Cellular Physiology and Biochemistry

Cell Physiol Biochem 2013;32(suppl 1):1-13
DOI: 10.1159/000356620
Published online: December 18, 2013
Accepted: December 06, 2013

1421-9778/13/0327-0001$38.00/0

Review

Synopsis of the 48th Annual Meeting of the Lake Cumberland Biological Transport Group and the Second Biannual Meeting of the Pendrin Consortium

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Key Words
Pendred syndrome • SLC26A4 • Ion transport • Epithelium • Cell volume regulation

Abstract
Ion transporters are the molecular basis for ion homeostasis of the cell and the whole organism. The anion exchanger pendrin is only one of a number of examples where a complete or partial loss of function and/or deregulation of expression of ion transporters may lead or contribute to pathological conditions in humans. A complete understanding of the function of ion transporters in health and disease may pave the way for the identification of new and focused therapeutic approaches. Exchange of knowledge and connectivity between the experts in the field of transport physiology is essential in facing these challenging tasks. The Lake Cumberland Biological Transport Group and the Pendrin Consortium are examples of scientific forums where investigators combine their efforts towards a better understanding of molecular pathophysiology of ion transport. This issue discusses the versatility of ion transporters involved in the regulation of cellular volume and other functions, such as the solute carrier (SLC) 12A gene family members *SLC12A4-7*, encoding the Na^+-independent cation-chloride cotransporters commonly known as the K^+-Cl^- cotransporters KCC1-4, and the betaine/γ-aminobutyric acid transport system (BGT1, SLC6A12), just to name a few. The issue further addresses the pathophysiology of intestinal and respiratory epithelia and related therapeutic tools and techniques to investigate interactions between proteins and proteins and small compounds. Finally, the current knowledge and new findings on the expression, regulation and function of pendrin (SLC26A4) in the inner ear, kidney, airways and blood platelets are presented.

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Introduction

The Lake Cumberland Biological Transport Group (http://www.cumberlandbio.org/) was founded in 1966 and includes scientists interested in tissue and cellular ion transport. The Meeting of the Lake Cumberland Biological Transport Group has been held annually since then at the Lake Cumberland State Resort Park in Jamestown, Kentucky, USA. The group is affiliated with the American Physiological Society.

The 48th Annual Meeting of the Lake Cumberland Biological Transport Group was held from June 16th through June 18th, 2013, and was convened by Silvia Dossena (Chair), Norma Adragna (Vice-Chair) and Eleanor Lederer (Chair Emeritus).

The Pendrin Consortium was founded two years ago as a spin-off from an exploratory workshop funded by the European Science Foundation (ESF) in Leogang, Austria [1]. The members planned to meet biannually since then, alternating the location of the meeting between Europe and the USA. The Pendrin Consortium is an international group of scientists that joined their efforts on the common theme of the "Proteomics, Epigenetics, and Pharmacogenetics of Pendrin" (PEPP). Pendrin (SLC26A4, PDS) is a transport protein whose malfunction or up regulation may be associated with the onset or exacerbation of a broad spectrum of diseases, including syndromic or non-syndromic deafness, hypertension, asthma and chronic obstructive pulmonary disease (COPD). "Proteomics" within this collaboration refers to how the pendrin protein alone or in conjunction with other proteins impacts the observed function; "epigenetics" refers to how inherited genetic information and genetic information not encoded in the DNA sequence translates to variations in the overall function of pendrin; and finally, "pharmacogenetics" explores how genetic differences in the pendrin gene could be translated into differences in the way that possible drugs affect pendrin function [1].

The Second Biannual Meeting of the Pendrin Consortium was held from June 19th through June 21st, 2013, at the Lake Cumberland State Park, in Jamestown, Kentucky USA, and was convened by Silvia Dossena (Chair), Charity Nofziger (Vice-Chair) and Markus Paulmichl (Chair Emeritus).

The organizers of the Second Biannual Meeting of the Pendrin Consortium are also members of the Lake Cumberland Biological Transport Group. Holding the two meetings in the same location and in close temporal succession allowed the organizers to extend the invitation to the Second Biannual Meeting of the Pendrin Consortium also to the members of the Lake Cumberland Biological Transport Group. This allowed scientific exchange between the two groups in terms of critical discussion and opportunity for collaboration.

Aims of the meetings

The Lake Cumberland Biological Transport Group Meeting is an excellent opportunity for principal investigators, post-doctoral fellows and graduate students to present either published data or work in progress with the aims of receiving feedback and encouraging open discussion. Cell biology, physiology, molecular biology and biochemistry centered on the theme of biological transport are the main topics of the meeting. This forum also provides trainees with future job opportunities and principal investigators with opportunities to find qualified trainees. Likewise, the broad diversity of themes facilitates collaborations within and between institutions, thus increasing the chances for scientific discovery, funding opportunities and publications, all taking place in a collegial atmosphere.

The aims of the Meetings of the Pendrin Consortium are to extend, fortify and intensify the scientific exchange and connectivity between the members, in the common effort of a complete understanding of the role of pendrin in health and disease. Extension of the existing collaboration between the Pendrin Consortium members would add significant momentum to the knowledge-transfer between the different groups and will aid in the successful strengthening, fortification, and sustenance of the research activity. Ultimate

goals of the Pendrin Consortium are (i) to identify possible therapeutic approaches for diseases linked to pendrin loss or reduction of function and (ii) understanding if reduction of pendrin function and/or expression can be regarded as a novel therapeutic strategy for the treatment of complex pathologies such as hypertension, asthma and COPD.

Scientific Content of the meetings

The 48th Annual Meeting of the Lake Cumberland Biological Transport Group comprised a total of 26 scientific talks distributed in ten sessions which covered a wide range of topics including kidney, lung and liver disease, membrane transport proteins trafficking, regulation and structure-function relationships, novel drug discovery, signal transduction and protein-protein interactions.

The Second Biannual Meeting of the Pendrin Consortium included a total of 14 scientific talks divided in five sessions, focusing on pendrin and ranging from the functional and molecular characterization of this protein to its transcriptional regulation and trafficking, and including studies on mouse models for its dysfunction. Communications on preliminary clinical investigations paving the way for future genetic and molecular studies were also solicited.

The participants at either one or both meetings were invited to contribute original papers or reviews focusing on the topics – or closely related topics – presented at the conference. These contributions are collected in the current special issue, which is composed of 13 original manuscripts and 5 reviews. Owing to their main topics, the papers have been divided into the following sections:

a) The 48th Annual Meeting of the Lake Cumberland Biological Transport Group: This section includes 7 original papers and 3 reviews, distributed in the following subsections:
- Versatility of ion transporters involved in the regulation of cellular volume
- Pathophysiology of intestinal and respiratory epithelia and related therapeutic tools
- Technical approaches of general interest

b) The Second Biannual Meeting of the Pendrin Consortium: This section includes 6 original papers and 2 reviews, distributed in the following subsections:
- The inner ear
- The kidney
- The airways
- Non-conventional pendrin expression sites
- Transcriptional regulation of pendrin

a) The 48th Annual Meeting of the Lake Cumberland Biological Transport Group

This section concerns the physiology of ion transporters involved in functions as diverse as the regulation of cellular volume, transepithelial ion fluxes and regulation of neuronal excitability, just to name a few.

Versatility of ion transporters involved in the regulation of cellular volume

Volume regulation is a ubiquitous function essential to cell survival. When exposed to an anisosmotic medium, cells swell or shrink in response to an osmotically-driven water influx or efflux, respectively. To restore the original volume, swollen cells extrude ions, typically K^+ and Cl^-, therefore inducing an efflux of water. In contrast, after cell shrinkage, cells accumulate ions or other osmotically active solutes [2]. It is becoming increasingly evident that ion transporters involved in the regulation of cellular volume are functionally versatile

molecules and may be involved in various homeostatic mechanisms. Some examples will be given in the following.

The solute carrier (SLC) 12A gene family comprises at least seven branches of homologous genes, *i.e. SLC12A1-7*, encoding Na^+-dependent or Na^+-independent cation-chloride cotransporters (CCC). The *SLC12A1-3* genes encode the Na^+-dependent K^+-$2Cl^-$ cotransporters NKCC2 and NKCC1 and the Na^+-Cl^- cotransporter NCC, respectively [3]. The *SLC12A4-7* genes encode the Na^+-independent cation-chloride cotransporters, commonly known as the K^+-Cl^- cotransporters KCC1-4, and are the focus of a comprehensive review presented by Gagnon and Di Fulvio [4]. KCCs are widely distributed, extrude Cl^- ions from the cell by exploiting the chemical gradient of K^+ and play a major role in the regulatory volume decrease after cell swelling or in maintaining a low intracellular concentration of Cl^-, a major prerequisite in depression of neuronal excitability by inhibitory neurotransmitters. Although the genes encoding the NCCs in mammals are only four, the number of transcripts due to alternative splicing and translation from alternative initiation sites is stunning, and led the authors to formulate the fascinating hypothesis of the existence of several protein isoforms with multiple functions – some of which perhaps are still undiscovered [4].

Kempson and colleagues give an overview on the functional roles of another versatile transporter, the betaine (trimethylglycine)/γ-aminobutyric acid (GABA) transport system (BGT1, SLC6A12) [5]. In the kidney, BGT1 is localized in the basolateral membrane and transports betaine with both Na^+ and Cl^- ions. BGT1 is upregulated by hyperosmolarity and induces accumulation of betaine in the intracellular environment, protecting the cell from the hyperosmolarity of the inner medulla. In contrast, liver BGT1 is active under iso-osmotic conditions, and betaine serves mainly as a methyl donor and prevents homocysteine toxicity improving methionine synthesis. Abnormal methionine metabolism in the liver is one of the consequences of alcohol abuse and appears to be linked to the pathogenesis of alcoholic liver disease. Based on these observations, the authors suggest that dietary betaine supplementation may have a number of potential useful applications, including treatment of nonalcoholic fatty liver, alcohol-induced liver damage and hyperhomocysteinemia, a risk factor for atherosclerotic disease [5].

ICln (nucleotide-sensitive chloride current protein) is an excellent example of a multifunctional ion channel. Being initially described as critically involved in the activation of the swelling-induced Cl^- current IClswell [6], ICln was later discovered to interact with a number of different proteins and be involved in multiple functions, including regulation of cellular morphology, platelet activation, angiogenesis, cell migration and RNA processing [7]. In this issue, Dossena et al. illustrate a strategy – the Operon-Based Partner Protein Quest, OBPQ – that was used to identify some of the ICln partner proteins [8], and can be applied to other membrane transporters [9]. This strategy is based on the evidence that, in the nematode *C. elegans*, genes organized in the same operon are spatially and temporally co-expressed and may therefore encode functional or molecular partner proteins. This concept can be successfully translated to the human system and lead to the identification of protein-protein interactions otherwise difficult to predict.

Regulation of cellular volume can be altered in pathological states. In an elegant series of experiments performed by Blanco and colleagues, the biophysical mechanisms and kinetics of cell water volume changes elicited by ammonia (NH_3) and ammonium (NH_4^+) in neuronal cell lines derived from mouse [10] are characterized. This research is directly relevant to the brain edema associated with hyperammonemic syndromes and acute liver failure. The authors provide experimental evidence showing that *isosmotic* NH_4Cl solutions result in swelling, and that ionization of NH_3 inside the cell, rather than direct transport of NH_4^+ into the cell, is most responsible for said swelling.

Cell volume regulation is a homeostatic function conserved throughout evolution and also occurs in jellyfish [11]. Two original papers from the group of La Spada focus on the features of the stinging cells (nematocytes) from *Pelagia noctiluca*, a Cnidarian Scyphazoan jellyfish indigenous to the Straight of Messina, Italy. In the first study, Morabito et al. investigate how alterations in seawater pH vary the ability of nematocytes to regulate their

volume, as well as to discharge their toxin-containing venom [12]. These authors propose the nematocyte and its homeostatic functions as novel bioindicators for the quality of the marine environment.

In a second series of experiments, Morabito and colleagues begin to unravel the mechanisms by which *P. noctiluca* crude venom modulates ion transport in human erythrocytes [13]. In particular, the authors provide evidences implicating modulation of the Band 3 anion exchanger and the potassium chloride cotransporter, KCC, possibly *via* induction of oxidative stress. These experiments underscore that transporters typically involved in the regulation of cellular volume in mammalian cells can be molecular targets of toxins from marine animals.

Pathophysiology of intestinal and respiratory epithelia and related therapeutic tools

Substances present in the environment, such as nutrients and pollutants, may positively or negatively affect the biology and function of tissues in contact with the external milieu, such as the intestinal and respiratory epithelia.

The gut microbiota or flora, is the collection of all the microorganisms that naturally inhabit the intestine, and its composition can be altered by diet or pathological state [14]. In fact, the anti-diarrheal effect of carrot soup was documented over 100 years ago by an Austrian pediatrician, Ernst Moro [15]. With the continuously rising need for alternative approaches against gastrointestinal bacteria infections, Engevik and colleagues initiated studies regarding an oligosaccharide derivative from carrots, galursan HF 7K (GHF7K) and its potential as such an alternative. They show that the composition of the gut microbiota in mice was favorably altered by dietary supplementation with GHF7K. Accompanying changes in the ion composition of the intestinal fluid were also documented [16]. In a separate study, the same group showed that loss of Na^+/H^+ exchanger (NHE) 2 activity, which resulted in an acidic intestinal lumen pH, ultimately culminated in changes in gut microbiota composition [17]. These investigations strengthen a cause-effect relationship between ion transport and microbiota in the gut.

Bazzini et al. determined the consequences of cigarette smoke extract (CSE) exposure in human bronchial epithelial cells (16-HBE), a model for studying the effects of tobacco smoke *in vivo* and *in vitro*. CSE increased cell mortality and induced oxidative stress, as evidenced by a decrease in reduced glutathione and increase in reactive oxygen species intracellular concentrations. These effects could be reversed by the mucolitic drug S-carboximethilcysteine lysine salt (S-CMC-Lys), that was proposed as an efficient therapeutic tool to counteract CSE-induced oxidative cellular injuries [18].

Technical approaches of general interest

Tools for predicting or detecting interactions between proteins and proteins and small compounds may help elucidate the structure-function relation of membrane transporters and, besides solving a specific research issue, can be of general interest. The OBPQ described earlier is one of such approaches [9].

In addition, Dorney et al. [19] presented the optimization of a powerful yet underserved technique, the Surface-Enhanced Raman Spectroscopy (SERS). By SERS, the authors determined the concentration (in the sub-picomolar range) of the quaternary benzo-phenanthridine alkaloid chelerytrine (CET) within different subcellular compartments in human lens epithelial cells. Due to its ability to trigger apoptosis and circumvent multi-drug resistance mechanisms, CET is acknowledged as a potential anti-cancer effector. Moreover, CET is a known inhibitor of the Na^+/K^+ pump. Accordingly, CET was found to be recruited at the plasma membrane level, possibly *via* binding to the Na^+/K^+ pump. Interestingly, the method presented can be adapted for efficient and sensitive detection of other small compounds with visible absorption resonances within the complex cellular matrix, without the use of fluorescent or radiochemical probes.

b) The Second Biannual Meeting of the Pendrin Consortium

This section focuses on the functional and molecular characterization of the anion exchanger pendrin and its role in physiological and pathological conditions.

Pendrin was firstly cloned in 1997 [20] and identified as the molecular entity leading, when mutated, to Pendred syndrome, a pathological condition described 100 years earlier as an association between deafness and goiter not due to environmental factors [21]. Later, functional studies established that pendrin is an electroneutral anion exchanger capable of transporting a broad range of monovalent anions, including iodide, chloride, bicarbonate, thiocyanate, hydroxide and formate, but with no affinity for divalent ions such as sulfate [22]. Pendrin is expressed on the apical aspect of a variety of epithelial cells, being particularly abundant in the thyroid. The function of pendrin in the thyroid is controversially discussed [23], but it is common opinion that this transporter is responsible for the iodide efflux from the thyrocyte to the follicular lumen, and thereby participates in the organification of iodide during the process of thyroid hormones synthesis. The expression and function of pendrin in other organs such as the inner ear, kidney and airways will be discussed in detail in the following.

The inner ear

In the inner ear, pendrin was found in specific subsets of non-sensory cells within the cochlea, endolymphatic duct and sac and vestibular labyrinth, where it functions as a Cl^-/HCO_3^- exchanger and controls the pH and volume of the endolymph [24]. In the last ten years, the work of Wangemann and colleagues illuminated the role of pendrin in the physiology of development of the inner ear [24-34]. Mouse models allowed tremendous advances in this field [35]. In this issue, Prof. Wangemann provides an overview of the currently existing mouse models for pendrin dysfunction and their characteristics [36], with specific regard to the inner ear. Pendrin knock-out mice give insights on the pathological consequences of a complete lack of pendrin expression [37, 38], while knock-in [39] and N-ethyl-N-nitrosourea (ENU) mutagenesis-induced [40] mice represent models for expression of pendrin allelic variants with lack or reduction of function. Interestingly, mouse models for lack of pendrin expression specifically in the endolymphatic sac [41], or in the cochlea and the vestibular labyrinth [42] were recently developed and characterized. These studies showed that pendrin expression is only required during a critical time period during embryonic development, and that maintenance of hearing without pendrin in a fully developed inner ear is possible. These findings suggest that a temporally and spatially limited therapy directed to the endolymphatic sac and focused on the prenatal phase of development can restore normal hearing in patients with deafness linked to pendrin mutations [36].

Mutations in the pendrin gene may be responsible for sensorineural hearing loss in the context of two distinct pathological conditions, *i.e.* Pendred syndrome and non-syndromic enlarged vestibular aqueduct (EVA). Pendred syndrome is an autosomal recessive disease where deafness is accompanied by a partial iodide organification defect at the level of the thyroid. This disorder is disclosed by a positive perchlorate discharge test, and may lead to subclinical or overt hypothyroidism with or without goiter. Pendred syndrome is usually associated with homozygous or compound heterozygous biallelic mutations in the pendrin gene, while non-syndromic EVA has been found in association with one, two or no pendrin mutations [22]. Common radiological findings at the level of the inner ear associated with pendrin mutations include EVA and Mondini's dysplasia.

In this issue, Roesch and collaborators reviewed temporal bone computed tomography scans of 75 patients having severe sensorineural hearing loss, with ages ranging from 13 months to 84 years [43]. All patients received cochlear implantation, either on one side or both, at the General Hospital of Salzburg, Austria, between years 2009 and 2011. In those patients with inner ear malformations consistent with pendrin malfunction, sequencing of the pendrin gene and functional characterization of possible pendrin allelic variants [44] will confirm or exclude pendrin mutations as the genetic cause of the observed deafness.

Definite diagnosis of Pendred syndrome will require careful assessment of thyroid function.

The incidence of Pendred syndrome is difficult to assess and has been evaluated between 7.5-10 in 100,000 newborns [45], with a broad spectrum of mutations that may differ between distinct populations [46]. The incidence and type of pendrin mutations in the Austrian deaf population is currently unknown. The approach of Roesch et al. [43] will prospectively allow the recruitment of a sufficient number of patients that will represent a cohort for studying Pendred syndrome/non syndromic EVA in the region of Salzburg. The exact diagnosis and identification of the genetic cause of deafness is essential in order to properly assist the patient and is extremely important to infer the progression of the disease, or – in case of syndromic deafness – the possible involvement of other organs. Despite the lack of specific therapies targeting the mutated pendrin gene or protein, identification of pendrin mutations *via* sequencing of the pendrin gene are of upmost importance to (i) exclude other genetic or environmental causes of deafness for which a specific therapy may be available, (ii) predict a possible worsening of deafness in case of moderate or fluctuating residual hearing, (iii) highlight the importance of monitoring thyroid function after puberty and (iv) assist families with genetic counseling by predicting the probability that deafness will occur in the next generation.

The kidney

In the kidney, pendrin is expressed on the apical membrane of non-alpha intercalated cells of the distal cortical segments of the nephron, where it plays a major role in bicarbonate secretion [38, 47] and chloride reabsorption [48], and contributes to mineralocorticoid-induced hypertension [49]. Despite the absence of any kidney phenotype in Pendred syndrome patients and mouse models in basal conditions, pendrin knock-out mice become hypotensive under NaCl restriction [48], and show severe salt wasting, increased urine output, profound volume depletion, renal failure, and metabolic alkalosis in the setting of a concomitant lack of function of other salt-reabsorbing transporters (such as the thiazide-sensitive Na^+-Cl^- cotransporter NCC) [50]. These observations led to the hypothesis that NCC and pendrin may compensate for the loss of each other, masking their respective roles in salt reabsorption [50]. In line with this hypothesis, Xu and collaborators generated NCC/carbonic anhydrase II (CAII) double knock-out mice by crossing mice with single deletion of NCC and CAII [51]. In NCC and CAII single knock-out mice, pendrin expression was significantly upregulated [52] and reduced [53], respectively. The NCC/CAII double knock-out mice displayed significant downregulation of pendrin, along with polyuria and salt wasting. Interestingly, the inability to concentrate urine was associated with defective trafficking of the water channel aquaporin 2 (AQP2). Based on these evidences, the authors suggested that targeted inhibition of NCC and pendrin may provide a strong diuretic regimen for the treatment of fluid overload in patients with congestive heart failure, nephrotic syndrome, diuretic resistance and generalized edema [50, 51]. On the other hand, these studies highlight that thiazide therapy in Pendred syndrome patients may lead to severe adverse reactions [54].

From these and other studies, it is becoming increasingly evident that, in the kidney, salt and water reabsorption requires a tight interplay between pendrin and ion [55] and water [50, 51] channels, even if not expressed in the same cell type. Interestingly, pendrin was recently found to co-localize with aquaporin 5 (AQP5) [56]. In line with their previous findings, Procino et al. elicited a series of experiments concerning a possible regulatory relationship between pendrin and AQP5 in type-B intercalated cells within the context of chronic potassium depletion, a pathological state that increases renal bicarbonate reabsorption and leads to metabolic alkalosis and decreased pendrin expression [57]. The authors show for the first time that along with pendrin, AQP5 expression also decreases following long-term potassium depletion. While overexpression of AQP5 did not alter pendrin function, trafficking of the two proteins to different subcellular locals was identical. The authors suggest that Cl^- influx and water transport *via* pendrin and AQP5, respectively, may be a mechanism by which type-B intercalated cells detect the external osmolarity.

The airways

In the airways, pendrin is believed to function mainly as Cl^-/HCO_3^- exchanger and play a role in controlling the airway surface liquid thickness, mucus production and antimicrobial activity [58-60]. While in the inner ear and thyroid it is the loss or reduction of function of pendrin that leads to pathological phenotypes, at the level of the respiratory epithelium it is an increased expression and/or activity of the transporter that may be noxious. Currently, very little is known about signaling events that may control pendrin function in the lung.

In this issue, Tamma et al. show that pendrin abundance in the plasma membrane of a continuous epithelial cell line from human lung (NCI H292) increased following short-term challenge with the adenylate cyclase activator, forskolin [61]. This is the first evidence that pendrin is regulated by the cAMP/protein kinase A (PKA) signal transduction cascade in the lung. The authors also demonstrate involvement of the RhoA GTPase, as well as changes in the polymerization state of the actin cytoskeleton in regards to forskolin –stimulated changes in pendrin trafficking in NCI H292 cells. All of the aforementioned findings were analyzed with fluorescence resonance energy transfer (FRET) in fixed and/or living cells, thereby underscoring the versatility of this technique.

Non-conventional pendrin expression sites

While being classically described as expressed in the thyroid [20, 62], inner ear [63, 64] and kidney [20, 47], pendrin transcript and/or protein were lately found in a variety of other tissues and organs, including placenta [65], Sertoli cells [66], endometrium [67], mammary gland [68], heart [69, 70], airways [59, 71], liver [72] and developing teeth [73]. In this Issue, Pelzl et al. provide the first evidence of pendrin expression in murine platelets [74]. Interestingly, pendrin abundance was upregulated by the mineralocorticoid deoxycorticosterone (DOCA) in a serum and glucocorticoid inducible kinase (SGK1) -dependent manner. It is plausible that pendrin activity may influence platelet functions, including volume regulation, intracellular pH, transport of peroxynitrite, and directly or indirectly affect platelet aggregation. Elucidating the physiological role of pendrin in platelets may help to explain the multiple adverse cardiovascular effects of mineralocorticoid excess, including heightened thrombogenicity [75], and deserves further investigation.

Transcriptional regulation of pendrin

The promoter of the pendrin gene contains pH, hormone and cytokine responsive elements. Acidic pH decreases and alkaline pH increases pendrin promoter activity in kidney and inner ear epithelial cell lines, but not in thyroid cells. Aldosterone reduces pendrin promoter activity in kidney, but has no effect in thyroid and inner ear cells [76].

Another hormone effective in controlling pendrin expression at the level of the kidney is uroguanylin (UGN), a peptide secreted from the intestines in response to oral salt intake. It was recently shown by Rozenfeld et al. that UGN decreases pendrin expression *via* transcriptional repression of the pendrin promoter *via* heat shock factor 1 [77]. In this issue, the same group presents a thorough review of UGN, as well as a related peptide hormone, guanylin, with respect to their classical natriuretic effects and non-classical roles in tissues ranging from the intestine and kidney to the airways, olfactory organs and reproductive system [78].

The pro-inflammatory cytokines interleukin 4 (IL-4) and interleukin-13 (IL-13), crucial in the development of bronchial asthma and COPD, have recently been shown to increase pendrin promoter activity and mRNA expression by a signal transducer and activator of transcription (STAT) 6-dependent mechanism [79]. In a follow-up from their previous findings, Vanoni and colleagues describe the differential contribution of two STAT6 DNA consensus motifs with respect to IL-4 stimulated increases in pendrin promoter activity [80]. A detailed knowledge of the mechanisms regulating pendrin expression may lead to the development of new therapeutic approaches for the control of blood pressure and respiratory distresses, and is therefore of upmost importance.

Conclusion

The multiple functions of ion transporters are essential in the homeostasis of the cell and the whole organism. Impairment or disregulation of ion transport is seen in several diseases, for which a detailed understanding of the molecular biology and physiology of the ion transporters involved may lead to development of focused and individualized therapeutic approaches. Exchange of knowledge and connectivity between the experts in this field is essential for facing these challenging tasks.

Acknowledgements

C. Nofziger is supported by the Roche Postdoc Fellowship Program (#231). We sincerely thank Elisabeth Mooslechner for her expert secretarial assistance. This work was further supported by the FWF (P18608) and the FP-7 (PIRSES-GA-2008-230661) grants to M. Paulmichl.

Conflicts of Interest

There are no conflicts of interest or disclosures.

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