Spatial distancing: Investigation of a defense mechanism for pathogen immune evasion

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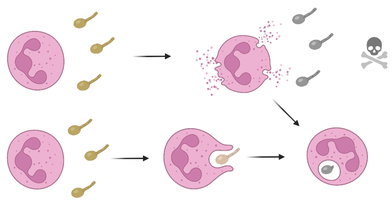
Abstract

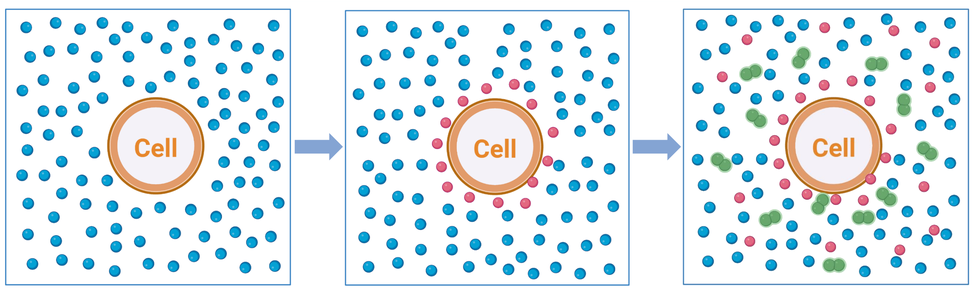
- Some **pathogens**, such as *Candida albicans*, can **evade** the **immune system** and **survive** in the host during **infections**. However, such mechanisms are not yet unraveled
- In this study we **investigate** and **simulate** a possible **immune evasive mechanism** referred to as **spatial distancing**: microbial pathogens secrete **defensive molecules** that **bind** to **antimicrobial peptides** and **diffuse away** from the cell due to molecular gradient
- 2 different modeling techniques were used: **Partial Differential Equations** and **Agent-Based Modeling**
- Results suggest **spatial distancing** as an **effective way** for microbial pathogens to **escape** the **immune system**

Introduction

- Immune system: a barrier against pathogens during infections
  - Extracellular killing via antimicrobial peptides (AMPs)
  - Phagocytosis with labeling via opsonins

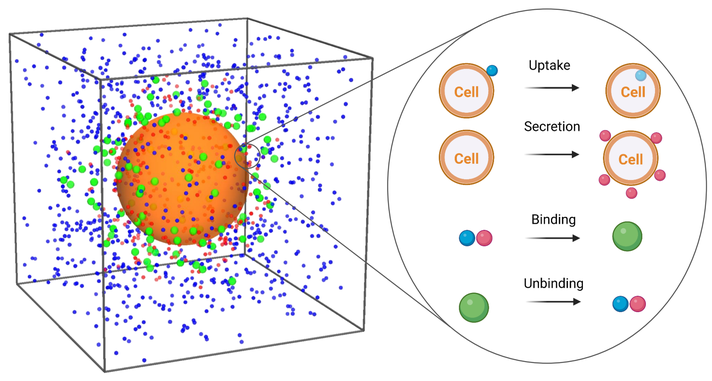


Mechanism



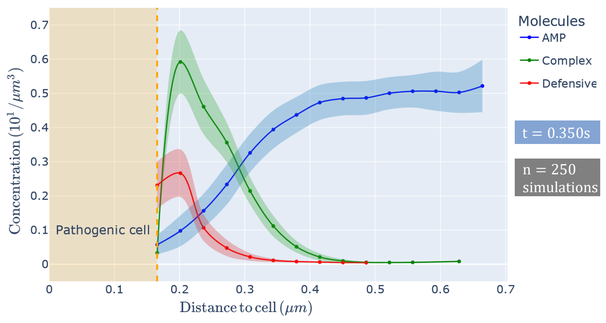
Agent-Based Modeling approach

- **Environment:** 3-dimensional, continuous
- **Molecules**: single agents performing Brownian motion
- **Suited for low concentrations:** formations of complexes are rare events



- Downscaled system with factor 10^{-3}

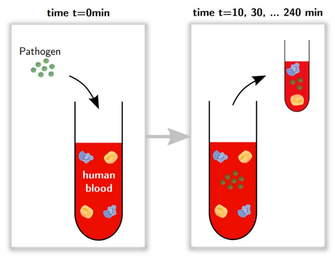
Time-resolved spatial distributions of molecules



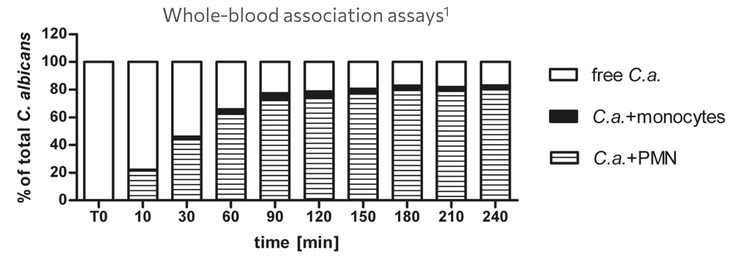
- Secretion of defensive molecules at the cell surface
- Formation of complex
- Concentration of AMPs lowered in the vicinity of the cell

Biological evidence

- *C. albicans* can escape the immune system



Whole-blood association assays[1]



Partial Differential Equation model

- **Environment:** 3-dimensional, continuous
- **Molecules:** concentrations diffusing on a discrete grid according to the gradient
- **Suited for high concentrations:** formations of complexes are frequent events

AMP

$$\frac{\partial [A]}{\partial t} = D_A \nabla^2 [A] + K_{off}[C] - K_{on}[A][D] - K^A_{deg}[A]$$

Defensive molecule

$$\frac{\partial [D]}{\partial t} = D_D \nabla^2 [D] + K_{off}[C] - K_{on}[A][D] - K^D_{deg}[D]$$

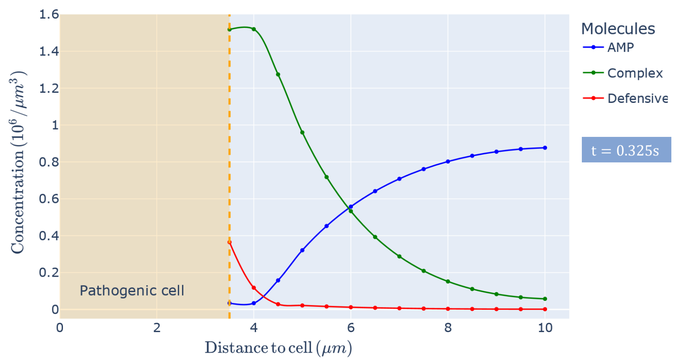
Complex

$$\frac{\partial [C]}{\partial t} = D_C \nabla^2 [C] + K_{on}[A][D] - K_{off}[C]$$

Parameter	Description	Unit
S_D	Secretion rate of defensive molecule	$\mu m^{-3} s^{-1}$
U_A	Uptake rate of AMP	s^{-1}
D_A	Diffusion coefficient of AMP	$\mu m^2 s^{-1}$
D_D	Diffusion coefficient of defensive molecule	$\mu m^2 s^{-1}$
D_C	Diffusion coefficient of complex	$\mu m^2 s^{-1}$
K^A_{deg}	Degradation rate of AMP	s^{-1}
K^D_{deg}	Degradation rate of defensive molecule	s^{-1}
K_{on}	Association rate [AMP – Defensive molecule]	$\mu m^3 s^{-1}$
K_{off}	Dissociation rate [AMP – Defensive molecule]	s^{-1}

Initial condition	Description	Unit
$[A]_{t=0}$	Concentration of AMP	μm^{-3}

Time-resolved spatial distributions of molecules



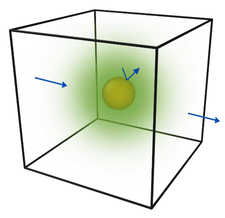
Boundary conditions

- **At the cube limit**: periodic boundaries
- **At the cell surface**: reflective boundaries

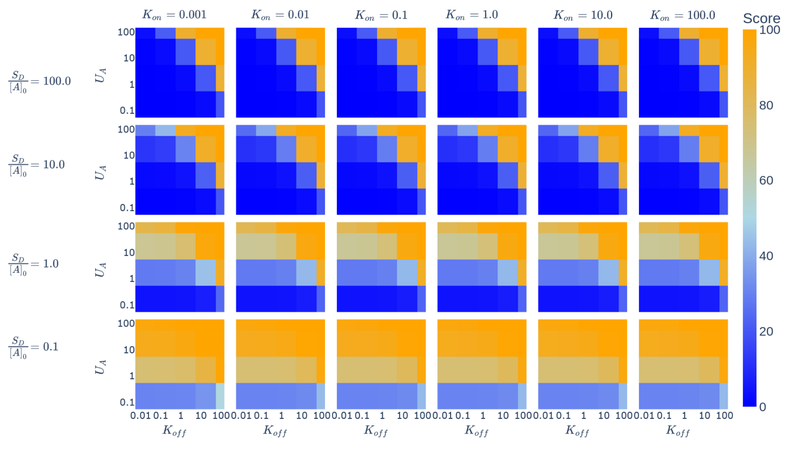
$$\left.\frac{\partial [A]}{\partial x}\right|_{memb} = 0, \quad \left.\frac{\partial [D]}{\partial x}\right|_{memb} = 0, \quad \left.\frac{\partial [C]}{\partial x}\right|_{memb} = 0$$

$$\left.\frac{\partial [A]}{\partial t}\right|_{x=memb} = -U_A [A]_{memb}$$

$$\left.\frac{\partial [D]}{\partial t}\right|_{x=memb} = S_D$$



Parameter screening



$$\text{Score} = \frac{\text{A}_{\text{uptaken}}}{\text{A}_{\text{total}}} \cdot 100$$

- High S_D and low K_{off} rates lead to a reduction in the uptake of AMPs by the pathogenic cell
- Beneficial regime for the pathogenic cell with a wide range of parameter combinations

Conclusion

- **Secretion** of **molecules** by the pathogenic cell **reduces** the **concentration** of **AMPs** in the **vicinity** of the **microbial cell**
- **Both PDE** and **ABM** approaches show **qualitatively similar dynamics**, suggesting **spatial distancing** as an **effective immune evasion mechanism**
- **Inhibition** of **molecules secreted by pathogens** in defense against AMPs could be a **target** for **therapeutic interventions**
- **Experimental validation:**
  - Binding assays between **LL37** (AMP) and **Msb2** (secreted by *C. albicans*)[2] show **high affinity** between both molecules

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References

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[2] Swidergall, M. *et al.* 2013. *American Society for Microbiology*.57:3917-3922

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