Network pharmacology for mechanistically redefined comorbidities

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SUMMARY

Diabetes, atherosclerosis, hypertension and stroke are common comorbidities and the leading causes of death and disability worldwide. Current therapies are symptom-oriented, do not target the underlying cause and are therefore imprecise. One main reason for this unmet medical need is that these complex diseases are defined by a symptom in an organ and not by a molecular mechanism. Network medicine, however, shows that within the diseasome these comorbidites relate to the same cluster and, thus, likely share common hidden causal pathomechanisms. Targeting these mechanisms would be prefered to syptomatic therapy and, sicne these mechanisms are small signalling modules, network pharmacology is preferable to single-target approaches. One example of such a causal signalling module is the reactive oxygen species (ROS) and cGMP signaling (ROCG) network.

Pharmacologically, several drug classes target this network, including NADPH oxidase (NOX) inhibitors and nitric oxide (NO) donors. In this thesis, a NOX inhibitor panel approach was successfully applied to pharmacologically validate the pathomechanistc involvement of a specific NOX isoform. In addition, NO-cGMP signalling was found to be halted by chronic elevation of NO as part of a chemical feedback loop that converts the NO receptor, soluble guanylate cyclase (sGC), to the heme-free and NO-insensitive apo-sGC. Therefore, other drug classess such as sGC stimulators and apo-sGC activators will be superior to NO donors for chronic use.

In a comorbidity model of stroke plus diabetes, a network pharmacology approach using subthreshold doses of a NOX and an NO synthase (NOS) inhibitor plus apo-sGC activator, resulted in a substantial neuroprotective effect. This approach is now in clinical trials. Also in diabetes, NADPH oxidase 5 (NOX5) was found as the most direct neighbour to NO-cGMP-related proteins. This connection was functionally validated both in a subgroup of hypertensive patients and in NOX5-knock in mice where NOX5 induced NOS uncoupling as a causal mechanism to induce age-related hypertension.

Collectively, network pharmacology targeting causal disease modules represents a new approach to precisely define, diagnose and cure hitherto complex comorbidities such as diabetes, atherosclerosis, hypertension and stroke. Further validations in clinical trials is needed and planned to start in late 2020.