Development of a Systems Pharmacology Model for Inflammatory Bowel Disease

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BACKGROUND AND OBJECTIVES

Inflammatory Bowel Disease (IBD) is a gastrointestinal tract disorder characterized by periods of remission and relapse causing functional impairment of the gut wall. IBD includes Crohn Disease (CD) and Ulcerative Colitis (UC) [1, 2]. The objective of the current work was to develop a Systems Pharmacology (SP) model for IBD able to evaluate therapeutic targets for different types of IBD patients, focused on the Crohn Disease Activity Index (CDAI) change in each scenario. We also intended to identify subgroup of patients non responder to the current gold standard, anti-TNFα therapy, and propose alternative therapies for such individuals.

METHODS

NETWORK BUILDING AND EVALUATION

The development of the theoretical disease network (*Figure 1*) was based on an exhaustive bibliographic review. Once the most relevant relationships were identified, the network was built using Boolean functions (*Figure 2*).

IL1β = ((MACR OR DC) AND LPS AND NFkB AND NOT (IL1β AND IL10)

Figure 2. Boolean function for IL1β node

This Boolean Network model was implemented in the SP platform SPIDDOR [3]. The network contains 44 nodes (24 of them reported to be altered in IBD patients) and 226 interactions. Simulations of IBD like immune response were performed assuming chronic response to four different types of microbial antigens (PGN, MDP, LPS and GLY). CDAI was analysed through the increase or decrease of the relative expression of the main node associated to clinical manifestations in IBD (Metalloproteinases (MMPs)).
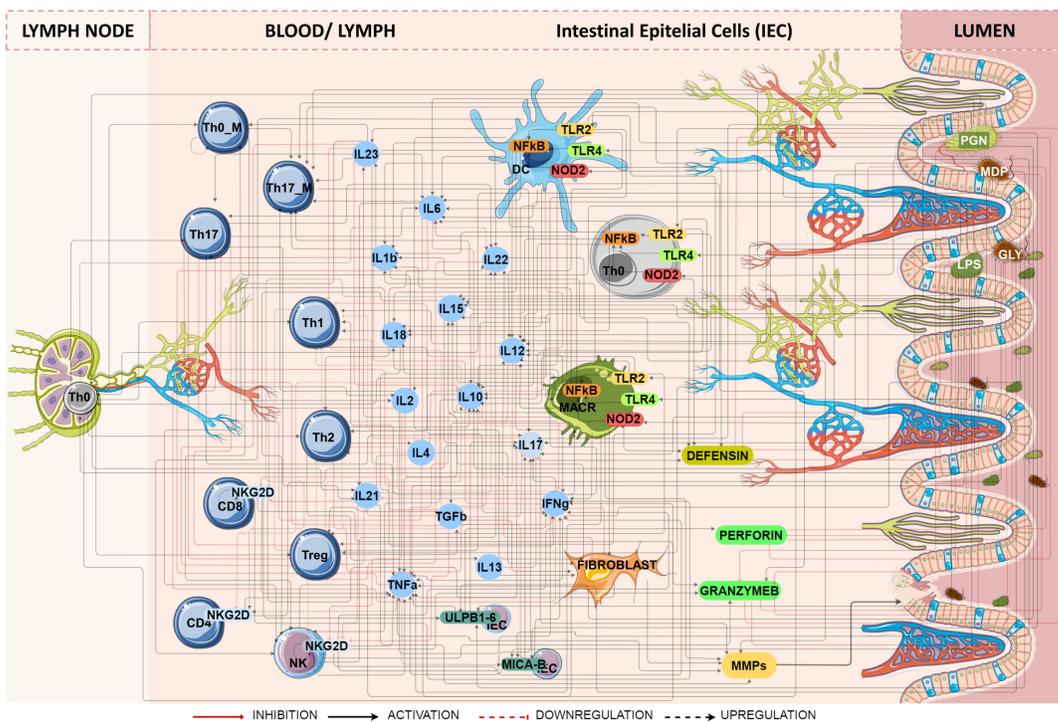

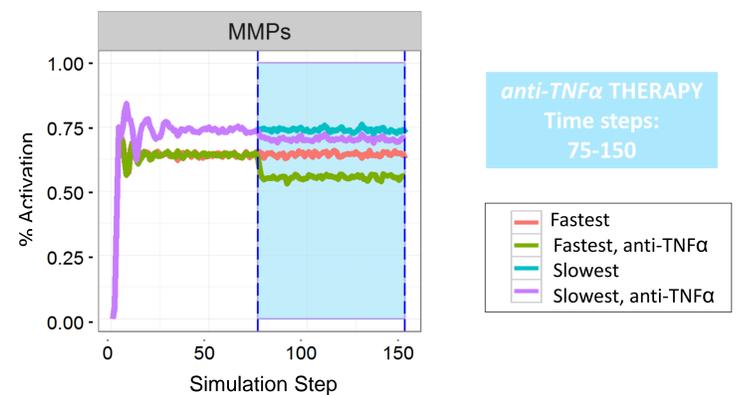*Figure 1. Graphical representation of the Boolean Network for IBD*

Figure 3. MMPs relative expression for patients with different antigen elimination under anti-TNFα therapy

The network was evaluated comparing the obtained results of the simulations after reaching the attractor state of the relative expression of the selected nodes, with the results reported in clinical trials for five investigated molecules: anti-IFNγ, anti-TNFα (*Figure 3*), anti-IL2, anti-IL17 and anti-IL21 for different IBD patients.

RESULTS

The SP model was able to replicate acute infectious episodes in healthy subjects and in IBD like patients with active disease condition with an altered response (*Figure 4*). Only anti-TNFα and anti-IL17 decreased the simulated CDAI score in typical IBD patients. Anti-IFNγ, anti-IL2 and anti-IL21 did not show improvement of the simulated CDAI score when administered alone. Simulations of an anti-TNFα therapy show less efficacy in patients with antigen impairment elimination (alteration in NK or Defensins function) (*Figure 5*). A combined simulated therapy of anti-IL17, anti-TNFα and anti-IFNγ showed an improvement in the CDAI score compared to anti-TNFα alone (*Figure 6*).
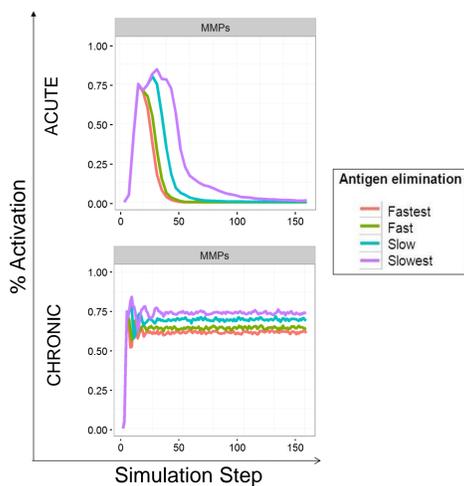

Figure 4. MMPs relative expression for a simulated individual with an acute infection or a simulated patient with a chronic infection (IBD)
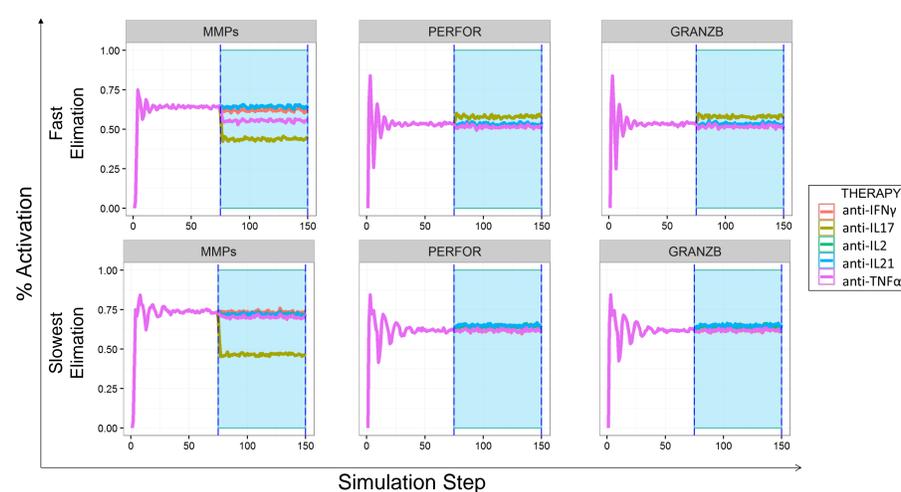

Figure 5. MMPs, Perforin and GranzymeB relative expression for individuals with fast or slow antigen elimination under different treatment
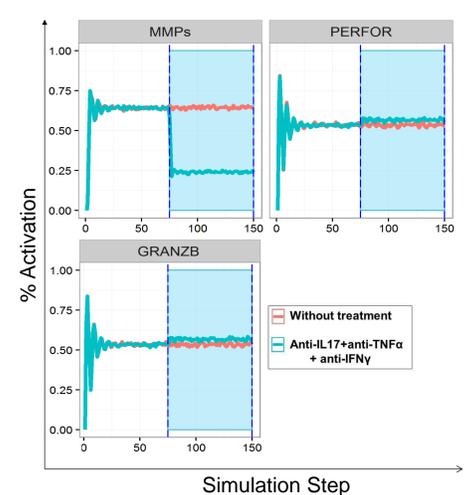

Figure 6. MMPs, Perforin and GranzymeB relative expression under triple therapy simulation

CONCLUSIONS

The obtained results satisfactorily replicate the results from clinical trials. Anti-TNFα may not show efficacy in individuals with impaired antigen elimination. A combination of anti-IL17, anti-TNFα and anti-IFNγ could show more improvement in the CDAI score than other therapies. The proposed SP model is potentially useful to identify new therapeutic targets and to optimize therapy combinations. Simulation of more polymorphisms could lead to a realistic patient stratification.

REFERENCES

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