Overlapping effects of miR-21 inhibition and drugs for idiopathic pulmonary fibrosis: rationale for repurposing nintedanib as a novel treatment for ischemia/reperfusion injury

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Abstract

A specific anti-miR-21 has emerged as an effective treatment for ischemia/reperfusion (I/R) injury in a pig model of myocardial infarction (MI), but the perspectives for clinical translation are limited. Anti-miR-21 blunts profibrotic pathways, whose excessive activation is detrimental in the post-MI setting. Repurposing anti-fibrotic drugs approved for other indications is a possible strategy. We compared the molecular effects of anti-miR-21 and the 2 drugs approved for idiopathic pulmonary fibrosis (nintedanib and pirfenidone) through a bioinformatic approach. We report that nintedanib and anti-miR-21 share many targets, including the proto-oncogene SRC. Conversely, pirfenidone and anti-miR-21 do not have common mechanisms of action. In summary, the molecular mechanisms activated by nintedanib are partially overlapping with those elicited by anti-miR-21. Nintedanib could be evaluated in animal studies or clinical trials on MI.

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Background: Reperfusion strategies have considerably reduced the mortality associated with ST-segment elevation myocardial infarction (STEMI). Nonetheless, ischemic/reperfusion (I/R) injury still represents an important issue, and the prevalence of heart failure (HF) after STEMI is increasing at an alarming pace. Intracoronary infusion of a specific miR-21 inhibitor after reperfused MI has been reported to reduce cardiac fibrosis and hypertrophy and improve cardiac function in pigs. This is accompanied by transcriptional changes that include a suppression of the inflammatory response and mitogen-activated protein kinase activity, this last effect deriving from decreased macrophage and fibroblast activation. Possible drawbacks of anti-miR-21 therapy are the high costs of this therapy, and the need for intracoronary administration, preferably some days after reperfusion (given that cardiac miR-21 is not up-regulated acutely but rather progressively and several days after myocardial ischemia), and in multiple doses (because of the progressive nature of miR-21 upregulation). Oral drugs with anti-fibrotic actions, currently approved for other indications, could have similar molecular effects than anti-miR-21, while overcoming the limitations of anti-miR-21. We tested this hypothesis by examining the two drugs approved for idiopathic pulmonary fibrosis (nintedanib and pirfenidone).

Methods: We identified the regulatory profile of miR-21, which included 588 target genes. Only 99 of these interactions were supported by robust experimental data (i.e., information from reporter gene assays), and were then considered for further examination. The biological significance of these 99 targets was evaluated through over-representation analysis, and 13 genes were identified as potentially related to cardiovascular diseases. Afterwards, we retrieved all known targets and main downstream interactions of nintedanib and pirfenidone by using data from Drugbank (www.drugbank.ca). Finally, we cross-validated these datasets by using neural network analyses (STRING v11.0) to search for protein-protein interactions, focusing on those shared by miR-21 inhibition, nintedanib and pirfenidone.

Results: Nintedanib and anti-miR21 had many targets in common, which could indicate an overlap in their corresponding mechanisms of action. The proto-oncogene SRC, which participates in gene

transcription, immune response, apoptosis and migration, emerged as the leading signaling effector. By blocking SRC expression and many downstream effectors of SRC, as well as platelet-derived growth factor, nintedanib could decreased miR-21 expression. The molecular effects of nintedanib include inhibition of inflammation, fibrosis and angiogenesis, and then ultimately a relief from I/R injury, in a similar fashion than anti-miR-21. Contrary to nintedanib, no overlap between the effects of pirfenidone and anti-miR-21 was found.

Conclusion: anti-miR-21 has emerged as a potential treatment for I/R cardiac injury, but its applicability in clinical practice is burdened by several limitations. Drug repurposing may allow to simulate the molecular effects of miR-21 inhibition. A bioinformatic analysis allowed to find that nintedanib can exert beneficial effects similar to those reported for anti-miR-21, while no overlap is found in the case of pirfenidone. Because of the remarkably strong overlapping with the targets of miR-21, there is a stronger rationale to assess nintedanib than pirfenidone as a cardioprotective therapy. If confirmed by experimental evidence, nintedanib could enter the stage of clinical trials to assess its efficacy in human patients with STEMI.

Compliance with Ethical Standards

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

Informed consent: not required.

Figure legend

Figure 1. Molecular mechanisms shared by anti-miR-21 and nintedanib.

ERK, extracellular regulated kinases; FLT, FMS-like tyrosine kinase; I/R, ischemia/reperfusion; KDR, kinase insert domain receptor; LCK, lymphocyte-specific protein tyrosine kinase; LYN, Lck/Yes novel tyrosine kinase; miR-21, miRNA 21; PDGF, platelet-derived growth factor; PTEN, phosphatase and tensin homolog; STAT3, signal transducer and activator of transcription 3; TUBB, tubulin beta class I; VEGF, vascular endothelial growth factor. Solid black lines represent the pathological effects of miR-21. Dashed lines define the potential beneficial effects attributable specifically to the therapies under study.

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