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Single cell transcriptomic analysis of SGLT2 expression supports an indirect or off-target role for the cardioprotective benefits of empagliflozin in heart failure

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Sodium-glucose cotransporter 2 inhibitors (SGLT2i), such as empagliflozin, have shown remarkable benefits in reducing cardiovascular events and mortality in patients with heart failure irrespective of diabetes. Because of the magnitude of the benefits and broad application in both heart failure with reduced and preserved ejection fraction, there have been concerted efforts to identify a mechanism for the observed benefits. One hypothesis is that SGLT2i act directly on the heart. Given empagliflozin's high specificity to SGLT2, we reasoned that SGLT2 expression would be a requirement for cells to respond to treatment via the expected drug target. Here, we present a comprehensive transcriptomic analysis of *SLC5A2*, which encodes SGLT2 at the single cell level in multiple datasets from healthy and HF donors, confirming its expression in a subset of kidney epithelial cells but minimal expression in other cell types. This was true irrespective of developmental stage, disease state, sequencing method or depth, and species. Therefore, it is likely that the cardioprotective benefits of SGLT2i cannot be explained by "canonical" interactions with SGLT2.

SGLT2i are a class of drugs commonly prescribed to reduce blood glucose in patients with type 2 diabetes mellitus. They promote excretion of glucose in the urine by inhibiting renal reabsorption in the proximal tubule[1]. Because SGLT2 is a cotransporter of sodium and glucose, SGLT2 inhibition results in natriuresis along with glucouresis. These combined effects have been reported to contribute to a reduction in blood pressure and body weight in diabetic patients who take SGLT2i[1]. Recent clinical trials have shown that SGLT2i, or "gliflozins", reduce cardiovascular events and mortality in heart failure (HF) patients irrespective of ejection fraction (EF)[2]. Notably, these cardioprotective benefits are absent in other glucose lowering drugs and are seen even in nondiabetic patients and thus cannot be explained by the amelioration of hyperglycemia[3]. Moreover, the cardioprotective effects of SGLT2i are extremely rapid, becoming apparent within weeks of treatment[4,5]. The exact mechanisms by which SGLT2i exert their beneficial effects on the heart remain under study, and several groups have proposed that they act directly on cells within the heart[6,7]. Since empagliflozin (empa), which was the first SGLT2i shown to improve HF outcomes in patients with either reduced (HFrEF) or preserved (HFpEF) ejection fraction, is highly selective for SGLT2 compared to SGLT1 (> 2500 fold), we reasoned that cardiac SGLT2 expression would be necessary for SGLT2i to confer their cardioprotective effects through direct interactions with their expected target, namely, sodium-glucose cotransporters[8]. Here, we examined the expression of *SLC5A2*, which encodes SGLT2, at the single cell level, with a focus on cells in the cardiovascular system, from multiple published datasets (Table 1).

Results

We assessed SLC5A2 expression in a human single cell transcriptomic atlas, the Tabula Sapiens[9], to identify organs where *SLC5A2* is expressed. Our analysis revealed a cluster of *SLC5A2*-positive cells within the kidney

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Dataset	Data Description	Sequencing method	No of cells	References
Tabula Sapiens	Data from 15 human donors with diverse ethnicities, balanced gender distribution, an average age of 51 years and have a variety of medical backgrounds	Droplet based sequencing and Smart seq2	483,152 cells across 24 different organs with 475 distinct cell types	The Tabula Sapiens Consortium[9]
Human Heart failure	Data collected from hearts of 27 healthy individuals and 18 individuals with dilated cardiomyopathy (DCM)	Droplet based sequencing	270,475 cells with 15 major cell types	Koeing et al.[12]
Human myocardial infarction	Data comprises 31 samples from 23 individuals, including four non-transplanted donor hearts as controls. Samples were collected at various time points after the onset of clinical symptoms, targeting tissues from necrotic regions (including ischemic and border zones) and unaffected myocardium (remote zone and and six hearts in advanced stages of myocardial infarction (fibrotic zone) to study fibrogenesis	Droplet based sequencing	191,795 cells with 11 distinct cell types	Kuppe et al.[13]
Integrated adult and fetal heart	Data from 7 fetal hearts aged 8 to 12 weeks post-conception combined with data from multiple regions of 6 healthy adult hearts, sourced from the Heart Cell Atlas	Droplet based sequencing	30,889 cells from fetal hearts and 29,779 cells from adult hearts with 19 distinct cell types	Knight-Schrijver et al.[14]
Tabula Muris	Data collected from three female and four male, three-month-old C57BL/6JN mice (10–15 weeks)	FACS-based cell capture in plates and microfluidic droplet-based capture	100,605 cells derived from 20 organs	Tabula Muris Consortium, Schaum et al.[17]

Table 1. Description of datasets and sequencing method.

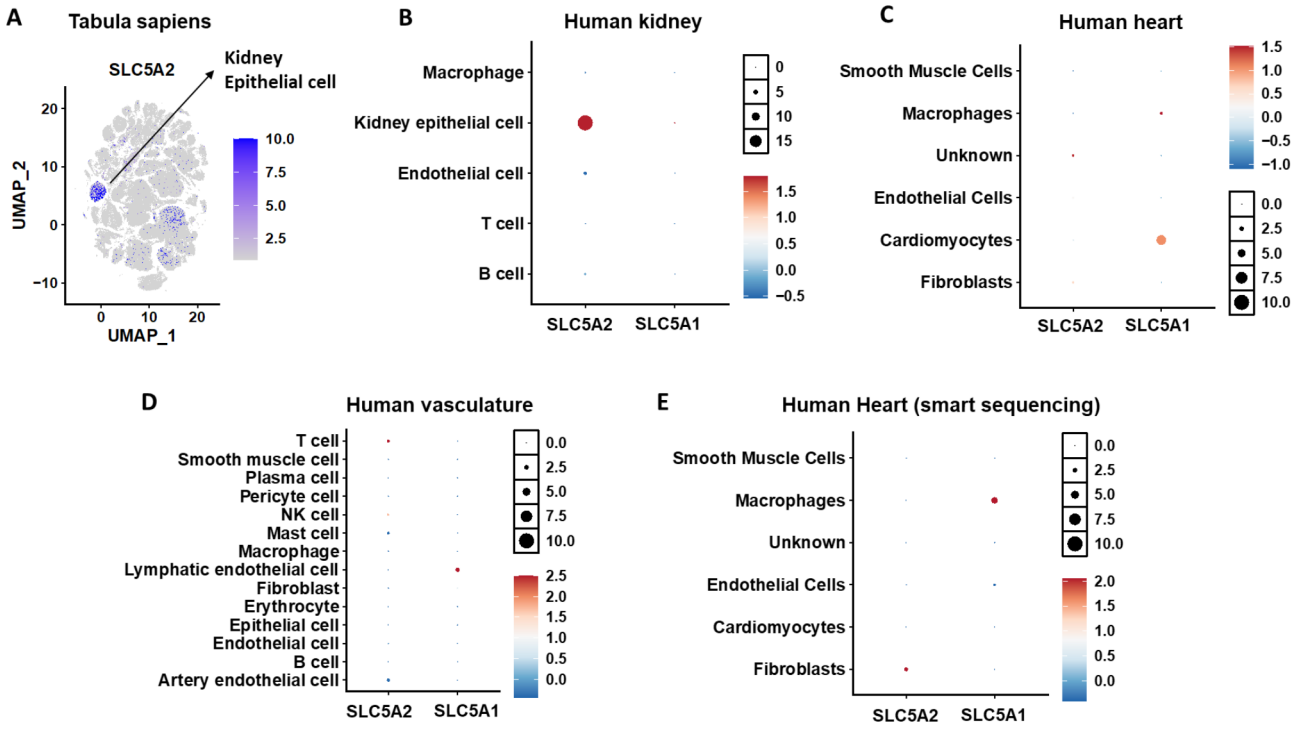

Fig. 1. Expression of SLC5A2 in the single cell human transcriptomic atlas confirms presence of SLC5A2 in kidney epithelial cells but absence in other cell types. (**A**) Feature plot showing the expression of SLC5A2 in Tabula Sapiens, a multiple-organ, single-cell transcriptomic atlas of human cells. (**B**) Expression of SLC5A2 and SLC5A1 in different cell populations in the human kidney. The dot plot depicts the expression of genes and percentage of cells expressing the gene in each cluster. (**C**) Expression of SLC5A2 and SLC5A1 genes in cells in the human heart. (**D**) Dotplot showing the expression of SLC5A2 and SLC5A1 in human cells from large vessels. (**E**) Dotplot showing the expression of SLC5A2 and SLC5A1 genes across human heart cells from datasets generated by deep-sequencing (Smart-seq).

(Fig. 1A). Detailed inspection of renal cell clusters revealed that *SLC5A2* is expressed within a subset of epithelial cells (Fig. 1B), confirming previous reports on SGLT2 expression in the proximal tubule[1]. In addition, *SLC5A1*, which encodes for SGLT1, an SGLT isoform found primarily in the small intestine[1], was not expressed in kidney cells as expected (Fig. 1B).

Due to the notable effects of SGLT2i in HF, we next focused our analysis on cells within the cardiovascular system. We initially postulated, due to empagliflozin's high affinity for SGLT2 and its established cardioprotective benefits, that there would be high expression of SLC5A2 in the cardiovascular system. However, we were unable to detect significant *SLC5A2* expression in any cells in the heart (Fig. 1C). In contrast, *SCL5A1* was expressed in

a small subset of cardiomyocytes, which is in accordance with previous reports[10,11]. In addition, analysis of large blood vessels demonstrated that no cells expressed either *SLC5A2* or *SCL5A1* (Fig. 1D). It is possible that the expression of *SLC5A2* is low and was therefore not detected by traditional single cell transcriptomic methods. Therefore, we analysed deep-sequencing (Smart-seq) data from the Tabula sapiens atlas which confirmed the lack of meaningful *SLC5A2* expression in all cell types in the heart (Fig. 1E).

Next, we considered that SGLT2 expression in the heart may be low in healthy conditions but induced in diseases such as HF. We therefore analyzed *SLC5A2* expression in datasets from human hearts with HF. Analysis of transcriptomic data from nonischemic failing and healthy hearts again showed the lack of *SLC5A2* expression in any of the heart cell types (Fig. 2A)[12]. Analysis of a myocardial infarction dataset[13] also revealed a lack of *SLC5A2* expression and similar expression of *SLC5A1* between cardiomyocytes in both healthy and infarcted hearts (Fig. 2B), demonstrating that cardiac *SLC5A2*/SGLT2 expression is not induced in in these relevant disease states. Analysis of a human fetal dataset[14] to assess if *SLC5A2* expression may be temporally regulated based on life stage confirmed the lack of expression in cardiac cells in the fetus (Fig. 2C). There have been murine studies which have reported cardiac benefits of empagliflozin in various disease conditions such as diabetes[15] and doxorubicin toxicity[16]. We sought to determine if a species-based difference in SGLT2 expression might account for these results. Analysis of the Tabula Muris, a mouse single cell transcriptomic atlas[17], revealed that *SLC5A2* was only detected in kidney epithelial cells, thus showing conserved expression patterns across both human and mouse (Fig. 2D).

Discussion

In summary, we have presented a comprehensive transcriptomic analysis at the single cell level showing that there is no prominent expression of *SLC5A2*/SGLT2 in the heart, irrespective of developmental stage, disease state, sequencing method or depth, and species. Given that empagliflozin's affinity for SGLT1 is >2500-fold lower than for SGLT2, we can rule out that the observed benefits in HF are due to interaction with SGLT1[8]. We conclude that the cardioprotective benefits of SGLT2 inhibition are thus likely due to either the indirect effects of this class of drug, conferred through renal and metabolic effects, or possible off-target drug interactions within the heart, or a combination of both.

Improved renal function and cardiorenal physiology could ameliorate cardiovascular health by a combination of factors such as natriuresis[1], reduction in cardiac interstitial edema[18], improved cardiac bioenergetics due to a shift towards ketone metabolism[19], changes in iron metabolism[20], and reduced preload and afterload[21].

The prevailing school of thought holds that human cardiomyocytes do not express SGLT2[22–24], which is supported by our analyses of the Tabula Sapiens atlas and heart disease datasets[9,12,13] showing that not only do cardiomyocytes not express SLC5A2 under normal conditions, but that expression is also not induced in the disease state. Recently, one group has reported that SGLT2 expression in explanted cardiomyocytes can be induced by high glucose[25]. Our analysis is in direct contrast to this finding. Moreover, we show that neither cardiomyocytes, nor any other cell type within the heart expresses *SLC5A2* and thus the interaction of SGLT2i such as empagliflozin with cardiac SGLT2 cannot explain their cardioprotective effects.

There have been several reports which have assessed the direct effects of empagliflozin treatment on cardiomyocytes in vitro. In human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), empagliflozin treatment blunted the hypertrophic effect of high glucose, leading to decreased cell size and *NPPB* expression[26]. In skinned CMs from HFpEF patients, empagliflozin reduced stiffness with a correlated decrease in intracellular H_2O_2[27].

It is important to note that the relevance of the aforementioned studies to clinical data is unclear as the concentration of empagliflozin used (5 µM for both cited studies[26,27]) far exceeds the peak plasma concentration (259–687 nM)[28] reported in patients given therapeutic doses. In addition, due to the endothelial barrier serving as a potential barrier for drug delivery, it is likely that the concentration of empagliflozin that reaches cardiomyocytes in vivo is even lower[29]. In another report which used cardiomyocytes isolated from diabetic db/db mice, empagliflozin was found to increase cytosolic and mitochondrial ATP levels, which were initially lower in diabetic mice compared to healthy controls. This study used a more clinically relevant dose range of 10-1000 nM of empagliflozin[15]. Additionally, a recent report using SGLT2-knockout mice in a heart failure model showed that, while a lack of SGLT2 expression was not cardioprotective, empagliflozin treatment was beneficial regardless of SGLT2 expression, further supporting the notion that SGLT2i are acting in an off-target manner[30]. There have been several proposed off-targets for empa and SGLT2i in general, most notably NHE1[31,32], although this viewpoint has been challenged[33,34]. Drug-binding experiments which screen for SGLT2i interactions with cardiomyocyte surface proteins would be a much-welcomed addition to the growing field of study concerning the cardioprotective effects of this class of drugs, to serve as robust evidence for direct interaction and to inform further pharmacological studies.

Methods

Single-cell transcriptomic data analysis

Single cell/nuclei data for heart, kidney and vasculature, including deep sequencing data were extracted from the Tabula Sapiens and Tabula Muris datasets deposited at the figshare repository. Other datasets that include data from failing and healthy heart, dataset from myocardial infarction and fetal heart were downloaded from the CELL x GENE Explorer database. Data were processed and plots were generated using the Seurat package (version 4.4.0) in R.

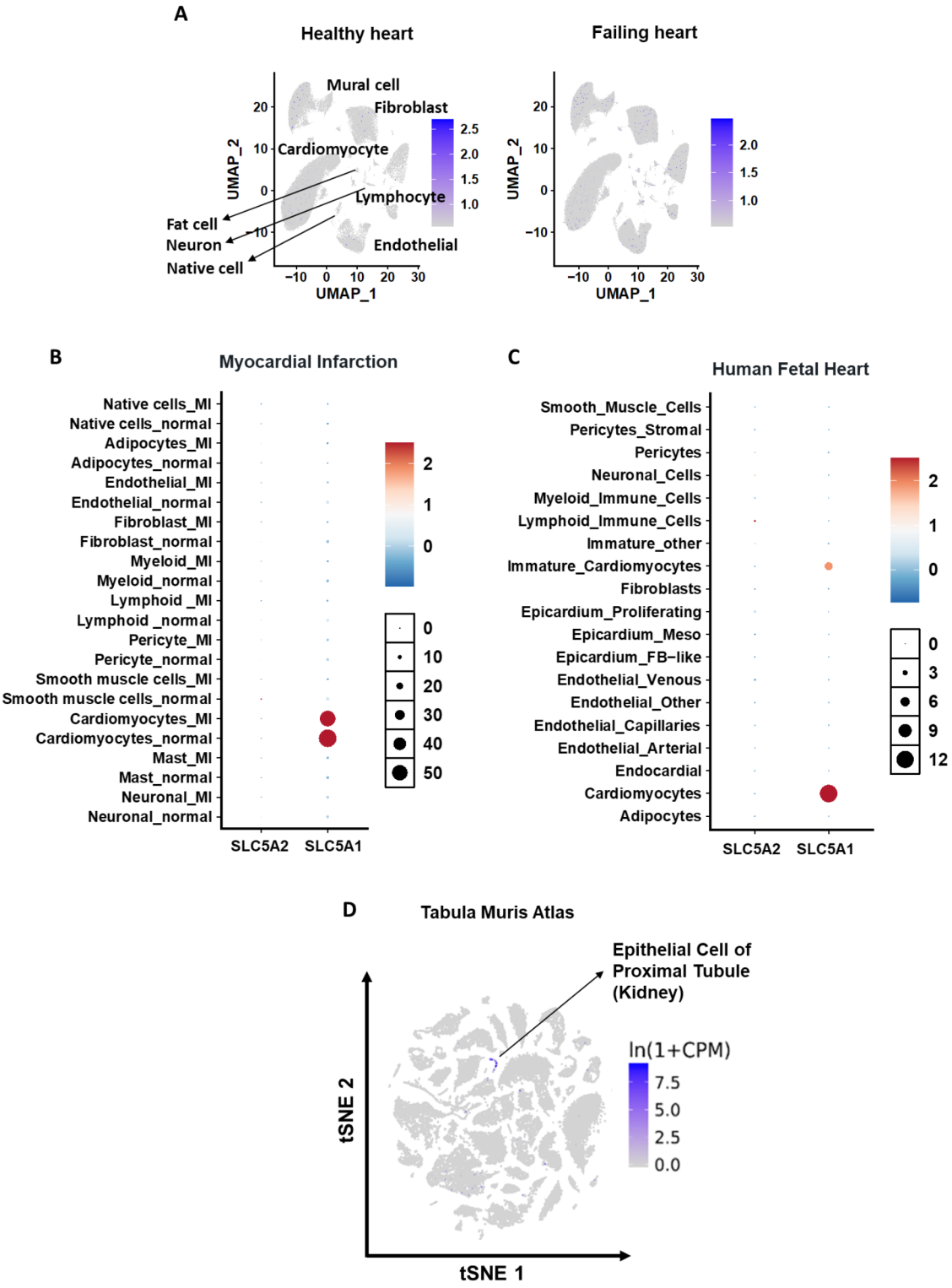

Fig. 2. SLC5A2 is not expressed in cardiac cells in diseased adult human hearts or fetal datasets and is only expressed in epithelial cells in the kidney in the Tabula Muris mouse dataset. (**A**) Feature plot displaying the expression of SLC5A2 in the single cell cardiac transcriptome of normal and failing nonischemic hearts. (**B**) Expression of SLC5A2 and SLC5A1 genes in cells from the myocardium from patients with myocardial infarction and healthy controls (normal). (**C**) Expression of SLC5A2 and SLC5A1 genes across different cell types in human fetal hearts. The dataset contains single-cell RNA sequencing of dissociated cells from 7 fetal hearts between the ages of 8- and 12- weeks post-conception. (**D**) Feature plot showing the expression of SLC5A2 in cells from the Tabula Muris atlas, a compendium of single cell transcriptomic data from mouse containing nearly 100 K cells from 20 organs and tissues.

Tabula sapiens dataset
The dataset was obtained from the Human Reference Atlas available through the CellxGene tool. It includes data collected from 59 specimens, comprising 483,152 cells across 24 different organs.

Human heart failure dataset
The dataset includes snRNA-seq and scRNA-seq data from the hearts of 28 healthy individuals and 17 individuals with dilated cardiomyopathy (DCM). The final integrated dataset comprises 270,475 transcriptomes, representing 15 major cardiac cell types.

Human myocardial infarction dataset
The dataset consists of 191,795 cells obtained through single-nuclei RNA sequencing of 31 samples from 23 individuals. This includes four non-transplanted donor hearts serving as controls, as well as samples from tissues with necrotic areas (comprising the ischemic and border zones) and unaffected left ventricular myocardium (referred to as the remote zone) from patients with acute myocardial infarction. These samples were collected at various time points following the onset of clinical symptoms, such as chest pain. Additionally, six human heart specimens from later stages of myocardial infarction (referred to as the fibrotic zone) were analyzed to investigate fibrogenesis.

Integrated adult and fetal heart dataset
This dataset includes single-cell RNA sequencing data from 7 fetal hearts aged 8 to 12 weeks post-conception, with cells dissected from either the base or apex. Additionally, it comprises single-cell and single-nuclei RNA sequencing data from multiple regions of 6 healthy adult hearts, sourced from the Heart Cell Atlas. The dataset features 30,889 cells from fetal hearts and 29,779 cells from adult human hearts.

Tabula muris dataset
The Tabula Muris dataset was obtained from the 'Mouse Atlas,' a comprehensive collection of single-cell transcriptomic data from the model organism Mus musculus. This dataset includes 100,605 cells derived from 20 organs of three female and four male, three-month-old C57BL/6JN mice. Single-cell RNA sequencing was conducted using two approaches: microfluidic droplet-based capture and FACS-based cell capture in plates.

Data availability
The datasets analysed during the current study are available in the public Tabula Sapiens (https://tabula-sapiens.sf.czbiohub.org/) and Tabula Muris (https://www.czbiohub.org/sf/tabula-muris/) atlases. Other analysed datase ts were directly accessed through the cited articles they pertained to.

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Author contributions

O. Mourad and S.S. Nunes conceptualized the study. O. Mourad and S.S Nunes wrote the original manuscript. S. Vohra analyzed the single cell RNAseq data and generated figures and descriptions. O. Mourad curated the data and compiled and edited data figures and descriptions. O. Mourad and S. Vohra assessed the literature to identify RNAseq databases for data analysis. O. Mourad, S. Vohra, and S.S. Nunes were responsible for reviewing and editing the manuscript. S.S. Nunes obtained funding for the study.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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