A multi-scale modeling of the innate immune response to fungal respiratory pathogens

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BACKGROUND

Invasive pulmonary aspergillosis is a severe pneumonia in immunocompromised hosts. It is caused by the inhalation of the spores of the saprophytic fungus *Aspergillus,* characterized by the growth of hyphae within the tissues of the lung. Iron acquisition is a critical component of microbial pathogenesis that is essential to microbial virulence. An important component of the innate immune response is to sequester iron from the pathogen, an instance of nutritional immunity, which involves several processes at different spatial and temporal scales, ranging from molecular events inside several types of immune cells, tissue-level events, and involvement of the liver. As fungal pathogens have evolved mechanisms to actively acquire iron from the host, a "battle for iron" plays out in the very early stages of infection. Our hypothesis is that host-centric interventions can result in a favorable outcome of this battle.

THE MODEL

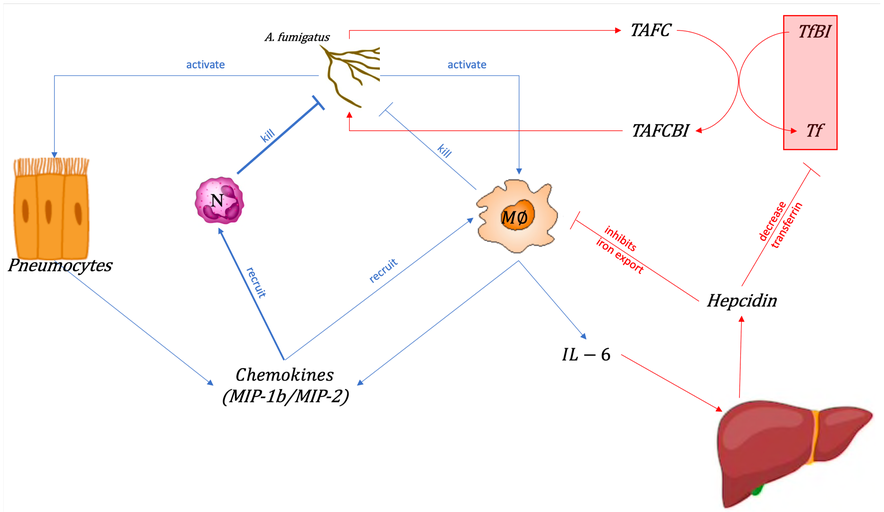
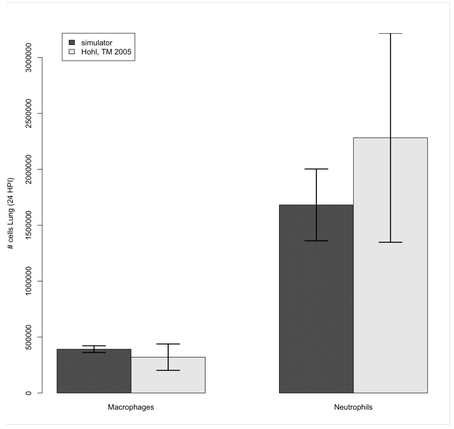


Figure 1: A Simplified description of the model. *Aspergillus* induces macrophages (*MØ*) and epithelial cells to produce chemokines and cytokines that attract neutrophils (N); neutrophils and macrophages kill *Aspergillus*; *Aspergillus* secretes the siderophore TAFC that chelates iron from transferrin bound to iron (TfBI); macrophages secrete IL-6 which instructs the liver to secrete hepcidin; hepcidin reduces the level of serum transferrin (Tf) and inhibits macrophage iron export. Neutrophil recruitment and killing of *Aspergillus* is more pronounced than macrophage (thick arrows). Red arrows represent iron-related actions.

RESULTS



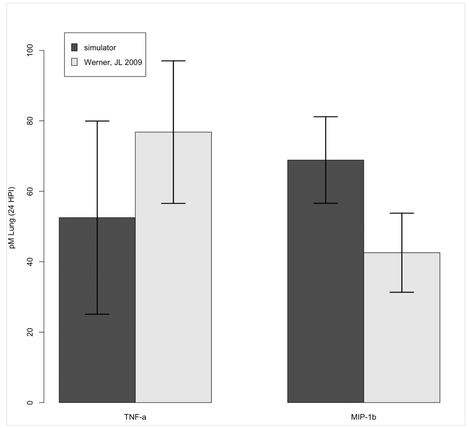


Figure 2: Model validation with data from the literature [1,2]. Simulated data were obtained from model parameters in the literature not including these two papers. Predicted quantity of leukocytes (macrophages and neutrophils) 24 hours post-infection was compared with quantities reported in the literature (left). Predicted lung concentration of TNF-a and MIP-1b 24 hours post-infection were compared with data from the literature (right). Dark bar predicted, light bar reported in the literature. Error bars represent standard deviation.

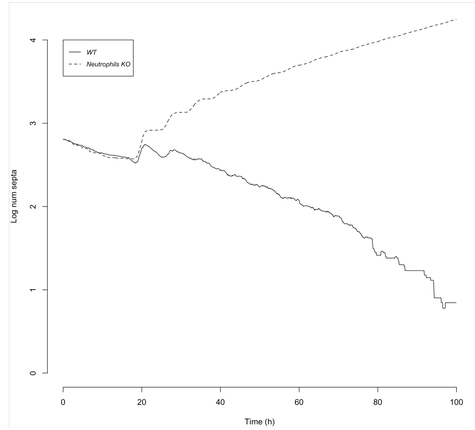


Figure 3: Sample simulation run. WT and neutrophil KO. WT evolves to clearance while KO shows unrestrained growth. The scale is in log base 10 for better visualization. Unbounded growth is to be interpreted as a failure of the innate immune response to control the infection.

Table 1: Sensitivity analysis performed with partial ranking correlation coefficient and Latin-hypercube-sampling. The table shows the mean plus or minus standard deviation. The table presents the parameters that were more than 1.96 standard deviations away from zero. In bold are the three top parameters by absolute correlation from each model. Parameters were subdivided into four groups: recruitment and chemotaxis (orange), iron-related (red), strength of the immune response (blue), and fungal biology (green). Notice that, in general, the highest partial correlations were related to recruitment and chemotaxis. But there were also many parameters related to iron immune response.

Parameter	Description	Neutropenic	Immunocompetent	
REC_RATE	global recruitment rate	**-0.5153 ± 0.0376**	**-0.5095 ± 0.0362**	Recruitment & a chemotaxis related parameters
MIP1b_QTTY	MIP-1b secretion rate	**-0.4404 ± 0.0409**	−0.0725 ± 0.0525	
MIP2_QTTY	MIP-2 secretion rate	−0.0006 ± 0.0503	**-0.3896 ± 0.0448**	
DIFFUSION_RATE	global diffusion rate	0.1474 ± 0.0459	**0.4940 ± 0.0394**	
TAFC_Up	TAFC uptake rate	0.1654 ± 0.0469	−0.0439 ± 0.0484	Iron related parameters
TAFC_QTTY	TAFC secretion rate	0.1793 ± 0.0457	0.0483 ± 0.0506	
K_M*_Tf_TAFC*	Michaelis constant of transferrin-TAFC reaction	−0.1253 ± 0.0511	−0.0503 ± 0.0464	
k_d *– LIP*	*A. fumigatus* metabolic sensibility to iron	−0.2096 ± 0.0465	0.0378 ± 0.0512	
TF_SLOPE	slope of the function hepcidin-transferrin	−0.1765 ± 0.0515	−0.0078 ± 0.0515	
PR_MA_PHAG	macrophage phagocytosis probability	−0.0720 ± 0.0468	−0.1492 ± 0.0477	Strength of the immune response (not including recruitment & chemotaxis)
INT_HYPHAE	probability to interact with hyphae (macrophage and neutrophil)	0.0045 ± 0.0512	−0.2496 ± 0.0469	
PR_KILL	probability to kill internalized conidia	−0.2661 ± 0.0488	−0.1977 ± 0.0504	
TIME_STATUS	time cells remain activate without stimulus	**0.4345 ± 0.0402**	0.1707 ± 0.0474	
INV_GROWTH_RATE	inverse of growth rate	−0.1646 ± 0.0502	0.0544 ± 0.0493	Fungal biology parameter

THE TEAM

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CONCLUDING REMARKS

Mathematical modeling can be an effective approach to the exploration of mechanisms of innate immunity in the lung in response to fungal pathogens. It allows the integration of known biophysics, biology, and immunology, as well as experimental data into a multi-scale computational model that can serve as an investigative tool to guide experiments.

1. Werner, JL et. al. (2009). Requisite Role for the Dectin-1 β-Glucan Receptor in Pulmonary Defense against Aspergillus fumigatus, J. Immunol. *182*, 4938-4946. doi:10.4049/jimmunol.0804250
2. Hohl, TM et al. (2005). Aspergillus fumigatus Triggers Inflammatory Responses by Stage-Specific b-Glucan Display. PLoS PATHOGENS 1(3). doi.org/10.1371/journal.ppat.0010030