DISCUSSION

Big Data-Enabled Repurposing of Clopidogrel for Focal Segmental Glomerulosclerosis Using Network Biology

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is a rare kidney disease characterized by glomerular lesions and damage to podocytes, terminally differentiated renal cells, that are part of the filtration apparatus in glomeruli. FSGS is often associated with nephrotic syndrome and may lead to end-stage renal failure. FSGS pathophysiology is complex with a number of molecular mechanisms being involved in its development and progression. We used a network-based drug repurposing approach to computationally screen for novel treatment options for FSGS in a systematic way. In brief, we first generated a network-based molecular pathobiology model for FSGS following previously established workflows. FSGS-associated molecular features (i.e., genes and proteins) were mapped onto a human protein–protein dependency network, and network clustering algorithms were used to identify dysregulated FSGS molecular mechanisms and biological processes. Key affected enriched mechanisms included glomerular filtration, cell adhesion and extracellular matrix derangements, inflammation, apoptosis, calcineurin signaling, renin–angiotensin–aldosterone system, and platelet activation as well as dysregulation of fibrinolysis. The network-based FSGS pathobiology model was subsequently used to computationally screen against a library of drug mechanism of action molecular models. The platelet inhibitor clopidogrel was identified as one of the top compounds significantly interfering with FSGS pathophysiology based on in silico graph alignment analysis. Due to its potential to beneficially interfere with key dysregulated molecular FSGS processes, its positive in vivo data in ameliorating renal sclerosis, and its favorable safety profile, clopidogrel appears as an attractive candidate for subsequent evaluation in clinical trials.

KEYWORDS

focal segmental glomerulosclerosis; kidney disease; drug repurposing; drug repositioning.

Focal segmental glomerulosclerosis (FSGS) is a rare kidney disease characterized by glomerular lesions and damage to podocytes, terminally differentiated renal cells, that are part of the filtration apparatus in glomeruli. FSGS is often associated with nephrotic syndrome and may lead to end-stage renal failure. FSGS pathophysiology is complex with a number of molecular mechanisms being involved in its development and progression. There is currently no specific approved therapy for FSGS, and treatment...
Regimens consist of renin–angiotensin–aldosterone system (RAAS) inhibitors, calcineurin inhibitors, and corticosteroids. Steroid-resistant nephrotic syndrome, however, is an issue in clinical practice, and novel treatment options for patients with FSGS are needed. The dual endothelin and RAAS antagonist sparsentan is an example of a novel compound that showed beneficial impact on proteinuria levels in patients with FSGS in the DUPLEX trial, however not significantly impacting the key outcome parameter, namely estimated glomerular filtration rate. The group of sodium/glucose cotransporter 2 (SGLT2) inhibitors has also shown benefit in the management of patients with FSGS. SGLT2 inhibitors have initially been developed for people with diabetes and cardiovascular complications, but have in the meantime also been evaluated for patients with diabetic kidney disease and subsequently for patients with chronic kidney disease in general. Drug repositioning presents a viable strategy to broaden the therapeutic options for nephrologists in order to optimize treatment of patients with FSGS.

We used a network-based drug repositioning approach to computationally screen for novel treatment options for FSGS in a systematic way (Figure 1). In brief, we first generated a network-based molecular pathology model for FSGS following previously established workflows. FSGS-associated molecular features (i.e., genes and proteins) were mapped onto a human

**Figure 1.** Drug repositioning of clopidogrel for FSGS. Clopidogrel was identified as the lead candidate in a network-based computational drug screen. Clopidogrel was subsequently validated in the adriamycin mouse model of FSGS and is currently tested in the ClopiD4FSGS phase II clinical trial. FSGS, focal segmental glomerulosclerosis; RAAS, renin–angiotensin–aldosterone system.
protein–protein dependency network, and network clustering algorithms were used to identify dysregulated FSGS molecular mechanisms and biological processes. Key affected enriched mechanisms included glomerular filtration, cell adhesion and extracellular matrix derangements, inflammation, apoptosis, calcineurin signaling, RAAS, and platelet activation as well as dysregulation of fibrinolysis. The network-based FSGS pathobiology model was subsequently used to computationally screen against a library of drug mechanism of action (MoA) molecular models. The platelet inhibitor clopidogrel was identified as one of the top compounds significantly interfering with FSGS pathobiology based on in silico graph alignment analysis. Clopidogrel significantly attenuated weight loss and albuminuria in the adriamycin mouse model of FSGS and also beneficially affected sclerosis and significantly attenuated weight loss and albuminuria in the adriamycin mouse model of FSGS and also beneficially affected sclerosis and tubular atrophy as determined in histopathological examination in vivo. Clopidogrel appears as a very interesting drug candidate as the affected molecular targets and biological mechanisms that are beneficially influenced by its MoA appear to be rather complementary to the current standard-of-care FSGS treatment regimens, namely RAAS inhibitors, calcineurin inhibitors, and corticosteroids. Based on these findings, a study plan was developed to test the impact of clopidogrel on FSGS progression in the ClopiD4FSGS study (EudraCT Nr: 2022-003313-11), a single-arm multicenter proof-of-concept 24-week phase II clinical trial. Conduction of this trial is further supported by evidence from other research groups that discuss the beneficial impact of clopidogrel on renal fibrosis and chronic kidney disease. In addition, nonadherence to antiplatelet drugs has been reported to be significantly associated with worse cardiorenal outcomes in patients with diabetes mellitus.

In summary, we have identified the antiplatelet drug clopidogrel as a promising novel treatment option for patients with FSGS. Due to its potential to beneficially interfere with key dysregulated molecular FSGS processes, its positive in vivo data in ameliorating renal sclerosis, and its favorable safety profile, clopidogrel appears as an attractive candidate for subsequent evaluation in clinical trials.

CONFLICTS OF INTEREST

P. Perco, Christoph A. Gebeshuber, and M. Ley are employees of Delta4 GmbH. L. Daniel-Fischer was partly funded by a research grant from Delta4 GmbH. C. Aufricht is a co-founder of Delta4 GmbH and member of the scientific advisory board. K. Kratochwill is a co-founder of Delta4 GmbH and part of Delta4’s management team. Delta4 GmbH has filed the patent application entitled “CLOPIDOGREL FOR USE IN THE TREATMENT OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)” (WO/2022/117862 A1).

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REFERENCES