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Commentary

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The surprising complexity of K_{ATP} channel biology and of genetic diseases

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Structural heterogeneity of the K_{ATP} channels

The ATP-sensitive K^+ channel (K_{ATP}) is composed of a large macromolecular complex in which four inwardly rectifying K^+ channel (Kir6.1 or Kir6.2, referred to herein as Kir6.x) subunits form a central pore surrounded by four regulatory sulphonylurea receptor (SUR) subunits (SUR1, SUR2A, or SUR2B) (1). Kir6.x and SUR assemble freely to form a functional K_{ATP} channel (Table 1) (1). The structural heterogeneity of the K_{ATP} channel leads to a huge variation of its functionality between and within different tissues. The diverse functions subserved by the K_{ATP} channels have been of increasing interest and reflect established roles such as in insulin secretion (2, 3) and newly identified functions such as controlling blood flow in the heart (4). Channelopathies of K_{ATP} channels have now become a focus because some of the diseases or syndromes have been found to be directly related to or caused by the mutations in subunits of K_{ATP} channels. Cantu syndrome (CS), for example, is one such disease characterized by gain-of-function (GoF) pathogenic variants in *ABCC9* (ATP Binding Cassette Subfamily C Member 9), and less commonly, in *KCNJ8* (Potassium Inwardly Rectifying Channel Subfamily J Member 8) (5). These genes encode SUR2 and Kir6.1 subunits, respectively of K_{ATP} channels. In this issue of the *JCI*, Colin Nichols and his team reported on their discovery that glibenclamide, a K_{ATP} channel (SUR) blocker, can reverse cardiac hypertrophy to correct some of the cardiovascular dysfunctions in CS and alleviate the symptoms of CS (6).

The complexity of CS and other genetic diseases

McClenaghan et al. (6) used a CS mouse model in which *ABCC9* or *KCNJ8* mutations were expressed in the smooth muscle cells (SMCs). In this model, the K_{ATP} channels in SMCs become overactive to recapitulate CS in the heart and vasculature. The apparent simplicity of mutations in the K_{ATP} channel subunits and of many other genetic diseases belies the complexity of their presentations. CS shares a property with many other genetic diseases where the mechanisms underlying the tissue complexities are not obvious. In the case of CS, for example, soft tissue and bone changes occur and how they arise mechanistically from the K_{ATP} channel mutations is unclear. Table 1 shows a compendium of K_{ATP} channel subunit composition by organ system and tissue and cell type, and reports on the related phenotypes in CS (5). We are, for example, still uncertain exactly why there is increased hair growth. How are all of these aspects of CS mechanistically linked to the mutations of the K_{ATP} channel subunits? A broad understanding of the molecular origins of the specific manifestations of CS is absent. However, our observations in CS are similar to those found in many other genetic diseases with components that develop over time and that probably arise indirectly from primary mutations. Examples are wide-ranging and could include autism in Timothy's syndrome, memory dysfunction in presenilin-1–linked Alzheimer's disease, the origins of complex gait dysfunctions in Parkin-dependent Parkinson's disease, or enhanced/excessive X-ROS signaling in Duchenne Muscular Dystrophy. These specific manifestations of known genetic diseases have much to do with the chain of biological changes that somehow depends on the primary mutation (including possible epigenetic consequences) of these diseases. While the changes are associated with the diseases, they also constitute a profound warning to us. It is important to acknowledge our incomplete understanding of genetic diseases and their complex consequences, which arise from a focused genetic anomaly. Such a situation

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Table 1. K_{ATP} subunit composition by system, organ, tissue, and cell type

System/organ/tissue/cell types			K_{ATP} composition	Phenotype in Cantu syndrome
Cardiovascular	Heart	Ventricle	Kir6.2/SUR2A (3, 8–10) Kir6.2/SUR2B (11) Kir6.1/Kir6.2/SUR1/SUR2A (10)	Congenital heart defects (PDA), cardiomegaly, pericardial effusion, arrhythmia, heart failure (5)
		Atrium	Kir6.2/SUR1 (9, 10) Kir6.2/SUR2B (10, 11)	
		Conduction system	Kir6.1/ Kir6.2/SUR2A (12)	
	Vessel	Vascular smooth muscle	Kir6.1/SUR2B (13)	Edema, pulmonary hypertension, dilated and tortuous arteries (5)
		Arterial endothelial cell	Kir6.1/ Kir6.2/SUR2B (14, 15)	
		Capillary endothelial cell	Kir6.1/Kir6.2/SUR2B (10, 13)	
		Brain pericyte	Kir6.1/SUR2 (16)	
		Descending vasa recta pericytes	Kir6.1/6.2/SUR2B (17)	
Nervous	Brain		Kir6.1/SUR1 (10) Kir6.1/Kir6.2/SUR1/SUR2 (18) Kir6.2/SUR2B (3, 11)	Headaches, seizure (5)
		Hippocampus pyramidal	Kir6.2/SUR1/SUR2 (8, 18) Kir6.1/SUR1 (18)	
		Hippocampus interneuron	Kir6.2/SUR1 (18)	
		Dorsal vagal neurons	Kir6.2/SUR1 (19)	
		Hypothalamus	Kir6.2/SUR1 (20)	
		Basal ganglia	Kir6.1/SUR1 (21) Kir6.2/SUR1 (22)	
Musculoskeletal		Skeletal muscle	Kir6.2/SUR2A (3, 8, 11, 23) Kir6.2/SUR1 (8, 23) Kir6.1/SUR2B (23) Kir6.1/Kir6.2/SUR2A (10)	Macrocephaly,joint hypermobility, hypotonia, Osteochondrodysplasia (5)
		Human periodontal ligament	Kir6.1/Kir6.2/SUR2 (24)	
		Osteocyte-like cell	SUR2 (25)	
Digestive		Colonic smooth muscle	Kir6.2/SUR2B (26, 27)	Constipation, delayed intestinal motility, gastro-esophageal reflux (5)
		Gastric smooth muscle	Kir6.1/SUR2B (10, 27, 28)	
		Interstitial cells of Cajia	Kir6.1/Kir6.2/SUR1 (28)	
Endocrine		Pancreatic islet beta cell	Kir6.2/SUR1 (3) Kir6.1/SUR1 (10)	Data not available (N/A)
		Chromaffin cells	Kir6.2 (29)	
		Pituitary gland	SUR (30)	
Urinary		Kidney	Kir6.2/SUR2B (8, 11) Kir6.1/SUR1/SUR2B (10)	N/A
		Urethral smooth muscle	Kir6.1/6.2/SUR2B (31)	
		Bladder smooth muscle	Kir6.2/SUR1, Kir6.2/SUR2B (32)	
Integumentary		Hair follicles	Kir6.1/Kir6.2/SUR1/SUR2B (33)	Hypertrichosis, wrinkle or loose skin(5)
		Skin	Kir6.1/Kir6.2/SUR2A (10)	
Respiratory		Lung	Kir6.2/SUR2B (8, 11) Kir6.1/SUR1/SUR2B (10)	Dyspnea, exercise intolerance, pulmonary hypertension, recurrent respiratory infection (5)
		Alveolar epithelial cells	Kir6.1/SUR2B (34)	
Immune		Spleen	Kir6.1/SUR1/SUR2B (10)	N/A
Reproductive		Myometrium	Kir6.1/SUR2B (35) Kir6.2/SUR1 (weak)(35)	Hypermenorrhea (5)

may mean that simple genetic corrections could constitute incomplete therapies, particularly when instituted late in the arc of the disease expression. We still need to be exquisitely careful when we attempt to make apparently simple and direct genetic corrections. As we improve our knowledge, though, we also need to develop useful treatments for affected individuals with known genetic diseases even if the corrections are incomplete.

Clinical implications

Adoption of any new therapeutic option necessitates minimal side effects. Sulfonylureas inhibit both SUR1 and SUR2 subunits, and therefore inhibit beta cell K_{ATP} channels, resulting in increased insulin secretion. Clinically, the most common side effect of sulfonylurea use is hypoglycemia, which would be a feared complication of initiating this therapy in nondiabetic patients. In the current study by McClenaghan et al. (6), the authors treated a CS mouse model with glibenclamide (Glyburide), a well-known and widely used medication with established FDA approval. Glibenclamide was well tolerated, even at the high doses required to reverse the cardiomyopathy. Treated mice experienced transient hypoglycemia, which resolved by the second day of therapy.

It was recently reported that an infant with CS (*ABCC9* variant) and severe pulmonary hypertension was initiated on glibenclamide after failing to improve on standard therapy; treatment was well tolerated by the patient with nominal hypoglycemic episodes that resolved spontaneously (7). While future therapies may directly target CS-specific subunits, these early results with glibenclamide use in CS provide hope for an existing FDA-approved, off-the-shelf therapy. In humans, this approach is practical and palliative (7) and should fill the gap in treatment approaches until a better understanding of CS enables a cure.

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