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Cardiac protection by pirfenidone after myocardial infarction: A bioinformatic analysis

Aims: Left ventricular (LV) remodelling after myocardial infarction (MI) is promoted by an intense fibrotic response, which could be targeted by an anti-fibrotic drug such as pirfenidone.

Methods: We explored the relationship between protein modulation by pirfenidone and post-MI remodelling, based on publicly available molecular information and transcriptomic data from a swine model of MI. We also compared the effects of pirfenidone and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), mineralocorticoid receptor blockers (MRA) and beta-blockers.

Results: We identified 6 causative motives of post-MI remodelling (cardiomyocyte cell death, impaired myocyte contractility, extracellular matrix remodelling and fibrosis, hypertrophy, renin-angiotensin-aldosterone system activation, and inflammation), 4 pirfenidone targets and 21 bioflags (indirect effectors). When considering both targets and bioflags, pirfenidone showed a broad relationship encompassing all 6 motives. Here, we found that p38γ-MAPK12 blockade by pirfenidone could inhibit cardiomyocyte apoptosis, cardiomyocyte hypertrophy and inflammation. Furthermore, pirfenidone can modulate extracellular matrix remodelling and cardiac fibrosis by targeting the TGFβ1-SMAD2/3 pathway and other effector proteins such as matrix metalloproteases 2 and 14, PDGFA/B, and IGF1. Importantly, using a protein-protein interaction analysis, we identified that pirfenidone's modulation of Furin and SerpinE1, could also improve ECM remodeling, cell migration, apoptosis and vascular endothelial affectation. Finally, Furin and SerpinE1 modulation could be synergistically improving the AGE/RAGE signalling cascade, highly represented in our post-MI dataset.

All the gold standard drugs were found to be important for specific clinical motives, but pirfenidone had a more widespread action on the molecular pathways active in the post-MI setting.

Conclusions: A bioinformatic approach allowed to identify several possible mechanisms of action of pirfenidone with beneficial effects in the post-MI LV remodelling, and suggests additional effects over guideline-recommended therapies. These findings support clinical studies evaluating the beneficial effects of pirfenidone in patients with MI.

Recent Publications

1. Oriol Iborra-Egea. Increased stem cell proliferation in atherosclerosis accelerates clonal hematopoiesis. Cell. 2021 Mar 4;184(5):1348-1361.e22
2. Oriol Iborra-Egea. Molecular signature of cardiogenic shock. Eur Heart J. 2020 Oct 14;41(39):3839-3848
3. Oriol Iborra-Egea. An outlook on biomarkers in cardiogenic shock. Curr Opin Crit Care. 2020 Aug;26(4):392-397
4. Oriol Iborra-Egea. Protein-based cardiogenic shock patient classifier. Eur Heart J. 2019 Aug 21;40(32):2684-2694

Biography

Iborra has specialized in the study of new approaches to precision medicine in heart failure, and has been awarded the extraordinary doctorate award for his research. Additionally, Iborra has participated in several, large proteomic studies in cardiovascular research: from novel biomarker discovery in cardiogenic shock to miRNAs analysis and their prognostic/clinical value, as well as gained expertise in combining big data and molecular biology to identify hidden molecular mechanisms of action.The main goal is to allow, for the first time, preventive management instead of reactive procedure improving the patients' quality of life and the clinicians' management, reducing costs and frictions for the national health systems.

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