing DAX-1 but not SF-1 in different organs (Ikeda et al., 2001) suggests that DAX-1 function extends beyond the regulation of SF-1 - dependent genes. Indeed, DAX-1 inhibits the transcriptional activity of multiple transcription factors, like retinoic acid receptor α (RARα) and retinoid X receptor α (RXRα) (Zanaria et al., 1994), liver receptor homologue-1 (LRH1) (Suzuki et al., 2003), estrogen receptors α and β (ERα and ERβ) (Zhang et al., 2000), glucocorticoid receptor (GR) (Zhou et al., 2008), androgen receptor (AR) (Holter et al., 2002; Agoulnik et al., 2003), progesterone receptor (PR) (Agoulnik et al., 2003), nerve growth factor-inducible gene B (NGFIB; also known as Nurr 77) (Song et al., 2004), estrogen-related receptor γ (ERRγ) (Park et al., 2005), peroxisome proliferator-activated receptor gamma (PPARγ) (Kim GS et al., 2008), hepatocyte nuclear factor 4 (HNF-4) (Nedumaran et al., 2009). The mechanisms through which DAX-1 inhibits the transcriptional activity of those transcription factors involve both DNA binding and heterodimerization (Zanaria et al., 1994; Zazoupoulos et al., 1997; Zhang et al., 2000; Suzuki et al., 2003). It has been suggested that DAX-1 interacts with the coactivator groove of the nuclear receptors' LBD through its N-terminal LXXLL motifs (Zhang et al., 2000), However, recently a structural study has shown that mouse Dax-1 interacts with LRH-1 as a homodimer via an unusual C-terminal repressor helix (Sablin et al., 2008). DAX-1 - mediated transcriptional repression involves interaction with corepressors. They can silence the activity of the basal transcriptional machinery and/or lead to chromatin modifications. For example, the N-CoR (Crawford et al., 1998) and Alien (Altincicek et al., 2000) corepressors have been reported to interact with DAX-1. However, when DAX-1 surface residues (which in other nuclear receptors are involved in direct interaction with corepressors) are mutated, DAX-1 transcriptional silencing properties are not perturbed (Lehmann et al., 2003). These data indicate that cofactors other than known nuclear receptor corepressors may mediate DAX-1 transcriptional silencing activity.

DAX-1 nucleo-cytoplasmic shuttling, RNA binding activity and association with actively translating polyribosomes as part of a messenger ribonucleoprotein complex in steroidogenic cells suggest that this factor has a role in post-transcriptional regulations (Lalli et al., 2000). Overall, from the analysis of DAX-1 - regulated genes (reviewed in Lalli and Sassone-Corsi, 2003), it clearly emerges that DAX-1 acts as a global negative regulator of steroid hormone production by silencing the expression of multiple genes involved in steroidogenesis (Lalli et al., 1998).

Role in sexual differentiation

Based on DAX-1 gene localization inside the critical region in Xp21, whose duplication causes the DSS syndrome (see Implicated in section below) (Bardoni et al., 1994), a role for this factor in the sexual differentiation process has been hypothesized.

In the mouse, the Dax-1 transcript is first detectable in the genital ridge at 11.5 days post coitum (dpc) and was shown to be downregulated in the male gonad but still expressed in the developing ovary at later times (Swain et al., 1996). Furthermore, gonadal female differentiation was induced by the overexpression of a genomic DNA fragment containing the Dax-1 gene in mouse strains harboring a "weak" Sry allele (M. domesticus poschiavinus, Sry transgenic XX animals) (Swain et al., 1998). On the basis of these findings in mice and the DSS phenotype in humans, an essential role as an "antitestis gene" was initially attributed to DAX-1 (Goodfellow and Camerino, 2001). In contrast with those results, the Dax-1 transcript was still detected at equivalent levels in mouse and rat testis and ovary at 12.5-15.5 dpc and was shown to be downregulated in the ovary at later stages (Ikeda et al., 1996; Nachtigal et al., 1998). The Dax-1 protein is also expressed in both testis Sertoli and

Leydig cells and throughout the ovarian primordium at 12.5-14.5 dpc in the mouse (Ikeda et al., 2001). Moreover, DAX-1 transcripts were detected in human embryos both in the male and female gonadal ridges during the critical period of sex determination (Hanley et al., 2000). Finally, during embryogenesis the expression of DAX-1 homologues both in the male and the female gonad has been reported in pig, chicken, alligator, frog and some fish species (reviewed in Lalli and Sassone-Corsi, 2003). Collectively, these findings suggest that DAX-1 exerts a specific function in distinct cell populations both in the male and in the female gonads. While essential in males, multiple evidence indicates that DAX-1 activity is dispensable in female gonadal development. Indeed DAX-1 regulates the development of peritubular myoid cells and the formation of testis cords, thus being crucial for testis differentiation (Meeks et al., 2003a). Its absence has been linked to male-to-female sex reversal in certain genetic backgrounds, associated with a failure in upregulation of Sox9 expression in the developing male gonad (Meeks et al., 2003b; Bouma et al., 2005; Park et al., 2008). Moreover, spermatogenesis defects where identified in the testis of AHC/HHG patients, which display disorganization of seminiferous tubular structures and Leydig cell hyperplasia (Seminara et al., 1999, Mantovani et al., 2002). On the other hand, Dax-1 null mice do not display ovarian defects or AHC/HHG, but instead develop a progressive degeneration of the testicular germinal epithelium (Yu et al., 1998). Furthermore, a female individual carrying a homozygous nonsense mutation in DAX-1 and affected by isolated HHG exhibited normal ovaries (Merke et al., 1999). Collectively, these findings show that DAX-1 is important for male, but not female gonad development and function.

To explain the female or ambiguous gonadal differentiation phenotype in XY individuals upon DAX-1 overexpression (due to duplication affecting Xp21) (Bardoni et al., 1994), two molecular mechanisms have been proposed (Lalli and Sassone-Corsi, 2003):

1. Repression of MIS production by fetal Sertoli cells. This is due to DAX-1 inhibitory action during male sexual development on the synergistic interaction of SF-1 and Wilms tumor 1 (WT1), which activates the MIS gene promoter (Nachtigal et al., 1998). DAX-1 also inhibits the transcriptional cooperation between GATA4 and SF-1 (Tremblay and Viger, 2001), which acts to mediate the expression of MIS. DAX-1 overexpression would thus repress the expression of MIS during the stage crucial for sexual differentiation.

2. Repression of testosterone production by fetal Leydig cells. Given DAX-1 negative role on steroidogenesis, its overexpression would inhibit testosterone biosynthesis in fetal Leydig cells and thus impair sexual secondary character masculinization.

More recently, another mechanism for DAX-1 overexpression in interfering with normal male sex determination has been proposed, that involves inappropriate repression of SF-1 activation of the testis SOX9 enhancer (Ludbrook et al., 2012).

Role in adrenal development

In the developing human adrenal cortex, a gradient of DAX-1 expression exists from the outer, definitive zone (form which the adult adrenal cortex will be formed) to the internal, fetal zone that produces high amount of steroids (Battista et al., 2005). Adrenocorticotropic hormone (ACTH) stimulation leads to nuclear localization of DAX-1 in fetal cells cultured on collagen, while angiotensin II promotes protein localization only in the cytoplasm in fetal cells cultured on either collagen or fibronectin (Battista et al., 2005). A model has been proposed whereby DAX-1 inhibits the expression of steroidogenic genes in definitive zone cells, whereas its cytoplasmic localization in fetal zone cells allows for production of high levels of steroids (Lalli and Sassone-Corsi, 2003). The loss of function of DAX-1 in AHC would stimulate enhanced differentiation in adrenal definitive zone cells through the abnormal early expression of genes involved in steroid hormone production and the depletion of progenitor cells, thus causing adrenal hypoplasia and insufficiency. The physiological regression of the fetal zone would then produce adrenal hypoplasia.

During mouse adrenal development, Dax-1 expression has been described in the adrenal primordium (AP) starting from E10.5, being readily detectable at E12.5. At this stage, the expression pattern of DAX-1 overlaps with that of SF-1, whose expression is driven by the fetal adrenal enhancer (FAdE) (Zubair et al., 2008). Later, DAX-1 is found in the outer part of the AP (from which the adult adrenal cortex will originate), whereas FAdE expression is restricted to the inner part of the adrenal cortex (identified as the X-zone postnatally). These data suggest that Dax-1 may suppress FAdE expression during the transition from the fetal to the adult adrenal differentiation program and suggests that a fine balance between SF-1 and DAX-1 is needed for normal adrenocortical development. This also helps to explain how loss of function of two transcription factors as SF-1 and DAX-1, one activator and one repressor of transcription, leads to the same adrenal hypoplasia phenotype.

Role in embryonic stem cells

In 2003 Dax-1 has been identified as one of the transcripts that are highly expressed in mouse ES cells (Mitsui et al., 2003). Later, it was reported that differentiation of mouse ES cells is induced by Dax-1 knockdown by RNA interference or gene

inactivation by homologous recombination (Niakan et al., 2006). More recently, it has been shown that Dax-1 is part of the core protein network which controls murine ES cells pluripotency and self-renewal through the interaction with other key factors and binding to a common group of gene promoters (Loh et al., 2006; Wang et al., 2006; Kim J et al., 2008). The essential pluripotency factors STAT3, Oct3/4 and Nanog control Dax-1 expression in mouse ES cells (Loh et al., 2006; Wang et al., 2006; Sun et al., 2008). Dax-1, in turn, binds to Oct3/4 to limit its transcriptional activity and thus avoid loss of ES cell pluripotency (Sun et al., 2009). It has been recently reported that β-catenin - dependent transcription affects DAX-1 expression in mouse ES cells and that Dax-1 knockdown rapidly induces the upregulation of early differentiation markers belonging to the three embryonic germ layers. This in turn causes enhanced differentiation at the cellular level and defects in ES viability and proliferation (Khalfallah et al., 2009). Indeed, Dax-1 has been reported to be rapidly downregulated at the mRNA and protein level by different treatments promoting ES cell differentiation (Khalfallah et al., 2009). Dax-1 also exerts its transcriptional repression activity in murine ES cells as in steroidogenic cell types and both its N-terminal and C-terminal domains exhibit a promoter-specific transcriptional silencing action (Khalfallah et al., 2009). Altogether these findings indicate that Dax-1 is an essential element in the molecular circuit involved in the maintenance of ES cell pluripotency. Indeed previous studies proposed an "additive" model for gene regulation in murine ES cells whereby promoters bound by only a limited number of pluripotency factors (including Dax-1) tend to be inactive or repressed, whereas promoters bound by more than four factors are active in the pluripotent state and repressed upon differentiation (Kim J et al., 2008). Lalli and Alonso proposed that Dax-1 is not to be considered as an essential pluripotency factor in murine ES cells, but rather that it acts as a specialized pluripotency keeper that mediates repression of a subset of differentiation genes under the control of upstream pluripotency factors (Lalli and Alonso, 2010). Remarkably, in human ES cells very low levels of DAX-1 are present and its expression is inconsistently modulated during their differentiation (Xie et al., 2009). This suggests that the pluripotency keeper role of DAX-1 in mouse ES cells is not conserved in human or that redundant pathways are activated.

Homology

Interspecies
Ortholog to NR0B1, Pan troglodytes
Ortholog to Nr0b1, Mus musculus
Ortholog to Nr0b1, Rattus norvegicus
Ortholog to nr0b1, Danio rerio

Mutations

Note

Since the identification of DAX-1 mutations as the cause of AHC (Muscatelli et al., 1994; Zanaria et al., 1994), several DAX-1 mutations have been described in individuals or families with X-linked AHC (reviewed in Jadhav et al., 2011). They include deletions, alterations of splice sites, missense, nonsense and frameshift mutations (deletions, insertions, duplications and complex deletions/insertions). Missense mutations represent about one-quarter of DAX-1 mutations and are localized in nearly all cases in the C-terminal domain of the protein (Lin et al., 2006).

The common feature of DAX-1 mutations causing AHC/HHG is that they affect the integrity of the protein C-terminal domain and impair transcriptional repression by DAX-1 (Muscatelli et al., 1994; Zanaria et al., 1994; Lalli et al., 1997; Ito et al., 1997; Crawford et al., 1998; Altincicek et al., 2000; Tabarin et al., 2000; Achermann et al., 2001). From the analysis of several different DAX-1 missense mutations found in AHC patients, it emerged that the impairment of transcriptional repression is dependent on an altered nuclear localization of the mutant proteins, which are not able to repress target gene expression, being retained in the cytoplasm (Lehmann et al., 2002; Lehmann et al., 2003). Remarkably, DAX-1 AHC mutant proteins localize in the cytoplasm, even if their nuclear localization signal (NLS), which resides in the N-terminal of the protein, is intact. A direct correlation between the cytoplasmic localization of DAX-1 AHC mutants and the reduction of their transcriptional silencing activity has been reported. Interestingly, the effect of AHC mutations was also observed when the protein C-terminus was fused to a heterologous NLS-containing DBD (Lehmann et al., 2002).

It has been shown that DAX-1 AHC mutants are more affected by limited proteolysis than the wild-type protein (Lehmann et al., 2003). As folded proteins have lower sensitivity to protease digestion than unfolded or misfolded polypeptides, these findings suggest that AHC mutations induce a misfolded state of the proteins, consistent with their localization at the level of certain residues that make critical contacts and stabilize the DAX-1 C-terminal domain. The misfolding of DAX-1 AHC mutants may explain the reduced RNA-binding capacity, which depends both on the N- and C-terminal domains of the protein (Lalli et al., 2000). Importantly, in addition to an impairment of transcriptional repression activity, DAX-1 AHC mutations may perturb protein nucleo-cytoplasmic shuttling and DAX-1 association to polyribosomes.

By structure-function analysis it has been demonstrated that the substitution of DAX-1 residues affected by AHC mutations with residues of analogous chemical nature does not alter protein function and localization, whereas substitution of a hydrophobic residue with a charged one (e.g. V269R, W291R) or of a charged residue with one of opposite charge (e.g. K382E, R425E) has the same consequences as AHC mutations (Lehmann et al., 2003). Notably, the I439S DAX-1 mutation, found in a patient affected by late-onset adrenal insufficiency and incomplete HHG, only partially perturbs protein nuclear localization and causes incomplete loss of DAX-1 transcriptional repression activity (Lehmann et al., 2002).
Finally, evidence indicates that also the DAX-1 helix 12 contains critical determinants for nuclear localization and transcriptional repression, as shown by the two AHC mutations M462stop and L466R (Lehmann et al., 2002; Lehmann et al., 2003).
Only two missense mutations have been reported to occur in the DAX-1 N-terminal region, the C200W mutation, associated with late-onset AHC (Bernard et al., 2006) and the W105C mutation, associated with isolated mineralocorticoid deficiency (Verrijn Stuart et al., 2007). Interestingly, a mild form of AHC was diagnosed in a patient carrying the nonsense mutation Q37X, predicted to cause a severe truncation of the protein, because of the expression of a partially functional amino-truncated of DAX-1 generated from an alternate in-frame translation start site (Ozisik et al., 2003).

Implicated in

Ewing tumors

Note

The Ewing family of tumors represents the cancer type where DAX-1 role and mechanisms of action have been better established. These highly malignant bone and soft tissue tumors are typical of children, adolescents and young adults. They derive from specific balanced chromosomal translocations, which lead to the expression of chimeric proteins harboring the N-terminus of the EWS gene product and the C-terminus of FLI1, a member of the ETS family of transcription factors (Arvand and Denny, 2001). While DAX-1 expression has been reported in Ewing tumors, it is not expressed in neuroblastoma and embryonal rhabdomyosarcoma, which are histologically similar small-round-cell tumors (Mendiola et al., 2006). The EWS/FLI1 fusion protein activates DAX-1 expression through the binding to a highly polymorphic GGAA-rich region in its promoter (García-Aragoncillo et al., 2008; Gangwal et al., 2008). Remarkably, a positive correlation exists between DAX-1 expression levels in Ewing tumor cells and the number of GGAA repeats at the level of the DAX-1 promoter (García-Aragoncillo et al., 2008). DAX-1 is required for Ewing tumor cell growth (García-Aragoncillo et al., 2008; Kinsey et al., 2006). In fact, its knockdown in Ewing cells caused accumulation in the G1 phase of the cell cycle, inhibition of cell proliferation in vitro and impairment of xenotransplanted cell growth in mice. Interestingly, despite the continued expression of the EWS/FLI-1 oncoprotein, the effect of DAX-1 knockdown on the proliferation of Ewing cells was still observed. This suggests that DAX-1 is a main mediator of EWS/FLI1-induced cell proliferation. In fact, from gene expression profiling it emerged that about 10% of the genes controlled by EWS/FLI1 in Ewing tumor cells are targets of DAX-1. Most of these genes participate in cell cycle control, particularly in the G1/S transition, like CDK2, SKP2, MCM10 and CDC6 (García-Aragoncillo et al., 2008). Collectively these data provide evidence for a key role played by DAX-1 in the acquisition of a transformed phenotype by Ewing tumor cells and indicate that DAX-1 can represent a molecular target for the treatment of this type of cancer.

Adrenocortical tumors

Note

In adrenocortical adenomas DAX-1 expression levels inversely correlate with hormone production (with aldosterone-producing adenomas exhibiting the lowest DAX-1 levels) (Reincke et al., 1998). In contrast, DAX-1 expression in adrenocortical carcinoma is extremely variable (Reincke et al., 1998). Low DAX-1 expression was confirmed in aldosterone-producing adenomas by another study (Lefrançois-Martinez et al., 2004) and was also present in cortisol-producing adenomas (Shibata et al., 2001). High DAX-1 levels were instead found in two cases of the rare deoxycorticosterone-producing adenomas, which cause a syndrome of mineralcorticoid excess (Shibata et al., 2001). Collectively these studies show the existence of an inverse correlation between the levels of DAX-1 expression and steroid hormone production in adrenocortical cancers. They also suggest that DAX-1 may affect the pattern of steroid hormones secreted by the tumor. Moreover, considering that DAX-1 acts as a repressor of SF-1 transcriptional activity (see Role in transcriptional regulation), its expression may represent an important mechanism to limit SF-1 pro-proliferative effect in adrenocortical cancer cells. Indeed, it has been demonstrated that SF-1 controls human adrenocortical cancer cell proliferation and tumor formation in mice in a dosage-dependent manner (Doghman et al., 2007; Doghman and Lalli, 2009).

Ovarian cancer

Note

A positive correlation between DAX-1 immunoreactivity and clinical stage, tumor grade, residual size of the tumor after neoadjuvant treatment and tumour Ki-67 labelling index has been reported for ovarian carcinoma (Abd-Elaziz et al., 2003). The same group showed a significant inverse correlation between DAX-1 immunoreactivity and patient survival.

Breast cancer

Note

DAX-1 immunoreactivity positively correlates with AR levels and nodal status in human breast cancer (Conde et al., 2004).

Endometrial cancer

Note

An inverse correlation was reported in endometrial carcinoma between DAX-1 immunoreactivity and histological grade, while a positive correlation with ERα and ERβ was shown (Saito et al., 2005).

Prostate cancer

Note

A negative correlation between DAX-1 immunoreactivity and Gleason score (a system used to assess the grade of malignancy) has been reported for prostate cancer (Nakamura et al., 2009a).

The commercial antibody used in most of the above studies does not specifically recognize DAX-1 in immunohistochemistry and Western blotting (Helguero et al., 2006; Lalli, 2013). This may create problems in the interpretation of data concerning DAX-1 expression in cell lines and tissues.

Lung cancer

Note

Microarray analysis showed that DAX-1 expression is high in lung cancer stem cells identified among A549 cells by Hoechst 33342 staining (side population: SP) (Seo et al., 2007). Interestingly, only SP cells were tumorigenic after injection in immunodeficient mice (Hadnagy et al., 2006). This suggests that DAX-1 may participate in the maintenance of cancer stem cells in some type of cancers, as shown for mouse ES cells (see Role in embryonic stem cells above). Moreover, it has been recently reported that DAX-1 silencing does not affect A549 cells proliferation, whereas it increases their sensitivity to topotecan (topoisomerase I inhibitor) and decreases the ability of cells to invade through Matrigel, colony formation in vitro and xenograft growth in mice (Oda et al., 2009). A positive correlation also exists between DAX-1 levels and nodal stage and tumor recurrence in lung adenocarcinoma. Promoter demethylation might be the cause of the high DAX-1 expression in a subset of lung adenocarcinoma samples. Indeed, it has been shown that low DAX-1 expression levels correlate with patient longer and disease-free survival (Oda et al., 2009). These results are promising for future studies on the role of DAX-1 in lung adenocarcinoma and potential related therapeutic strategies.

X-linked adrenal hypoplasia congenita (AHC) and hypogonadotropic hypogonadism (HHG)

Note

X-linked AHC is a disorder of adrenal gland development first described by Sikl in 1948, which occurs in fewer than 1:12,500 live births (Sikl et al., 1948; McCabe, 2001). It is characterized by a small and hypofunctional adrenal gland and absence of the adrenal cortex permanent zone, with residual cytomegalic cells (Uttley, 1968; Mamelle et al., 1975; McCabe, 2001). Adrenal insufficiency usually appears early in infancy; biochemical findings include low serum levels of glucocorticoids, mineralcorticoids and androgens and a failure to respond to ACTH stimulation (McCabe, 2001). AHC patients are generally treated with glucocorticoids and mineralcorticoids. Indeed, the disorder is lethal if untreated. This is due to dehydration and electrolyte imbalance as a consequence of mineralcorticoid deficit and to reduced resistance to stress. The X-linked syndrome constantly associates with HHG, which is diagnosed in patients affected by AHC who survive beyond pubertal age thanks to an appropriate hormonal replacement therapy. HHG is caused by combined hypothalamic failure in gonadotropin-releasing hormone (GnRH) release and pituitary defect in the production of gonadotropin (Habiby et al., 1996). The onset of gonadotropin production is selectively impaired in patients affected by AHC-associated HHG during puberty, while no perturbations of the physiological postnatal transient activation of the hypothalamic-pituitary-gonadal axis are registered (Takahashi et al., 1997; Kaiserman et al., 1998).

Phenotypic evaluation of patients with contiguous gene syndromes involving AHC along with various combinations of glycerol kinase deficiency, Duchenne muscular dystrophy, ornithine transcarbamoyltransferase deficiency and mental retardation allowed to narrow the locus to Xp21.3-p21.2 (Hammond et al., 1985, Bartley et al., 1986, Francke et al., 1987; Goonewardena et al., 1989). The analysis of genes present in this region of the X chromosome led to the cloning of the DAX-1 gene, whose mutations (see Mutations above) are responsible for X-linked AHC/HHG (Zanaria et al.,

1994; Muscatelli et al., 1994). The identification of DAX-1 as the gene responsible for X-linked AHC (Zanaria et al., 1994) had important implications for the diagnosis of individuals and families affected by this condition.
From a study published in 2006 and aimed at investigating the prevalence of DAX-1 and SF-1 mutations in children and adults affected by primary adrenal failure of unknown aetiology, it was estimated that DAX-1 mutations were present in 58% (37 of 64) of 46, XY phenotypic boys exhibiting adrenal hypoplasia and in all boys (8 of 8) affected by HHG and with a family history reminiscent of adrenal failure in males (Lin et al., 2006).
DAX-1 deletions including both microdeletions within the coding sequence or promoter and very large deletions also involving adjacent genes were found in about one-third of AHC patients (Lin et al., 2006).

Dosage sensitive sex reversal (DSS)

Note

DSS is a genetic defect, whose severity is variable with a list of signs and symptoms ranging from female external genitalia, ambiguous external genitalia and failed testicular development to streak gonads, primary amenorrhea and immature uterus. Male-to-female sex reversal was observed in patients with duplications of the X chromosome short arm (Bardoni et al., 1994). Bardoni and colleagues demonstrated that it originated from the presence of two active copies of an Xp locus. Alterations at this locus represented one of the causes of sex reversal in patients with a normal 46,XY karyotype (Bardoni et al., 1994). The locus was termed DSS (Dosage Sensitive Sex reversal) and was localized to an Xp21 region of 60 kb adjacent to the AHC locus (Bardoni et al., 1994). The identification of males lacking the DSS locus indicated that it was not essential for testis differentiation, whereas it was proposed to participate in ovarian development and/or function as a link between the formation of ovary and testis (Bardoni et al., 1994).

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