Immune Evasion by spatial distancing

Modeling *Candida albicans* Complement Regulator Pra1

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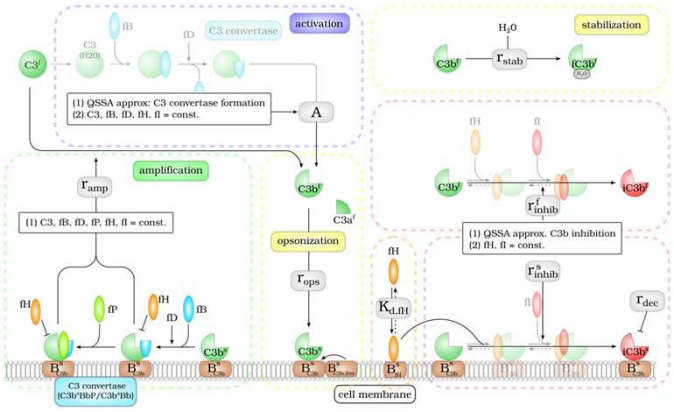
Biological Background:

The human **complement system** is part of the innate immune response and plays a key role in defending the host against invading pathogens. Its main task is the **recognition and subsequent opsonization** and lysis of foreign invaders. The central opsonin of the complement system is C3b which is a product of the proteolytic cleavage of C3. Since there exist a continuous default basal level of active complement molecules, a **tight regulation is required to protect the body's own cells** from opsonization and from complement damage. **One major complement regulator is Factor H**, which attaches to cell surfaces and subsequently controls complement activation. Furthermore, the invading pathogen *Candida albicans* has established evasion mechanisms to escape the host complement attack utilizing the molecule pH-regulated antigen 1(Pra1).

DynaCoSys Model:

- **Model predicts the opsonization level on the cell surface** based on the surface bound Factor H concentration
  - **Activation**: Cleavage of C3 by the alternative pathway
  - **Opsonization**: Binding of C3b from fluid phase to cell surface
  - **Regulation**: Deactivation of C3b in the fluid phase and cell surface
  - **Stabilization**: Binding of C3b with hydrogen in the fluid phase
  - **Amplification**: Creation of C3 convertase complex
- **Finite Element-based steady state analysis** describing the dynamics by a set of differential equations
  - **Ordinary differential equations** (ODEs) for cell-surface bound molecules
  - **Partial differential equations** (PDEs) for fluid phase concentration profiles in the cell environment
  - Investigation of time-resolved dynamics using an implicit Euler approach
- **Multi-Cell Model:** Mean-Field approximation of the DynaCoSys Model describing the interplay of several cells

Factor H mediated immune evasion:

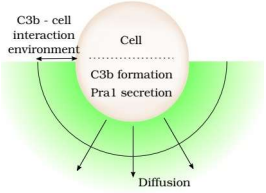


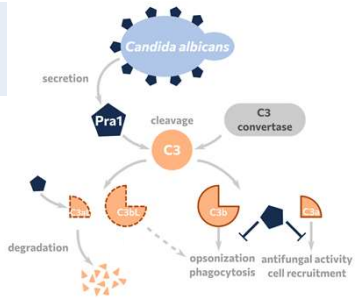
pH regulated antigen 1 (Pra1) mediated immune evasion:

Interaction between Pra1 and the complement system seems contradictory:

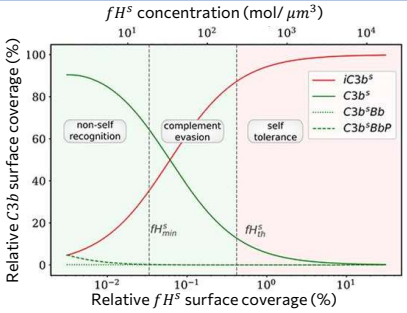
- Binding site for Factor H on the cell surface
- Binding of the cleavage products C3a and C3b
- Cleavage products C3a and C3b in fluid phase
- C3-cleaving protease resulting in products C3a-like(L) and C3bL
- C3bL may opsonize the fungal cell and interact with complement system

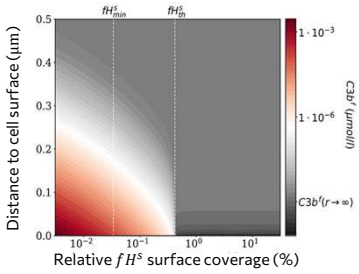
Hypothesis:
Pra1-C3(b) complex diffuses away from cell
→ Spatial distancing of C3(b)
→ Investigation with DynaCoSys Model





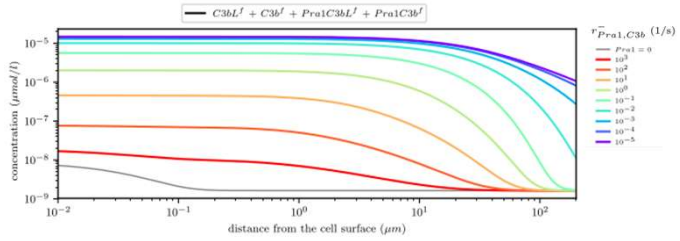
Result of the DynaCoSys Model:





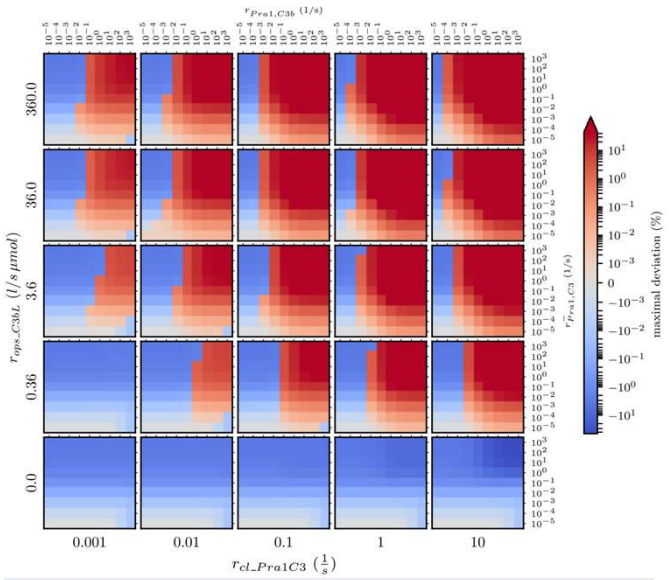
Identification of three different regimes:

- Non-Self-Regime: High opsonization level and C3b concentration close to the cell surface
- Complement-Evasion: Less amplification but still opsonzation levels
- Self-Regime: Only inactivated complement molecules on cell surface and low concentration profiles



Results:

- Pra1-mediated C3 cleavage decreases opsonization for non-cell surface binding C3bL
- Transportation of C3b and C3bL by Pra1 yields spatial distancing to the cell surface
- Pra1-secretion can inhibit complement activation by reducing the concentration of C3
- Immune evasion occurs via spatial distancing or for C3bL being unable to opsonize



Conclusion & Perspective:

- Identification of regimes of rates for Pra1-mediated immune evasion
- Spatial distancing has minor effect (0.03%) when C3bL is not able to opsonize
- Effect is increased to up to 80% if several cells in a system are considered
- Immune evasion via spatial distancing and C3 consumption is promising research topic on immune evasion in host-pathogen interactions

Further experiments needed:

- Role of C3bL and binding affinity needs to be further investigated by experiments
- C3 consumption of Pra1 for different cell concentrations

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References
[1] Tille A *et al.* (2020) *Frontiers in Immunology*, 11.