Cell Reports Medicine

CellPress
OPEN ACCESS

Preview

New use for an old drug: Metformin and atrial fibrillation

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https://doi.org/10.1016/j.xcrm.2022.100875

Lal and colleagues[1] reported an integrative approach—combining transcriptomics, iPSCs, and epidemiological evidence—to identify and repurpose metformin, a main first-line medication for the treatment of type 2 diabetes, as an effective risk reducer for atrial fibrillation.

Atrial fibrillation (AF) is the most common abnormal heart rhythm, which is associated with an increased risk of mortality and morbidity from stroke, heart failure, dementia, and impaired quality of life. Given the high residual risk of stroke and other cardiovascular events despite anticoagulation, recent guidelines have moved toward a more holistic or integrated care approach to AF management, which includes stroke prevention, symptom optimization with patient-centered symptom-directed decisions on rhythm or rate control, and management of comorbidities and lifestyle.[2]

New drugs for AF rhythm management have had varying success. Drug repurposing has broad importance for therapeutics innovation, and it has also proved important to develop interventions against the COVID-19 pandemic.[3] Nonetheless, developing promising and affordable approaches for the effective treatment of complex diseases such as AF is difficult without prior knowledge of the complete drug-target network. Novel new approaches are needed.

A study by Lal et al.[1] in a recent issue of *Cell Reports Medicine* identified metformin, which was repurposed as a drug candidate for AF using a 3-step approach. Their first step was to generate a network-based drug-repurposing network for AF: 265 human left-atrium tissue samples, including 251 from patients with AF and 14 from patients without it, were used for transcriptomic analyses. Differentially expressed genes (DEGs) were analyzed using classic network tools such as Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) that enriched for AF-dependent biological pathways. These pathways were then combined with ~2900 FDA-approved or clinically investigated drugs to assemble a drug network, identifying 9 potential candidates, including metformin, which was retained for further analyses. Metformin was discovered in 1922 and it has since been a mainstay treatment for type 2 diabetes.

This powerful first-step approach should be contextualized. Interestingly, metformin enhances the life span in invertebrate and vertebrate laboratory models, and similar gene-expression-based drug-repurposing studies targeting aging identified metformin, among others, as a pro-longevity agent.[4] Diabetes and AF are both age-associated and often co-morbid conditions. Metformin is being tested in the Targeting Aging with Metformin (TAME) trial[5] to develop effective next-generation drugs to increase healthspan and lifespan.

The second step by Lal et al.[1] was to test metformin in induced pluripotent stem cell (iPSC)-derived atrial cardiomyocytes (iCMs), which uncovered partial but significant overlap of functional and transcriptional effects with the human tissue. They concluded that their network proximity analysis predicted metformin as a repurposed drug for AF, inducing directional changes in AF disease-module genes. This was supplemented by large-scale health record data supporting metformin use for reduced AF risk.

Network medicine is a methodological approach that relies on network theory to model functional interconnectivity between molecular components in human cells. Rather than assuming that a disease is caused by defects in a sole gene, it is the interaction among several, if not hundreds of them, that are linked to a disease. Network medicine allows us to build those interactions and, crucially, to find clusters of proteins associated with biological roles. However, network medicine could be as effective as interaction maps are rightly modeled. Unfortunately, many connections remain unknown.

In addition, extracting meaningful information could sometimes be difficult as typical statistical assumptions based on normally distributed data cannot be applied. In this context, machine learning (ML) approaches could help in finding the missing links.[6] For instance, graph neural networks[7] have proven to be successful in building networks and modeling interactions purely based on data, which gives a higher degree of flexibility to find links not previously considered. A different approach known as transformational machine learning (TML)[8] was recently introduced as an ML branch that leverages its ability to model many similar problems at once to find associations between them without being explicitly interlinked. Although TML does not build a network, it showed that it can easily find new possible target candidates for already approved drugs.

The study by Lal et al.[1] has strengths, such as high-quality transcriptomic data from the left atrium of AF patients. In the

future, iCMs derived from the same AF patient would help to demonstrate the personalized and beneficial effects of metformin. The study confirms the robustness of drug-gene signature-based enrichments to validate network proximity-based predictions. However, the link between metformin intake and AF risk presented does not have a causal component, but it is of a cross-sectional nature. Future randomized clinical trials are required to confirm these findings.

For now, given that AF is often associated with aging and multimorbidity, a more holistic approach is currently promoted, given that single-drug solutions rarely cover all aspects of AF care, and adherence to such an approach is associated with improved clinical outcomes.[9] Indeed, despite the clinical complexity associated with AF and the associated high risks, evidence-based management is often suboptimal.[10] New, novel approaches to finding new drugs and new solutions are needed. The study by Lal et al.[1] may provide such an opportunity to help improve AF care and management.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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