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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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Mohamed El-Shazly

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The isolation of isoflavonoids and related analogues: A bright path to tackle hormonal related disorders

Phytoestrogens are plant constituents with a di-phenolic structure similar to estrogen. They are found in a wide variety of edible plants. They bind to estrogen receptors but preferentially to ER. They may act as weak estrogens in some circumstances. Phytoestrogens bind to both ER α and ER β but preferentially to ER β (8-40x more). They also inhibit tumor growth factors such as Protein Tyrosine Kinases (PTK) and DNA Topoisomerases involved in tumorigenesis. Phytoestrogens may inhibit Vascular Endothelial Growth Factor (VEGF) and possess antioxidant qualities. The importance of these secondary metabolites encouraged us to develop a cross-kingdom assay that carries a chemically inducible gene expression system, which was introduced to describe a novel strategy in which transgenic plants are used to measure the bioactivity of mammalian proteins. It is a new, low-cost, easy, and efficient estrogenic screening platform. In 2005, our group published the first report on a cross-kingdom bioassay utilizing transgenic pER8: GFP Arabidopsis for the detection of compounds possessing estrogen agonist or antagonist activities. The shoots of transgenic plants were used as a material for the screening of the estrogenic activity. In 2013, we developed for the first time a transgenic pER8:GUS Arabidopsis callus in a cross-kingdom assay to evaluate the estrogenic activity of 17β-estradiol (E2) and natural products. The transgenic plants were utilized to produce many calli, which stably expressed transfer genes by asexual reproduction. The optimum formula for calli induction and production were selected from sixteen solid media and six liquid media, respectively. This assay was used to evaluate the phytoestrogenic activity of many plants used in Asian folk medicine. The assay proved sensitive and selective for compounds with phytoestrogenic activity.

Recent Publications

1. Mohamed El-Shazly. The Antileukemic and Anti-Prostatic Effect of Aeroplysinin-1 Is Mediated through ROS-Induced Apoptosis via NOX Activation and Inhibition of HIF-1a Activity. Life 2022 May; 12(5):687

2. Mohamed El-Shazly. The effectiveness of Fuzi in combination with routine heart failure treatment on chronic heart failure patients. Journal of Ethnopharmacology. 2022 Feb: 289(25):115040

3. Mohamed El-Shazly. The Impact of Polyphenolic in The Management of Breast Cancer: Mechanistic Aspects and Recent Patents. Discovery. 2021 Dec; 177(12): 454-460

Biography

Mohamed El-Shazly is the head of pharmaceutical biology department, faculty of pharmacy and biotechnology, the German university in Cairo, Cairo, Egypt. He was graduated from the faculty of pharmacy, ain-shams university, Cairo, Egypt in 2000. In 2006, he received his master's degree from jacobs university bremen, bremen, Germany in nanomolecular science, and he pursued his Ph.D. focusing on the synthesis of pharmaceutical intermediates and natural products. In 2009, he received his Ph.D. and went back to Egypt to join his home institute. In 2011, he worked at the graduate institute of natural products, kaohsiung medical university, kaohsiung, Taiwan.

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Empagliflozin in heart failure with preserved ejection fraction: Decoding its molecular mechanism of action using artificial intelligence

Rationale: The use of sodium-glucose co-transporter 2 inhibitors (SGLT2i) to treat heart failure with preserved ejection fraction (HFpEF) is under investigation in ongoing clinical trials, but the exact mechanism of action is unclear. Here we aimed to use artificial intelligence (AI) to characterize the mechanism of action of empagliflozin in HFpEF at the molecular level.

Methods: We retrieved information regarding HFpEF pathophysiological motifs and differentially expressed genes/proteins, together with empagliflozin target information and bioflags, from specialized publicly available databases. Artificial neural networks and deep learning AI were used to model the molecular effects of empagliflozin in HFpEF.

Results: The model predicted that empagliflozin could reverse 59% of the protein alterations found in HFpEF. The effects of empagliflozin in HFpEF appeared to be predominantly mediated by inhibition of NHE1 (Na+/H+ exchanger 1), with SGLT2 playing a less prominent role. The elucidated molecular mechanism of action had an accuracy of 94%. Empagliflozin's pharmacological action mainly affected cardiomyocyte oxidative stress modulation, and greatly influenced cardiomyocyte stiffness, myocardial extracellular matrix remodelling, heart concentric hypertrophy, and systemic inflammation. Validation of these in silico data was performed *in vivo* in patients with HFpEF by measuring the declining plasma concentrations of NOS2, the NLPR3 inflammasome, and TGF-β1 during 12 months of empagliflozin treatment.

Conclusion: Using AI modelling, we identified that the main effect of empagliflozin in HFpEF treatment is exerted via NHE1 and is focused on cardiomyocyte oxidative stress modulation. These results support the potential use of empagliflozin in HFpEF.

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1. Oriol Iborra-Egea. Increased stem cell proliferation in atherosclerosis accelerates clonal hematopoiesis. Cell. 2021 Mar 4;184(5):1348-1361.e22
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