

M-27

Mathematical model of the factor H mediated self and non-self discrimination by the complement system

A. Tille, T. Lehnert, N. Reiher, P. Zipfel, M.T. Figge

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Alexander Tille¹, Teresa Lehnert¹, Nadine Reiher^{2,3}, Peter Zipfel^{2,3} and Marc Thilo Figge^{1,3}

¹Applied Systems Biology, Leibniz Institute for Natural Product Research and Infection Biology - Hans-Knoell-Institute, Jena, Germany
²Infection Biology, Leibniz Institute for Natural Product Research and Infection Biology - Hans-Knoell-Institute, Jena, Germany
³Faculty of Biological Sciences, Friedrich-Schiller-University Jena, Germany

complement system

- recognition and opsonization of invading microorganisms
- consists of a set of biochemical reactions on distinct pathways
- host cell protection with a tight regulation mechanism

aims of the model

- quantify reaction rates by fitting model to experimental data
- determine driving processes of the opsonization mechanism
- predict opsonization based on concentration of surface-bound factor H

mathematical model

- dynamics of protein concentration with ordinary differential equations
- simplified dynamic system: "as simple as possible, but not simpler"
- using quasi steady state approximation
- introducing effective rates: combination of unknown parameters

$$\frac{d}{dt} C3^f = r_{act} + r_{reg}(FH^s, C3^f) - S_{D-3D} \cdot C3^f - r_{reg} - S_{D-2D} \cdot B^s(FH^s, C3^f) \cdot C3^f - r_{inh} \cdot C3^f - r_{inh}^s \cdot C3^f$$
$$\frac{d}{dt} C3^s = r_{reg} - B^s(FH^s, C3^f) \cdot C3^f - r_{inh}^s \cdot C3^s - C3^s$$
$$\frac{d}{dt} C3^w = r_{inh}^s \cdot C3^s \cdot C3^w - \mu_{C3^w} \cdot C3^w$$

key molecules

- opsonin C3b:** - forms a molecular complex, that activates new C3b molecules
- regulator factor H (FH):** - plasma protein that can be bound to surfaces
- accelerates decay of C3b amplification complex
- mediates C3b degradation

reaction scheme of simplified mathematical model

capturing spatial information of the model

- a compartment model describes the molecule concentrations correctly

biological system → **compartment model**

well mixed system → **effective surface**

Scaling factor for 3D-2D interaction

results

- steady state analysis for varying parameters
- change of surface bound FH^s reveals sharp transition between two regimes
- self regime: neglectable opsonization
- non-self regime: massive opsonization, caused by a weakened regulation

experimental validation

in cooperation with Infection Biology Group, N.Reiher and P. Zipfel

idea:

- tuning surface-bound FH concentration of a model particle and measure C3b concentration on the surface

current experiments:

- coat latex beads with different concentrations of FH binding molecules

future experiments:

- investigate different mutants of *Candida albicans*, that express different amounts of FH binding molecules

summary

- model predicts opsonization level of a cell-based on the concentration of surface-bound FH
- simplified model is able to reproduce biological system qualitatively
- dominating processes of self and non-self regimes can be identified

perspective

- quantification of effective rates by model calibration with experimental data
- add a phagocytosis model/experiments
- investigate pathogens that are able to hide from complement (*C. albicans*)
- extend the model by more proteins to create a more realistic cell

CONTACT
Alexander.Tille@hki-jena.de
Research Group
Applied Systems Biology