Supplemental data for:

The heme-scavenger, hemopexin, protects against lung injury during aspergillosis by mitigating release of neutrophil-extracellular traps

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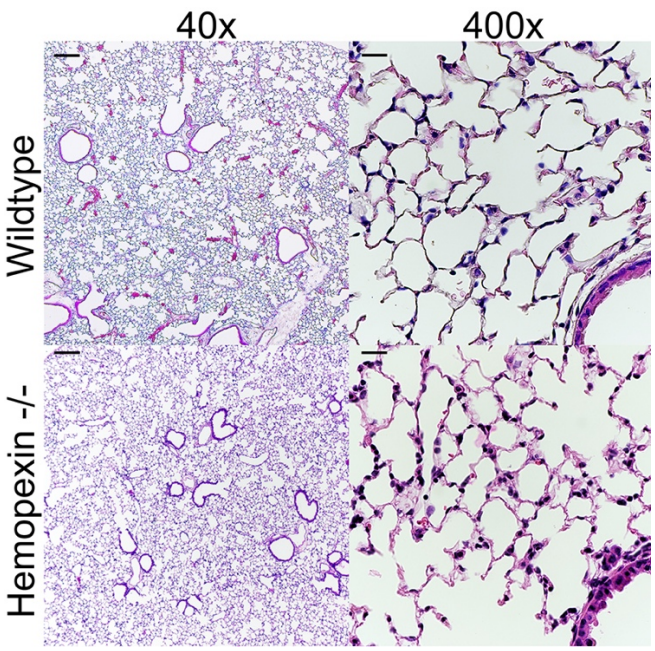

Figure S1. Lung histology (Hematoxylin and eosin stain) of uninfected wildtype and hemopexin-deficient mice. Representative images from 3 independent experiments. Original magnifications are indicated. Scale bars are 200μm and 20μm long in the 40x and 400x micrographs, respectively.

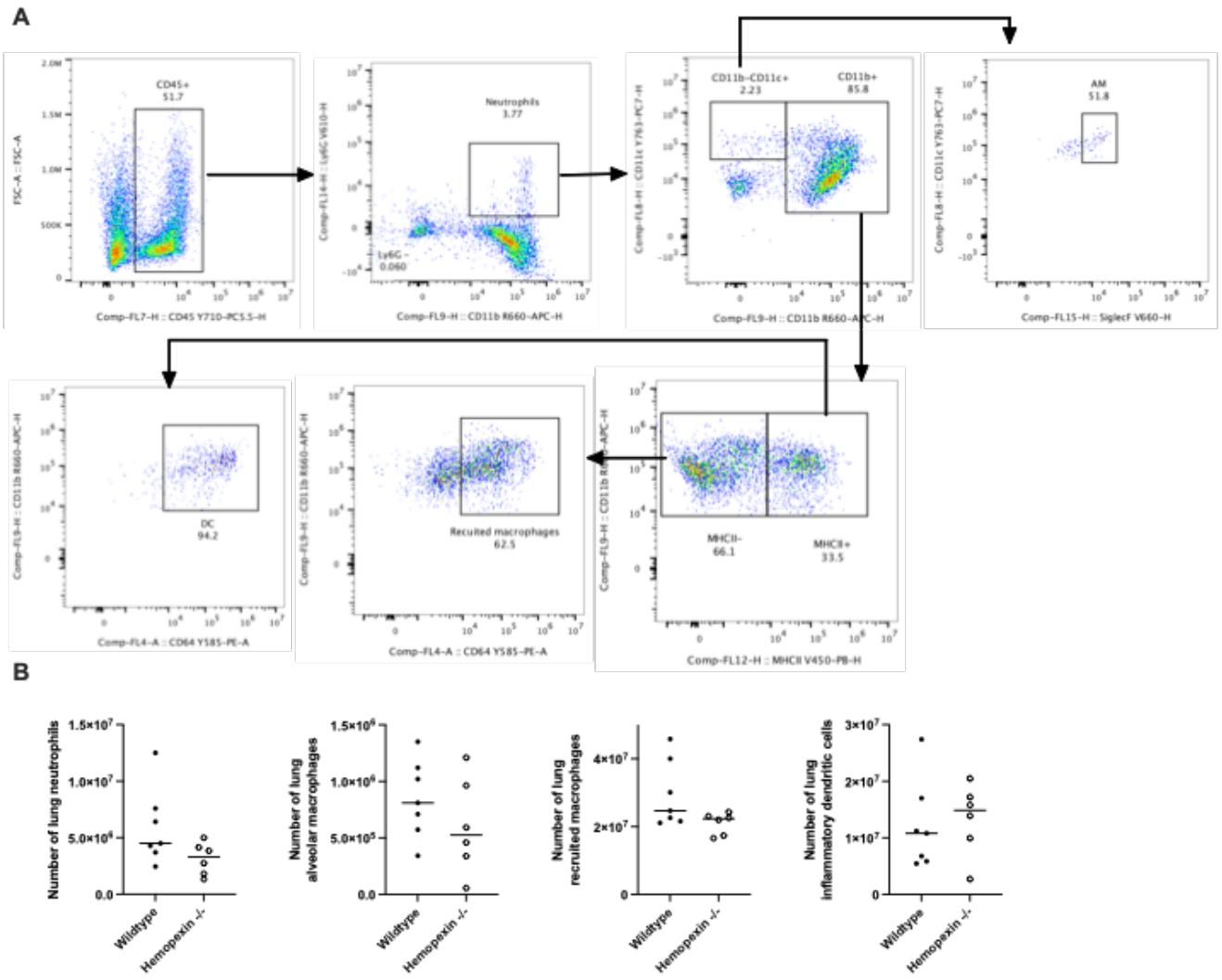

Figure S2. Lung flow cytometry on day 3 of aspergillosis. (A) Flow cytometry gating strategy of lung leukocyte subsets. Lung cells were first gated on single cells, then live cells, followed by the panels shown. (B) Absolute number of lung leukocyte subsets in wildtype and hemopexin-deficient mice on day 3 of infection. Dots represent individual animals and horizontal lines represent medians. Data shown are pooled from 2 independent experiments. No significant statistical differences by two-tailed Mann-Whitney.

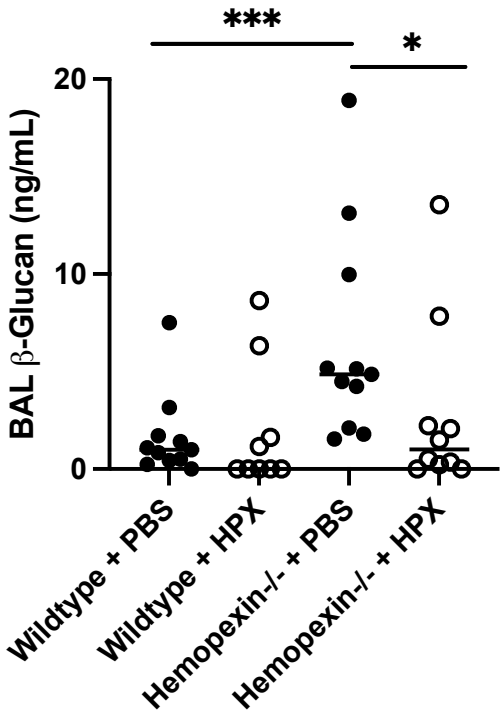

Figure S3. The effect of administration of intra-pulmonary hemopexin (HPX), as compared to PBS vehicle, on lung fungal burden (measured as BAL β-glucan concentration) on day 3 of infection. Dots represent individual animals and horizontal lines represent medians. Data shown are pooled from 2 independent experiments. * denotes *p* values of <0.05 by one-way ANOVA with Dunn's multiple comparison test.

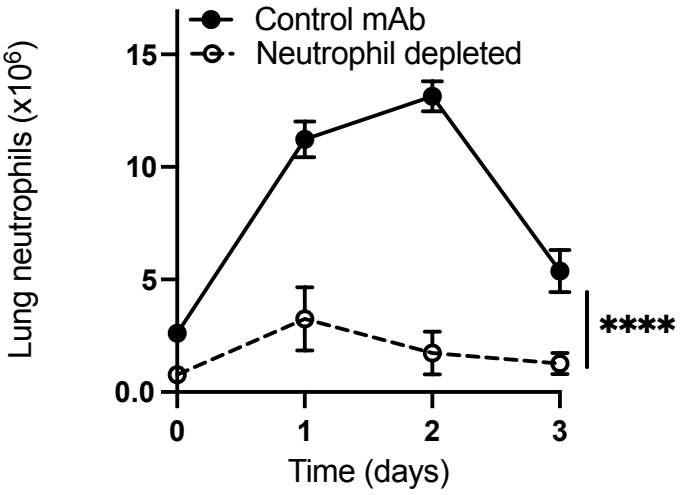

Figure S4. Number of lung neutrophils in the lung of wild type mice, after administration of neutrophil-depleting antibody (clone 1A8) or isotype control (clone 2A3) on day -1, followed by intrapulmonary challenge with *Aspergillus* conidia on day 0. Values represent mean ± SEM of n = 5 animals per group per time point, and time 0 refers to antibody-treated but uninfected animals. Data shown are pooled from 2 independent experiments. **** denotes *p* values of <0.0001 by two-way ANOVA.

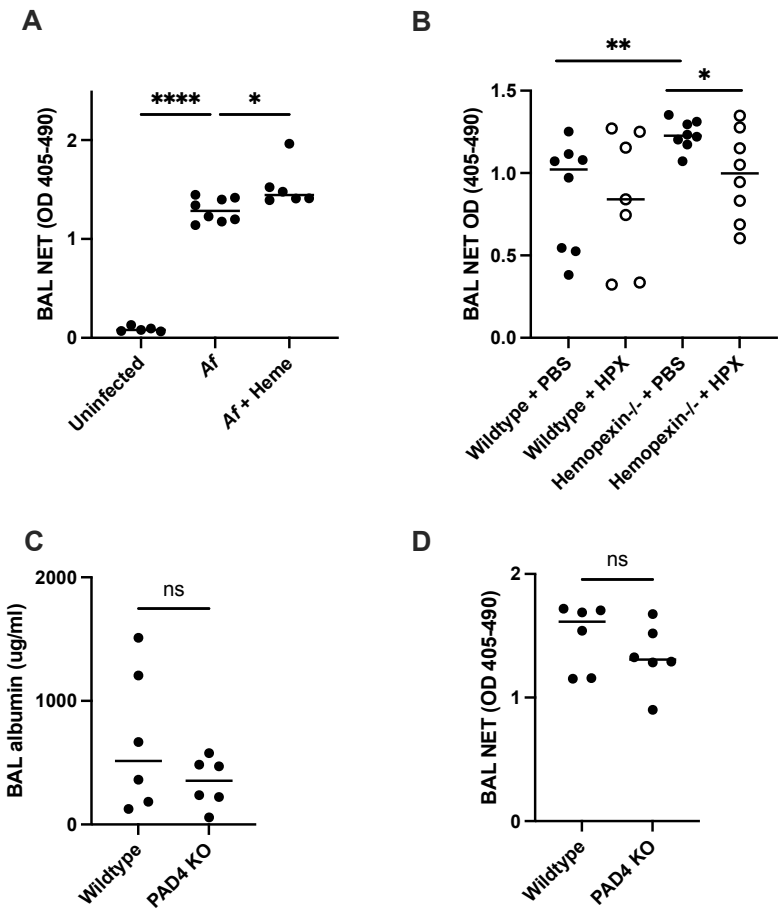

Figure S5. The effect of heme on lung NET formation in wildtype mice with neutropenic aspergillosis and the role PAD-4. BAL (A) Lung NET content of uninfected wildtype mice and *Aspergillus* infected neutropenic wildtype mice with or without administration of heme. (B) Lung NET content of neutropenic wildtype and hemopexin-deficient mice with neutropenic aspergillosis, with or without treatment with intrapulmonary hemopexin. (C-D) Extent of lung injury, as measured as BAL fluid albumin concentration and level of BAL NETs in neutropenic wildtype and PAD-4 deficient mice with aspergillosis. Dots represent individual animals and horizontal lines represent medians. Each panel represents pooled data from 2 independent experiments. *, **, and **** denote *p* values of <0.05, <0.01, and <0.0001 respectively. Statistical tests: A-B, one-way ANOVA; C-D, two-tailed Mann-Whitney.

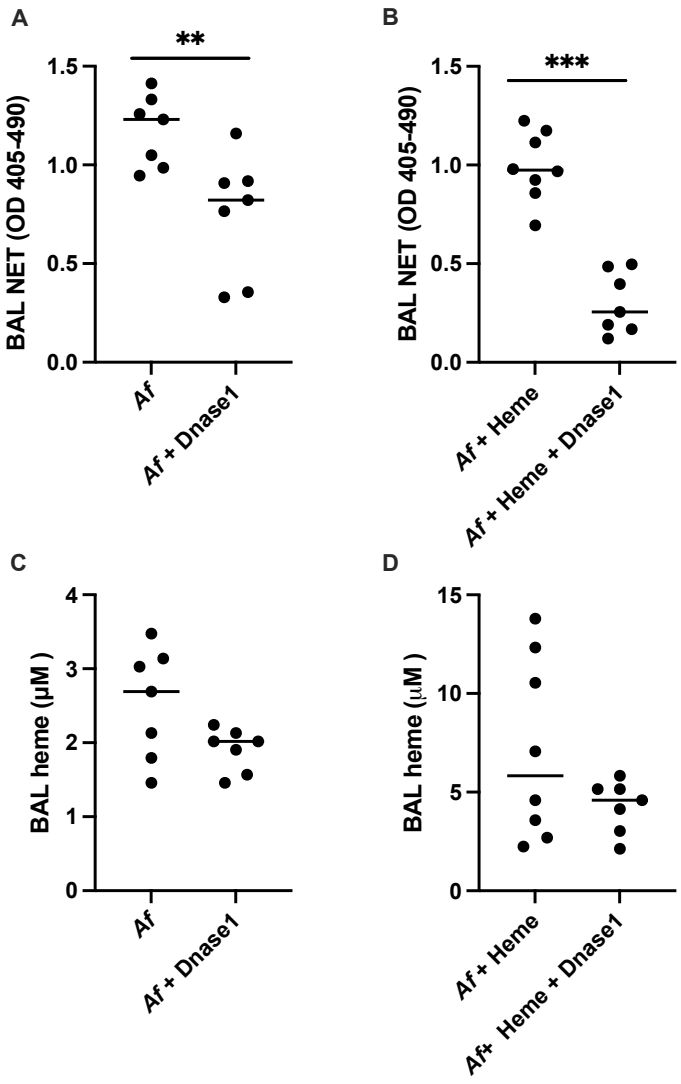

Figure S6. Effect of DNAse treatment on lung NET formation and extravascular heme in wildtype mice with neutropenic aspergillosis. (A, C) DNAse-1 was administered on day 2 and BAL NETs measured on day 3 of infection. (B, D) Dnase1 was administered on day 1 and measurements were taken on day 2 of infection. Dots represent individual animals and horizontal lines represent medians. Each panel show pooled data from 2 independent experiments. ** and *** denote *p* values of <0.01 and <0.001 respectively by two-tailed Mann-Whitney.

Computational model

Description of the base model

The base model is described in detail in [1]. We provide a general description of this model in this section for completeness: The model contains five cell types: *Aspergillus* (as resting conidia, swollen conidia, or hyphae), neutrophils, macrophages, and types I and II pneumocytes. Macrophages and neutrophils are motile cells and move randomly or biased towards a chemokine gradient, and die with a half-life (Table S1). Contact with hyphae and swollen conidia activates leukocytes and type II pneumocytes, leading them to secrete cytokines (TNF, IL10, CCL4, CXCL2). Leukocytes can phagocytose swollen conidia and kill hyphae. Type I pneumocytes inhibit hyphae elongation by a contact-mediated mechanism. Contact with the fungus and TNF each activate macrophages classically, to an M1 phenotype, whereas IL10, TGF, and apoptotic bodies activate macrophages to an M2 phenotype incapable of killing. Activated neutrophils also degranulate, releasing lactoferrin, a molecule that competes with fungal siderophore, TAFC, for iron.

Aspergillus starts as resting conidia. After four hours, it becomes swollen becomes visible for leukocytes and type II pneumocytes, and begins secreting siderophores. Both iron and heme serve as nutrients for fungal growth: with enough iron, *Aspergillus* conidia germinate, and hyphae will elongate and branch. Equation 1 computes the number of iterations for the next 40 um segment of fungi to grow, given the internal concentration of heme and iron. We use the reciprocal of Michaelean kinetics as a phenomenological equation to integrate heme and iron as nutrients that contributing to fungal growth.

$$t = T \cdot \frac{K_I \cdot I + K_H \cdot H + I \cdot H}{H \cdot I} \cdot EPI_{INH}$$

Equation 1: where "t" is the number of iterations until the next 40 um hyphal fragment grows. "T" is the inverse of the growth rate (r). K_I is the iron K_M, and K_H is the heme K_M. I and H are internal iron and heme concentrations. EPI_{INH} is the growth inhibition by alveolar epithelial cells.

Cytokines and TAFC released into the alveolus diffuse according to a partial differential equation [1], undergo decay (with a half-life), and diffuse into plasma.

Changes from the published base model

Although cells interact with their environment continuously, the experimental data that the model is based on is not continuous. In order for the model to more closely match the available experimental data, we revised the model so that each cell interacts with its environment every 30 minutes instead of every iteration. In every iteration, we select a subset of cells of a type (such as a subset of the macrophage) to interact with other cells and molecules, with any given cell is selected only every 15 iterations (30 minutes). Likewise, the Boolean networks are updated every thirty minutes.

We rewrote the state model from epithelial cells and neutrophils as Boolean networks. Neutrophils are activated by heme or *Aspergillus*. Activated neutrophils release lactoferrin and then change to either apoptotic or NETotic states, whereas non-activated neutrophils only die by apoptosis. Neutrophil apoptosis or NETosis occur with a half-life of 6h. NETs and hyphae kill type I pneumocytes, result in release of extracellular heme

into the alveolus. In addition to neutrophils, heme also activates M1 macrophages (described below). Once a type I epithelial cell dies, it results in the appearance of extracellular heme in the alveolus, simulating hemorrhage. The heme quantity is finite and is not replenished and does not diffuse, simulating clotting after hemorrhage. Once the type I pneumocytes die, their inhibition over hyphae elongation is lifted.

We refined the macrophage state model to a Boolean network model based on [104]. We ran the network until it reached equilibrium, and then assessed the macrophage phenotypes. Macrophages with activation of NFKB, STAT1, or STAT5 are classified as M1; STAT6 as M2A; ERK as M2B; and STAT3 as M2C.

Since the quantity of cytokines secreted by neutrophils was minimal in the previous model, we eliminated neutrophil cytokine secretion in this version. We also removed the IL6-hepcidin axis from the model, because this axis had little effect on the model outcome, and experimental evidence from our group showed that hepcidin did not affect infection evolution [69].

Table S1: Parameters of the revised mathematical model.

ID	Parameter	Description	*Value*	Reference
1	CCL4_QTTY	CCL4 secretion rate by macrophages and type II pneumocytes	$1.79 \times 10^{-20}\ \mathrm{mol \cdot cell^{-1} \cdot h^{-1}}$	[2,3,4,5,6,7,8,9, 10,11,12,13,14, 15,16,17,18,19,
2	CXCL2_QTTY	CXCL2 secretion rate by macrophages and type II pneumocytes	$1.11 \times 10^{-19}\ \mathrm{mol \cdot cell^{-1} \cdot h^{-1}}$	20,21,22,23,24, 25,26,27,28,29, 30,31]
3	TNF_QTTY	TNF secretion rate by macrophage and type II pneumocytes	$3.22 \times 10^{-20}\ \mathrm{mol \cdot cell^{-1} \cdot h^{-1}}$	
4	IL10_QTTY	IL10 secretion rate by macrophages	$6.97 \times 10^{-22}\ \mathrm{mol \cdot cell^{-1} \cdot h^{-1}}$	
5	TGF_QTTY	TGF secretion rate by macrophages	$1.01 \times 10^{-21}\ \mathrm{mol \cdot cell^{-1} \cdot h^{-1}}$	
6	Lac_QTTY	Amount of lactoferrin	$5.36 \times 10^{-18}\ \mathrm{mol \cdot cell^{-1}}$	[32]
7	Kd_CCL4	Kd of the CCL4 receptor	$180\ \mathrm{pM}$	[33]
8	Kd_CXCL2	Kd of the CXCL2 receptor	$91.667\ \mathrm{pM}$	[34,35]
9	Kd_IL10	Kd of the IL10 receptor	$140\ \mathrm{pM}$	[36,37,38,39]
10	Kd_TNF	Kd of the TNF receptor	$326\ \mathrm{pM}$	[40,41,42,43,44 ,45,46,47]
11	Kd_TGF	Kd of the TGF receptor	$26.5\ \mathrm{pM}$	[48,49,50]
12	D	Diffusion rate	$850\ \mu\mathrm{m^2/min}$	[51,52]
13	λ	Cytokine half-life	$1\mathrm{h}$	[53,54,55,56,57 , 58,59]
14	TF_CONC	Transferrin concentration	$32.25\ \mu\mathrm{M}$	[60,61,62]
15	APO_TF_REL_CON	Apo-transferrin relative concentration	40%	[62, 63]
16	TFFE_REL_CON	Mono-ferric transferrin relative concentration	16.57%	
17	TFFE2_REL_CON	Di-ferric transferrin relative concentration	43.43%	
18	MA_IRON_EXP	Macrophage iron export rate	$1367.30\ \mathrm{M^{-1} \cdot h^{-1}}$	[64]
19	MA_IRON_IMP	Macrophage iron import rate	$5.33 \times 10^{-12}\ \mathrm{L \cdot cell^{-1} \cdot h^{-1}}$	[64]
20	MA_INT_IRON	Macrophage initial internal iron concentration	$1.0086 \times 10^{-14}\ \mathrm{mol}$	[62]
21	TAFC_QTTY	TAFC secretion rate	$1.0 \times 10^{-15}\ \mathrm{mol \cdot cell^{-1} \cdot h^{-1}}$	[65]
22	TAFCBI_UPTAKE	uptake rate of TAFC bound to iron	$1.0 \times 10^{-12}\ \mathrm{L \cdot cell^{-1} \cdot h^{-1}}$	[66,67]
23	K_I	Michaelian constant for the iron substrate in Equation 1	$47.43\ \mu\mathrm{M}$	[68]
24	K_H	Michaelian constant for the heme substrate in Equation 1	$979.01\ \mathrm{nM}$	[69]
25	Kcat_Km_TAFC	Kcat/Km TAFC-Tf iron chelation reaction	$397.77\ \mathrm{M^{-1} \cdot s^{-1}}$	[63,65]
26	Kcat_Km_LAC	Kcat/Km lactoferrin-Tf iron chelation reaction	$399.20\ \mathrm{M^{-1} \cdot s^{-1}}$	[32]
27	r	Hyphae elongation rate	$80\ \mu\mathrm{m/h}$	[70]
28	PR_BR	Hyphae branch probability	33.3%	[70]
29	PR_SW	Conidia swelling probability	0.39%	[71,72]
30	T_SWELL	Time until conidia start swelling	$4\mathrm{h}$	[73]
31	MV_RT	Leukocyte movement rate	$1.44\ \mu\mathrm{m/min}$	[74, 75]
32	N_H_KILL	Neutrophil-hyphae killing probability	22.71%	[76,77,78,79]

33	MA_H_KILL	Macrophage-hyphae killing probability	9.85%	[80,81]
34	N_PHAG	Probability of neutrophil to phagocytose swollen conidia	14.72%	[79]
35	MA_PHAG	Probability of macrophage to phagocytose swollen conidia	90.55%	[82,83]
36	MA_MAX_CONIDIA	Maximum number of phagocytosed conidia inside a macrophage	18	[83]
37	N_MAX_CONIDIA	Maximum number of phagocytosed conidia inside a neutrophil	3	[83,84]
38	E_INT	Epithelial cell-Aspergillus (swollen conidia or hyphae) interaction probability	4.49%	[85]
39	PHAG_KILL	Leukocyte probability to kill ingested conidia	1.28%	[86]
40	MA_HALF_LIFE	Macrophage half-life	24h	[87]
41	N_HALF_LIFE	Neutrophil half-life	6h	[88]
42	PR_NET	Probability that an activated neutrophil will undergo NETosis instead of apoptosis	30%	[89]
43	H_VOL	Hyphae volume	$1.06 \times 10^{-12}\ \text{L}$	[90,91,92, 93]
44	SEPATE_L	Length of hyphal segments between septa	$40\ \mu\text{m}$	[92,93]
45	CONIDIA_VOL	Swollen conidia volume	$4.84 \times 10^{-14}\ \text{L}$	[91]
46	MA_VOL	Macrophage volume	$4.85 \times 10^{-12}\ \text{L}$	[94]
47	TURNOVER_RT	Molecule exchange rate between lung and whole-body serum	0.1823h^{-1}	[95]
48	MAX_N	Maximum number of neutrophils	522	[96, 97, 98, current manuscript]
49	MIN_N	Minimum number of neutrophils	15	
50	MAX_MA	Maximum number of macrophages	627	
51	MIN_MA	Minimum number of macrophages	15	
52	REC_RT	Leukocyte recruitment rate	9.77×10^{14}	[97]
53	ATII_NUM	Number of type II pneumocytes	640	[99, 100]
54	AVG_ATI_NUM	Average number of type I pneumocytes	320	
55	AF_INIT_IRON	A. fumigatus initial iron content	$3.83 \times 10^{-18}\ \text{mol}$	[91,68]
56	AF_INIT_HEME	A. fumigatus initial heme	$1.03 \times 10^{-18}\ \text{mol}$	[69]
57	HEME_UP	Heme uptake rate	$7.81 \times 10^{-4}\ \text{L} \cdot \text{cell}^{-1} \cdot \text{h}^{-1}$	[69, Current manuscript]
58	HEME_QTTY	Amount of heme that enters the alveoli upon hemorrhage	$2.07 \times 10^{-15}\ \text{mol}$	Current manuscript
59	PR_NET_KILL	Probability that NET will kill a type I epithelial cell	1.3%	[101, Current manuscript]
60	PR_HYPHAE_KILL	Probability that hyphae will kill a type I epithelial cell	2.51%	[102]
61	EPI_INHIB	Type I epithelial cells rate of inhibition of hyphae elongation	50%	[71]
62	NET_HALF_LIFE	NET half-life	3h	[103]

Notes: Parameters 1-5 were obtained as described [1]. Probabilities of phagocytosis, killing, and interaction refer to the likelihood of an event succeeding in one iteration if the appropriate conditions apply. The maximum number of cells and the average number of

epithelial cells is computed over the simulated space. Kcat, Enzymatic turnover number; Kd, dissociation constant; Km, Michaelis constant; TAFC, triacetylfusarinine C (*Aspergillus* siderophore); Tf, Transferrin.

Table S2: Interaction rules in the mathematical model.

ID	Interaction	Description	Type	Outcome	Reference
1	Macrophage -Neutrophil	Macrophage phagocytose apoptotic neutrophil	Probabilistic: Constant Probability	Phosphatidyl serine receptor activated	[9]
2	Macrophage -Aspergillus	Macrophage phagocytose swollen conidia	Probabilistic: Constant Probability	Dectin-2 receptor activated; conidia are internalized and subsequently killed	[4,105,106]
3	Macrophage -Aspergillus	Macrophage kills hyphae	Probabilistic: Constant Probability	Dectin-2 receptor activated; hyphae are killed	[4,80,81]
4	Macrophage -IL10	Macrophage with phenotype M1, M2A, M2B, and M2C secrete IL10	Deterministic: fixed amount	The local concentration of IL10 increases	[6,10,14,21,104, 107]
5	Macrophage -TGF	Macrophage with phenotype M2C secrete TGF	Deterministic: fixed amount	The local concentration of TGF increases	[6,10,14,21,107]
6	Macrophage -TNF	Macrophage with phenotype M1 and M2B secrete TNF	Deterministic: fixed amount	The local concentration of TNF increases	[2,3,5,6,10, 14,21,104,107,1 08]
7	Macrophage -CCL4	Macrophage with phenotype M1 secretes CCL4	Deterministic: fixed amount	The local concentration of CCL4 increases	[2,104,107]
8	Macrophage -CXCL2	Macrophage with phenotype M1 secretes CXCL2	Deterministic: fixed amount	The local concentration of CXCL2 increases	[5,104,108]
9	Macrophage -IL10	Macrophage primed by IL10	Probabilistic: constant probability	IL10 Receptor activated	[104,109]
10	Macrophage -TGF	Macrophage primed by TGF	Probabilistic: constant probability	TGF Receptor activated	[8,9,104]
11	Macrophage -TNF	Macrophage primed by TNF	Probabilistic: constant probability	TNF Receptor activated	[27,104]
12	Macrophage -Transferrin	Macrophage import/export iron from/to transferrin	Deterministic: import and export rate are proportional to the external levels of transferrin bound to iron and internal iron levels	Internal and external levels of iron and transferrin-bound iron change.	[64,110,111,112]
13	Neutrophil-Lactoferrin	Active Neutrophils release lactoferrin	Deterministic: fixed amount	The local concentration of lactoferrin increases	[77,113]
14	Neutrophil-Aspergillus	Neutrophils phagocytose swollen conidia	Probabilistic: constant probability	Neutrophils become active; swollen conidia are internalized and subsequently killed	[77]
15	Neutrophil-Aspergillus	Neutrophils kill hyphae	Probabilistic: constant probability	Neutrophils become active; hyphae are killed	[77,105]
16	Type II Pneumocyte -Aspergillus	Type II Pneumocyte interacts with swollen conidia or hyphae	Probabilistic: initial interaction has a fixed probability. Once the	Type II Pneumocyte becomes cytokine-secreting	[114,115]

			interaction is established it is stable		
17	Type II Pneumocyte -TNF	cytokine secreting Type II Pneumocyte secrete TNF	Deterministic: fixed amount	The local concentration of TNF increases	[31]
18	Type II Pneumocyte -CCL4	Chemokine secreting Type II Pneumocyte secrete CCL4	Deterministic: fixed amount	The local concentration of CCL4 increases	[116]
19	Type II Pneumocyte -CXCL2	Chemokine secreting Type II Pneumocyte secrete CXCL2	Deterministic: fixed amount	The local concentration of CXCL2 increases	[116]
20	Type II Pneumocyte -TNF	Type II Pneumocyte is primed by TNF	Probabilistic: constant probability	Type II Pneumocyte becomes cytokine/chemokine secreting	[31]
21	Aspergillus-TAFC	Aspergillus (hyphae and swollen conidia) with TAFC node “ON” secretes TAFC	Deterministic: fixed amount	The local concentration of TAFC increases	[68,117,118]
22	Aspergillus-TAFC	Aspergillus with nodes MirB and EstB “ON” import TAFC bound to iron *	Deterministic: proportional to the concentration of TAFC bound to iron	The local concentration of TAFC-bound iron decreases. Internal iron pool increases	[66,117]
23	TAFC-transferrin	TAFC sequester iron from transferrin bound to iron	Deterministic: Michaelian kinetics	The local concentration of TAFC and Tf-iron decreases Local levels of TAFC-iron and free-transferrin increases.	[65,118]
24	Lactoferrin-transferrin	Lactoferrin sequester iron from transferrin bound to iron	Deterministic: Michaelian kinetics	The local concentration of lactoferrin and Tf-iron decreases. Local levels of lactoferrin bound to iron and free-transferrin increases.	[32,119]
25	Macrophage -iron	Necrotic macrophage releases its iron content	Deterministic: the whole iron content of the cell is released	The local concentration of iron increases	NA**
26	Iron-Aspergillus	Dead hyphae release its iron content	Deterministic: the whole iron content of the cell is released	The local concentration of iron increases	NA**
27	Iron-Iron-transport-molecule	Lactoferrin, Transferrin, or TAFC chelates the whole iron in content of the voxel	Deterministic: the molecules race to chelate the iron in the voxel. The first to be selected chelates the whole iron content or the maximum of its capacity	The local iron concentration decreases to zero. Iron bound to carriers (TAFC-iron, Lactoferrin-iron, or Tf-iron) increase.	NA
28	Type I Pneumocytes-Aspergillus	Hyphae kill type I pneumocytes. Pneumocytes that	Probabilistic: constant probability to kill	Type I cell dies or is injured	[102]

		are not killed are injured.			
29	Type I Pneumocytes-Aspergillus	Live Type I pneumocyte decrease hyphae elongation rate	Deterministic: decrease the elongation rate by a fix percentage	Elongation rate decreases	[71]
30	Type I pneumocyte-Heme	Dead type I pneumocytes releases extracellular heme in the alveolus	Deterministic	Heme become available to interact with neutrophils and Aspergillus.	This work
31	Type I-Neutrophil	NET kill type I pneumocyte	Probabilistic: constant probability (default scenario). Deterministic: NET kill injured cells (alternative scenario)	Type I cell become dead	[101]
32	Heme-Aspergillus	Aspergillus uptake Heme	Deterministic: proportional to the Heme concentration	The local heme concentration decrease. Internal Iron and Heme concentration increases	[69]
33	Heme-Neutrophil	Neutrophils are primed by Heme	Probabilistic: constant probability	Neutrophils become active	[120]

* MirB and EstB respectively mediate the uptake and hydrolysis of TAFC-iron complex by *Aspergillus.*

** For simplicity, we assume that upon death, host and fungal cells release their iron in free form.

NET, neutrophil extracellular trap; TAFC, triacetylfusarinine C (*Aspergillus* siderophore); Tf, Transferrin

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