EPITHELIAL ANION TRANSPORT IN HEALTH AND DISEASE: THE ROLE OF THE SLC26 TRANSPORTERS FAMILY
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EPITHELIAL ANION TRANSPORT IN HEALTH AND DISEASE: THE ROLE OF THE SLC26 TRANSPORTERS FAMILY
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Editors: Derek J. Chadwick (Organizer) and Jamie Goode

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In introducing this symposium, I am expecting that this will be an interesting meeting for three reasons. First, I have much to learn. Secondly, this is an interesting family of transporters, because there are multiple members, there is rich diversity, and there are some common themes. Thirdly, this is a small meeting which should permit some excellent discussion.

I am not an expert on the SLC26 family, so what I can say by way of introduction is quite limited. Instead, I'll highlight what I would like to learn from this meeting. First, how do these channels work? Are they electrically conductive? Or are they neutral transporters? If they are conductive, what is their relationship to ion channels? I would like to know how selectivity is determined. As I look at some of the literature, the issues of selectivity should prove very interesting. I would also like to learn something about how this family has evolved. There are multiple members and we may learn something if we look at these transporters through evolution.

The second main question I would like to address is how they contribute to normal physiology, in many different epithelia. What are the common threads and what is unique? If you transplanted one of these transporters into a different place, would it adopt new functions depending on its new home? Or are the functions all intrinsic to the protein?

Third, I hope to learn more about how loss of their function disrupts physiology. What is the pathophysiology associated with loss or mutation? If we understand this better, might it allow us to do something about disease? These are the main things I would like to learn from this meeting.

As I looked through the history of the Novartis Foundation, I came across the following quote from Lord Beveridge, made at the inauguration of the Foundation in 1949. He said, ‘This place itself is not a laboratory for mixing compounds, but we do mean to make it a laboratory for mixing scientists’. So I hope we’ll mix it up, have a good time, and learn much over the next few days.
Overview of the SLC26 family and associated diseases

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Abstract. In the late 1990s the SLC26 family of anion exchangers emerged as the second, structurally distinct gene family capable of similar transport functions as the classical SLC4 or anion exchanger (AE) gene family. The observations leading to the characterization of the SLC26 family were firmly based on research on rare human diseases and aided by comparison to Caenorhabditis elegans. SLC26A1, or rat sulphate/anion transporter 1 (Sat1), was the first gene cloned in mammals, but not characterized in humans until the year 2000. Three rare recessive diseases in humans, namely diastrophic dysplasia (cartilage disorder resulting in growth retardation), congenital chloride diarrhoea (anion exchange disorder of the intestine) and Pendred syndrome (deafness with thyroid disorder) turned out to be caused by the highly related genes SLC26A2 (first called DTDST), SLC26A3 (first called CLD or DRA) and SLC26A4 (first called PDS), respectively. Subsequently, others and our laboratory cloned prestin, a cochlear motor protein gene (SLC26A5), a putative pancreatic anion transporter (SLC26A6), and SLC26A7–SLC26A11. Some SLC26 family members show highly specific tissue expression patterns, others are widely expressed. The SLC26 exchangers are capable of transporting, with different affinities, at least the chloride, iodide, sulfate, bicarbonate, hydroxyl, oxalate and formate anions, and have distinct anion specificity profiles.


Transport of small molecules across lipid membranes is a fundamental function of all cellular organisms. Hundreds of proteins with specialized transport capabilities are expressed in different tissues of multicellular organisms, and indeed in different domains of membranes in individual cells. The transporter proteins come in families, with different members sharing structural similarities but often with distinct properties and physiological functions that may or may not be interchangeable. Distinct expression patterns in different tissues also suggest that the corresponding genes have highly specialized regulatory elements, in spite of high similarity of coding sequences. Finally, just a few changes in protein sequences may cause radical differences in the transport properties. The SLC26 family of anion exchangers provides examples of a wide spectrum of all these features, and
is largely uncharacterized. This is not surprising, considering that most members of the whole gene and protein family were described only a few years ago. Many transporter proteins were first isolated based on their functional properties, the discovery of the SLC26 gene family has been driven by human disease gene cloning and thereafter genomic approaches, based on the homology of the gene family and availability of whole genome sequences. At the beginning of this odyssey, only one gene belonging to the SLC26 gene family was known in mammals, the rat sulphate anion transporter 1 (Sat1) gene. The next three SLC26 family members were identified by positional cloning of rare recessive human disease genes (Hästbacka et al 1994, Höglund et al 1996, Everett et al 1997) even though one of them, SLC26A3, had been first cloned as a suggested tumour suppressor gene (Schweinfest et al 1993). One gene was first characterized in gerbil rather than human based on its function, motor activity in cochlear cells of the inner ear (Zheng et al 2000). Finally, all the remaining five currently known SLC26 genes were identified by a genomic homology-driven approach in human (Lohi et al 2000, 2002) and in parallel, by other approaches (Waldegger et al 2001, Toure et al 2001, Vincourt et al 2002, 2003, Mount & Romero 2004). The nomenclature of this gene family follows the convention of other solute carrier genes, starting with SLC, followed by the family number and an A separating the individual gene number. The individual members of the SLC26 family got their number identities in July 2000 (for SLC26A1 to A6) and in January 2001 (for SLC26A7 to A11, based on the full or partial human cDNA sequences AF331521 to AF331526 submitted from our laboratory) after exchange of email messages between the author of this review, Dr Elspeth Bruford of the HUGO Gene Nomenclature Committee, and nomenclature reviewers, including Dr Matthias A. Hediger. The entire human SLC26 gene family with references to the earliest GenBank sequence database entries and diseases associated with them are presented in Table 1. In the following paragraphs, I will briefly describe the discovery of the different SLC26 genes. I will only discuss the molecular cloning of each gene, even though the existence of such transporters had been demonstrated earlier by functional studies, and for considerations of space, I have omitted most of the literature related to their functions. Much additional information has already been revealed about their specific functional properties and physiological roles, and some of the first mouse knockout models are also available. More detailed reviews of these studies will be presented by other papers in this book.

SLC26A1

The rat liver canalicular sulfate transporter was the first gene of the SLC26 family to be molecularly characterized in mammals, cloned by Bissig et al (1994) and characterized by Markovich et al (1994). Curiously, the human gene remained