CARDIOsym QSP model prediction of wound healing response following myocardial infarction

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ABSTRACT

Objectives: Cardiac wound healing post-myocardial infarction represents a complex balance between inflammation and fibrosis (Richardson 2017). A biphasic immune response post-infarction (Kologrivova 2021) regulates the repair process to produce a scar in the infarcted area. Inter-individual variability has shown various clinical outcomes, from relatively stable individuals to those subject to insufficient repair and heart failure (Cahill 2017). A quantitative, mechanistic model of cardiac pathophysiology was developed to provide insight into individual differences and in predicting post-infarction efficacy of potential therapies.

Methods: We utilize a quantitative systems pharmacology (QSP) approach to develop a mechanistic model of a left ventricle myocardial infarction with inflammatory and fibrotic responses. The model represents cardiomyocytes, innate immune cells (macrophages, neutrophils), fibroblasts, collagen production, and regulatory mediators. The model represents an infarct proximal region, including cardiomyocytes susceptible to further injury, inflammation, and fibrotic wound healing. It also represents a distal region, with lesser inflammation and fibrosis.

Results: Simulated cardiomyocytes post-infarction undergo necrosis in proportion to the simulated infarct size, releasing danger signals (Kohno 2009, Andrassy 2011). These signals induce an acute inflammatory response, where simulated macrophages and neutrophils increase orders of magnitude then shift to a chronic, reparative/fibrotic phase in accordance with human data (Lee 2012, van der Laan 2014, Czepluch 2013). Corresponding increased levels of inflammatory and fibrotic mediators (TNFα, IL-10, TGFβ, PDGF, MMP-9) were calibrated to data (Gruzdeva 2017, Chen 2014, Wallace 1998, Tan 2012) and regulate the timing of fibroblast activation to myofibroblasts (Fishbein 1978) and level of collagen deposition (Marijianowski 1997). A sensitivity analysis was conducted on mechanistic pathways impacting therapeutic outcomes and on individual variability in the inflammation/fibrosis balance with subsequent impact on infarct scar formation and susceptibility to heart failure.

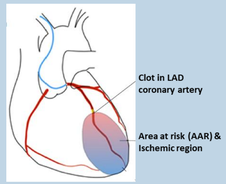
Conclusions: The mechanistic QSP model CARDIOsym describes the inflammatory and fibrotic responses post-myocardial infarction, consistent with the expected range of patient responses. This model is well-suited to study the effects of therapeutic interventions in modifying the balance between inflammation and fibrosis and determining effects on cardiac remodeling.

INTRODUCTION

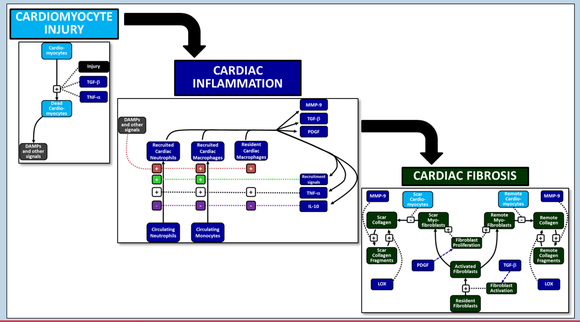
- Inflammation and fibrosis are critical to the wound healing process post-mycocardial infarction (MI)
- CARDIOsym applies a quantitative systems pharmacology (QSP) approach to capture the post-MI response within the left ventricle
- Calibration and validation with clinical and preclinical data demonstrate model capability to show a rapid immune response near the site of an infarction, inflammation in the rest of the heart, and a transition to myofibroblast activation with collagen deposition and ultimately infarction repair
- Model is capable of simulating treatments which influence inflammatory or fibrotic pathways

RESULTS

QSP Model

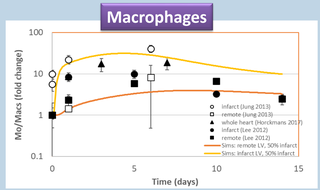


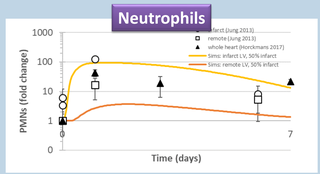
- QSP model designed to represent key pathophysiological processes post-myocardial infarction in the left ventricle
  - Distinct dynamic cardiac cell responses to MI: inflammation, fibrosis
- Cardiomyocyte death is initiating event
  - MI causes immediate cardiomyocyte necrosis
  - Cardiomyocyte apoptosis more enduring event
- Biphasic inflammatory response to MI
  - Acute response includes immune cell recruitment to clear cardiomyocyte debris and mediator release
  - Chronic response includes ongoing mediator release
- Fibrosis response follows inflammatory response, magnitude constrained by size of MI
  - Mediators released in inflammatory response initiate activation of fibroblasts

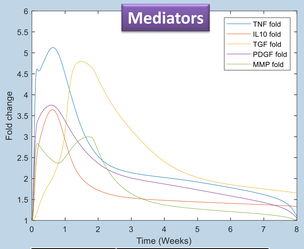


Model Calibration

- Calibration of base model compares well to available clinical data
  - Inflammation timing/magnitude also guided by mouse preclinical data
  - Macrophages and neutrophils demonstrate early and relatively prominent infiltration into infarct area, with infiltration into the rest of the ventricle following
  - Fibroblast activation follows which results in collagen production in the infarction and, to a lesser extent, the rest of the left ventricle
- In the simulations and in data, an early pro-inflammatory phase shifts to a pro-reparative phase
  - Both are necessary in balance for proper wound healing



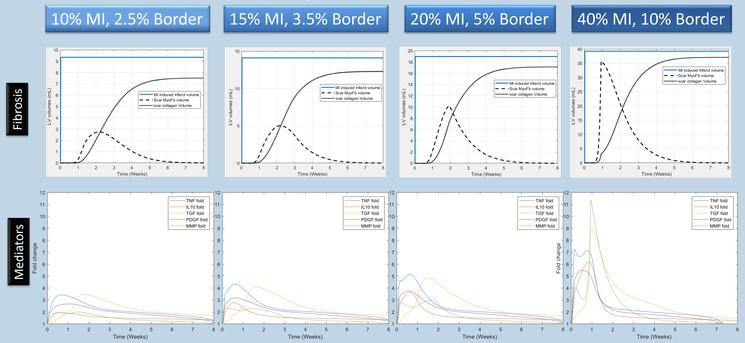




Mediator	Post-MI Production Level
TNF	2-3x
IL-10	2x
TGF-β	3.5x
PDGF	2x
MMP	1.4x

Sensitivity Analysis

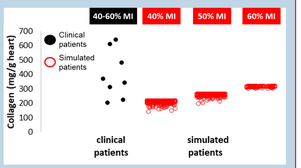
- Sensitivity of inflammation, fibrosis, and collagen deposition was examined with respect to infarct/border size
- As relative size of infarct grows, inflammation and activated myofibroblasts respond accordingly
- Collagen nearly fills infarct in all baseline individuals; highest infarct size collagen validated with literature

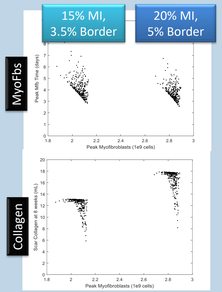


Simulated Populations

- Cardiac simulated populations (SimPops, n=300) have variability in inflammation and fibrosis-related parameters
- SimPops generate appropriate fibrotic responses to large myocardial infarction, including interpatient variability (Marijianowsky 1997)
- Interpatient variability leads to different simulated individual myofibroblast and collagen responses to mild myocardial infarctions
- Interpatient variability in scar formation captured within SimPops

Variables Used to Construct SimPops
Atherosclerotic mediator elevation
Inflammatory mediator production
Pro-fibrotic mediator production
Apoptosis sensitivity to inflammation mediators





METHODS

Developed a mechanistic model of cardiac response to myocardial infarction in the left ventricle

- Characterization of immune and fibrotic responses utilizing clinical and preclinical data
- Critical inflammation and fibrosis links captured through mathematical modeling
- Development of infarction model, inflammatory and fibrotic response to infarction, and delayed or persistent injury in the infarct border region and remainder of the ventricle
- Sensitivity analysis conducted within key pathways to assess model response to different infarct sizes as well as inflammation and fibrosis parameters
- Development of simulated population (SImPops) based on varying key biologically relevant and mathematically sensitive parameters which generate different inflammatory, fibrotic, and wound healing (collagen level) outcomes

CONCLUSION

- CARDIOsym has been successfully calibrated based on available data with a baseline individual and with SimPops which represent an array of potential patient outcomes
- CARDIOsym is well poised for examinations of potential treatments to impact healing post-MI, either for treatments currently in development or hypothesis test pathways for potential intervention

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