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Review Article

Pendred Syndrome and Role of Pendrin on Thyroid Physiology

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Background: Pendred syndrome (PS) is an autosomal recessive disorder characterized by sensorineural hearing impairment, presence of goiter, and a partial defect in iodide organification (PIOD), which may be associated with insufficient thyroid hormone synthesis. Mutations in the *SLC26A4/PDS* gene are found in patients with PS. Goiter development and developments of hypothyroidism are variable and depend on nutritional iodide intake.

Moreover, PS may present with goiter, hypothyroidism, and a positive perchlorate test, a definite etiologic diagnosis is impossible without molecular diagnosis in individuals who have a concomitant hearing impairment.

Etiology: Pendred syndrome (OMIM 274600) occurs due to biallelic inactivating mutations in the Pendrin gene (PDS/SLC26A4), which encodes Pendrinprotein. The SLC26A4 gene has been mapped to chromosome 7q22.3 in 1996.

Epidemiology: The prevalence of Pendred syndrome has been estimated to be between 7.5 and 10 per 100,000 individuals. More importantly, Pendred syndrome accounts for to up to 10% of hereditary deafness cases.

Pathophysiology: Pendrin is mainly expressed in tissues as diverse as the thyroid, the inner ear, the kidney, airways, mammary gland, testis, placenta, endometrium and liver. The localization and specific function of pendrin particularly in the thyroid gland, inner ear and kidney are well described.

Keywords: Pendred, Thyroid, *SLC26A4/PDS* gene, hypothyroidism, recessive disorder

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Introduction

Pendred syndrome (PDS) was first described by Vaughan Pendred in 1896 (1), in a family in which two of five children were deaf mutes and had large goiters.Pendred's syndrome is one of the most common forms of syndromic deafness (2). PDS is estimated to account for 5% of childhood deafness and increases to 7% in adults since it is diagnosed merely after the presence of goiter (3-5). Pendred syndrome is an autosomal recessive disorder that is classically defined by the combination of sensorineural deafness/hearing impairment, goiter, and an incomplete or partial organification of iodide with variable effects upon thyroid hormone biosynthesis (6). The sensorineural deafness is the most important clinical sign of Pendred syndrome (2, 7). It is most commonly present at birth, but may only become apparent during childhood (2, 8). The hearing loss is typically bilateral, severe to profound, and prelingual (3). It may fluctuate and in some cases, patients presented with progressive and/or postlingual hearing impairment (4,5, 9). The deafness is associated with inner ear malformations that range from an enlargement of the endolymphatic system that can be detected as an enlarged vestibular aqueduct EVA to a cochlear malformation in which the coils of the cochlea are replaced by a single cavityin the apical regionknown as Mondini dysplasia (4, 10, 11). These malformations of the inner ear that are essential for the diagnosis of PDS can be detected by high-resolution computed tomography (CT) or magnetic resonance imaging (MRI)(10, 12, 13).

Etiology

Pendred syndrome(OMIM 274600) occurs due to biallelicinactivating mutations in the Pendrin gene (PDS/SLC26A4), which encodes Pendrin protein.The SLC26A4 gene has been mapped to chromosome 7q22.3 in 1996(12, 14, 15). This gene is organized in 21 coding exons and contains an open reading frame of 2343 bp. The predicted gene product,pendrin is a highly hydrophobic 780 amino acid protein(6, 16). Pendrin is an86kDa protein with 13 putative transmembranedomains with both the amino- and carboxy-terminilocated inside the cytosol(8, 17-19). It functions as a transmembrane anion transporter in the thyroid and in the inner ear. It is a multifunctional anion exchanger that has an affinity to chloride, iodide, bicarbonate, and other anions (14).To date, more than 100 mutations of the PDS gene have been shown to be associated with PDS (20, 21)

Mutations in the pendrin gene SLC26A4 have been reported as the molecular basis for Partial Iodide Organification Defect (PIOD). SCL26A4 mutations are causative for Pendred syndrome, which is characterized by a combination of sensorineural hearing loss and a PIOD, with varying degrees of severity in both clinical features(22, 23). In addition to Pendred syndrome, mutations of this gene are also responsible for non-syndromic recessive deafness (NSRD) with enlarged vestibular aqueduct (EVA), or Mondini dysplasia(24). Overall, SLC26A4 mutations may account for between 5 and 10% of patients with prelingual hearing loss(25, 26).

Epidemiology

The prevalence of Pendred syndrome has been estimated to be between7.5 and 10 per 100,000 individuals.More importantly, Pendred syndrome accounts for to up to 10% of hereditary deafness cases(2, 8). Thus, it could be considered the most frequent cause of syndromic deafness.Assumed its autosomal recessive mode of inheritance, the risk for inheritance from heterozygous parents is 25%(2, 8).

Pathophysiology:

Pendrin is mainly expressed in tissues as diverse asthe thyroid, the inner ear, the kidney, airways, mammary gland, testis, placenta, endometrium and liver. The localization and specific function of pendrinparticularly in the thyroid gland, inner ear and kidney are well described(17, 20, 27, 28).

Inner Ear

At the level of the inner ear, pendrin is found in the endolymphatic duct and sacwhere it functions as a chloride/bicarbonate exchanger(21, 29). Recent studies using the PDS/SLC26a4 knockout mouse revealed that pendrinplays an important part in the creation of endolymphatic composition, fluid resorption, acid-base balance, and generation of the endocochlear potential(15, 20, 27, 30, 31).

Kidneys

In the kidneys, Pendrin protein is located at or near the apical membrane of type B and non A non B intercalated cells of the cortical collecting ducts.Pendrin acts as a chloride/anion exchanger, which leads to bicarbonate secretion to the tubular lumen and chloride reabsorption(14, 32, 33). Therefore, it plays an important role in the regulation of blood pressureand fluid

balance(15, 34).Defects in Pendrin protein can cause metabolic alkalosis(14, 20, 35, 36).

Bronchial Epithelium

Pendrin is also expressed in the airway epithelium at the apical membrane of bronchial epithelial cells. It helps to regulate airway surface liquid thickness via its function as a Chloride/bicarbonate exchanger. The defective pendrin gene affects mucus production and may play a vital role in patients with asthma and COPD. It also functions as SCN/Cl exchanger that helps in the innate defense mechanism of mucosal surfaces by secreting SCN, which is an antioxidant to the lumen(14, 15).

The role of pendrin in the thyroid

The thyroid follicles form the functional units of the thyroid gland and are essential for normal synthesis of thyroid hormone(37). Iodide is actively transported into thyroid follicular cells at the basolateral membrane of thyroid follicular cells. This is mediated by the sodium-iodide symporter (NIS/SLC5A5)(38), in a process that is dependent on the sodium gradient generated by the Na/K-ATPase (39). At the apical membrane, iodide is released into the follicular lumen where it is oxidized at the cell-colloid interface by thyroperoxidase (TPO) in the presence of hydrogen peroxide (H_2O_2), a process referred to as organification. The follicular lumen contains large amounts of thyroglobulin (TG), the matrix for the synthesis of T4 and T3. In this reaction, catalyzed by TPO selected tyrosyl residues are iodinated within the TG. This results in the formation of mono- and di-iodotyrosines (MIT, DIT). In the subsequent coupling reaction, which is also catalyzed by TPO, two iodotyrosines are coupled to form either T4 (DIT + DIT) or T3 (DIT + MIT) (40). Iodinated TG is engulfed by pinocytosis into the follicular cells digested in lysosomes, and then thyroid hormones; T4 (80%) of secreted thyroid hormone and T3 (20%) are secreted into the bloodstream. Unused MIT and DIT are deiodinated by an intracellular iodotyrosinedehalogenase (DEHAL1) (41, 42), which results in the release of iodide which is then recycled and used for thyroid hormone synthesis(37).

The mechanisms regulating iodide uptake at the basolateral membrane of thyrocytesare well known (38), but less is known about the efflux of iodide at the apical membrane. At the apical membrane iodide crosses the membrane simply because of the electrochemical gradient between the

cytosol and the follicular lumen. Autoradiography studies reveal that iodide first accumulates in the cytosol before it is transported into the follicle, and that apical iodide efflux is rapidly up-regulated by TSH. The concept that iodide crosses the apical membrane through a specific channel or transporter is based on several observations(43). Electrophysiological studies characterizing iodide efflux and performed with thyroid cell membrane vesicles suggested the existence of two apical iodide transporters that could be involved in iodide efflux(43, 44). One of these channels has a high permeability and specificity for iodide (Km_70 mM), while the second channel has a much lower affinity for iodide (Km _33 mM) (44). Several findings suggested that pendrin could be involved in mediating iodide transport into the follicular lumen and correspond to one of these channels(43). The expression of pendrin(PDS/SLC26A4) at the apical membrane of thyrocytes and its ability to transport iodide (iodide efflux) to the follicular lumen and/or maintenance of the follicular pH, suggest that pendrin maybe one of these iodide channels that regulate apical iodide efflux in the thyroid(29, 45, 46). Pendrin was formerly proposed to function as a sulfate transporter based on its sequence homology to known sulfate transporters and the presence of a sulfate transporter motif(8). However, the initial functional studies of pendrin in Xenopus oocytes demonstrated that pendrin is unable to transport sulfate but instead mediates uptake of iodide and chloride in a sodium-independent manner.Experimental data has supported the role of pendrinin its ability to mediate iodide efflux (47).

A number of studies using heterologous expression systems, including non-polarizedand polarized cells have demonstrated that iodide efflux is much higher in non-polarized Chinese hamster ovary cells stably expressing both NIS (Na Iodide Symporter) and pendrin compared to cells expressing NIS alone. Iodide efflux is dependent on continuous iodide uptake to maintain a high intracellular concentration (46, 47).

In time-course experiments measuring iodide release, human embryonic kidney cells transfected with NIS alone demonstrate a relatively slow, time-dependent iodide efflux, whereas cells expressing wild-type pendrin and NIS exhibit a very rapid efflux of iodide.

Electrophysiological studies using transfected COS-7 cells with pendrin have revealed that iodide efflux are more efficient

with higher extracellular chloride concentrations. These experiments suggest the possibility of iodide /chloride exchange(46).

Findings obtained in polarized MDCK (Madin–Darby canine kidney) cells also support the concept that pendrin plays a role in facilitating vectorial iodide transport at the apical membrane(20, 45).

At the molecular level, a defect in the Pendrin gene (SLC26A4) usually leads to the partial impairment of thyroid organification. Patients with biallelicmutations in the SLC26A4 gene(Pendred syndrome) have partial iodide organification defects (PIOD). This may be explained by an impaired iodide transport, and they can develop a goiter, most likely as a compensatory mechanism because of inefficient thyroid hormone synthesis (14, 15, 21, 48, 49).

Goiter development and hypothyroidism vary among affected individuals and seem to be partially dependent on nutritional iodide intake(29).

The impaired iodide organification defect observed in patients with biallelic SLC26A4 mutations is consistent with the potential role of pendrinas an apical iodide efflux channel in thyroid hormone biosynthesis(50). Nutritional iodide intake is an important modifier of the thyroid phenotype in PDS. With sufficient dietary iodide, about 90% of patients are clinically and biochemically euthyroid. In the remaining 10% with elevated TSH level, goiter is always present (50). The onset and presentation of goiter varies within and between families. It usually develops during childhood and ranges from no enlargement of the thyroid to the development of large goiters(51, 52). When evaluated with a perchlorate test, all patients with biallelic mutations in the SLC26A4 gene have a partial iodide organification defect, irrespective of the presence or absence of a goiter(53). The perchlorate test determines whether iodide is organified normally into thyroglobulin (TG)(54). Normally, less than 10% of radioiodide accumulated in thyrocytes are not rapidly organifiedinto thyroglobulin for the purpose of thyroid hormone synthesis. In contrast, patients with Pendred syndrome loose more than 15% thus indicating an impaired iodide organification(4, 7). However, the organification defect is only partial (7, 45, 53). This differs, for example, from the situation in patients who are homozygous for complete lyinactivating mutations in

thyroid peroxidase that result in a total iodide organification defect(37).

Despite the presence of a partial iodide organification defect, patients with Pendred syndromeonly develop hypothyroidism under conditions of a low nutritional iodide intake (48, 51, 55, 56). For example, patients from Japan and Korea (countries with a high iodide intake) with documented biallelic mutations in the SLC26A4 gene are always euthyroid (57, 58).

In contrast, patients with Pendred syndrome from iodide-deficient regions may present with congenital hypothyroidism (59). Many patients have elevated serum levels of thyroglobulin, a finding that correlates with goiter size (60, 61). It should also be noted that phenocopies of Pendred syndrome, i.e. deafness due to another etiologic cause in combination with goiter due to iodide deficiency, have been reported(16).

Of note, EVA is associated with syndromic and non-syndromicforms of sensorineural deafness(53). The diagnosis of Pendred syndrome in patients with EVA can be formally establishedby the demonstration of an iodide organification defect through the perchlorate test, while goiter is amore variable sign and dependent on iodide intake(20). However, it has been recently demonstrated that some families with features of PDS do not have the inner ear malformations or mutations in the PDS gene. This condition has been named as “pseudo-Pendred syndrome” (pseudo-PDS), and has been hypothesized to be of autoimmune origin (12, 62, 63).

On the other hand, some case reports have shown an association between congenital goitrous hypothyroidism and sensor ineural deafness with mutations in the thyroid peroxidase (TPO)

gene (62, 64). Accordingly, a TPO defect along with hearing impairment might be considered in the etiology of pseudo-PDS(12).

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