Mathematical Modelling of APP Processing influenced by SORLA in Alzheimer's Disease

Angelyn Lao[1], Vanessa Schmidt[2], Katja Rateitschak[1], Thomas Willnow[2] and Olaf Wolkenhauer[1]

Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid plaques in the brain of affected individuals. This project aims at modeling of neurodegenerative processes in AD. Our study focuses on the interactome of neuronal factors central to the proteolytic processing of amyloid precursor protein (APP) into Aβ, the main constituent of senile plaques. Factors considered in this model include proteases, trafficking adaptors, as well as a novel sorting receptor SORLA. Here, we have generated a panel of cell lines in which the amount of APP and of accessory factors can be varied. These novel cell lines are important research tools that have since been applied to produce quantitative data. The quantitative dose-response series have been used to estimate reaction constants of mathematical models describing APP processing. We have established nonlinear ordinary differential equation models describing the cleavage of APP by alpha and beta secretases, and the influence of SORLA herein. We have queried different mathematical models concerning the interactions with SORLA and we have simplified the models based on justifiable steady state approximations. For the resulting algebraic models, we have estimated the model parameters from the dose-response curves by nonlinear optimization methods. These results provide the bases for further modeling of neurodegenerative processes and for determination of individual risk of AD.

APP processing influenced by SORLA – network diagrams

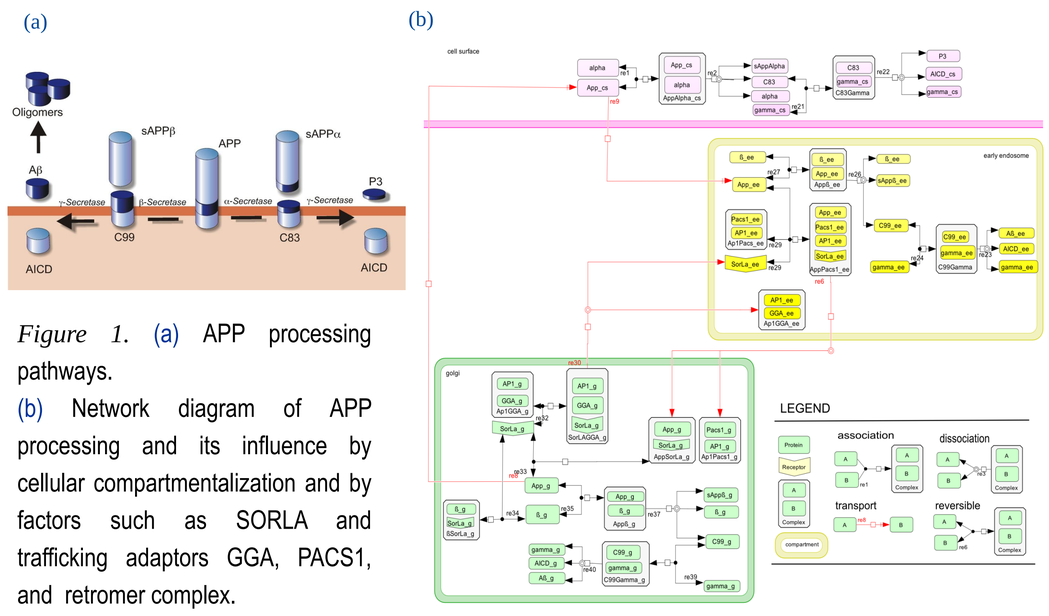


Figure 1. (a) APP processing pathways.
(b) Network diagram of APP processing and its influence by cellular compartmentalization and by factors such as SORLA and trafficking adaptors GGA, PACS1, and retromer complex.

Regulated expression of APP in cells

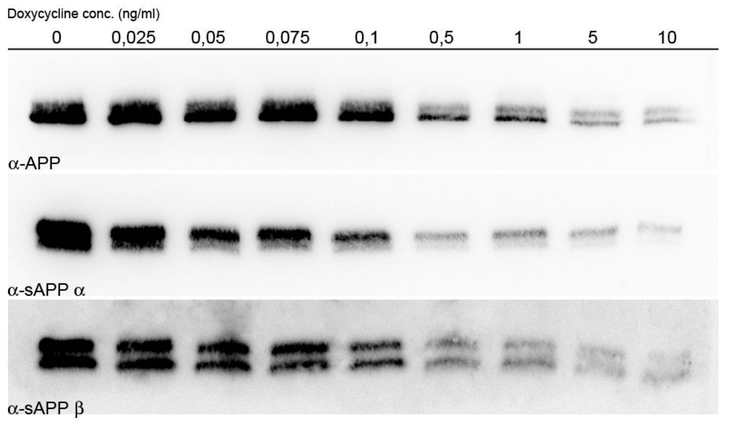
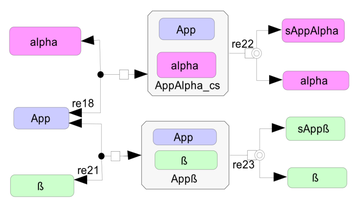


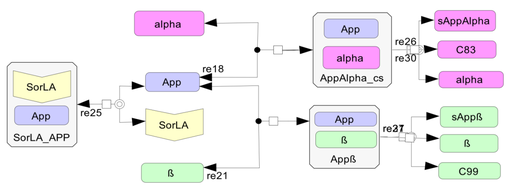
Figure 4. Cells were incubated with doxycycline of the indicated concentrations. Western blot analysis of cell media and lysates showed decreased amounts of APP and its processing products with increasing doxycycline concentration.

Subsystems - mathematical models

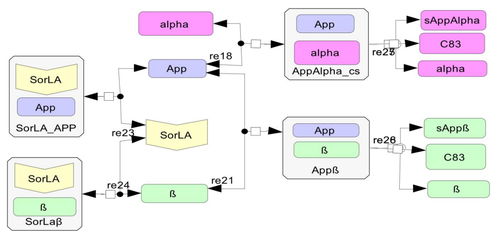
(a) APProI



(b) APProS I (Hypothesis 1)



(c) APProS II (Hypothesis 2)



(d) Simplified mathematical models

APProI

$$sAPP_\alpha = V_{maxa}\frac{APP}{K_{Ma} + APP}$$

$$sAPP_\beta = V_{maxb}\frac{APP}{K_{Mb} + APP}$$

$$APP_{Tot} = APP + C_{APP\beta}(APP) + C_{APP\alpha}(APP)$$

APProS I

$$sAPP_\alpha = V_{maxa}\frac{APP}{K_{Ma} + APP}$$

$$sAPP_\beta = V_{maxb}\frac{APP}{K_{Mb} + APP}$$

$$APP_{Tot} = APP + C_{APP\beta}(APP) + C_{APP\alpha}(APP) + C_{APPSorLA}(APP)$$

APProS II

$$sAPP_\alpha = V_{maxa}\frac{APP}{K_{Ma} + APP}$$

$$sAPP_\beta = \frac{V_{maxb}\cdot APP}{K_{Mb}\left(1 + \frac{SorLA}{K_{Db}}\right) + APP}$$

$$APP_{Tot} = APP + C_{APP\beta}(APP) + C_{APP\alpha}(APP) + C_{APPSorLA}(APP)$$

Figure 2. (a) APProI: competitive binding process of alpha and beta secretases for APP. (b) Hypothesis 1. APProSI: SORLA joins the competition for APP binding in APProI. (c) Hypothesis 2. APProSII: an extension of APProSI whereby SORLA also interacts with beta secretase.
(d) Table of simplified mathematical equations, derived from the rate equations of each subsystem. Nonlinear differential equations are simplified through justifiable assumption of a quasi-steady state and a conservation law. Note that "APP" (stands for the free APP) in each equations is replaced by their respective function of APP_{Tot} (total APP measured in experiments).

Comparison of experimental data and model simulations

Parameter value of the models have been determined on the basis of experimental dose-response series for APP-sAPPα and APP-sAPPβ by nonlinear optimization.

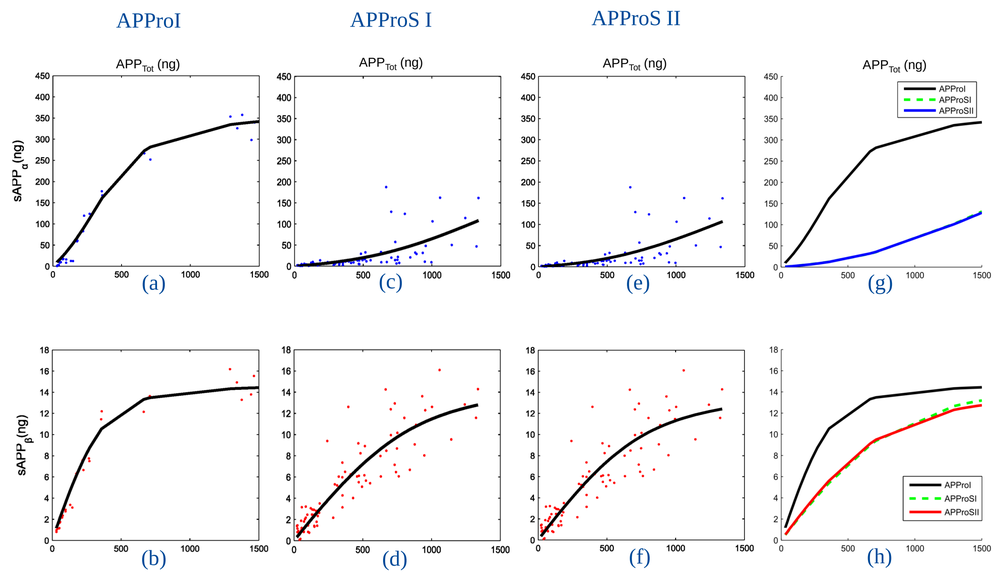


Figure 5. Comparison of experimental dose-response series for APP-sAPPα [blue dots] and APP-sAPPβ [red dots] to the simulation of mathematical models with optimized parameters. (a-b) CHO-ptetAPP [ELISA] with APProI. (c-d) CHO SORLA-ptetAPP [ELISA] with APProSI. (e-f) CHO SORLA-ptetAPP [ELISA] with APProSII. (g-h) Putting the respective plots of sAPPα and sAPPβ for APProI, APProSI and APProSII all together.

Results

- We have established a panel of cell lines in which the amount of APP and regulatory factors can be varied and quantitative data for APP processing can be derived.
- We have produced dose-response series of data (APP-sAPPα and APP-sAPPβ) from CHO-ptetAPP and CHO SORLA-ptetAPP [Western Blot Analysis and ELISA].
- Our collaboration have shown good agreement between the simulation results of models with optimized parameters and the experimental data.
- We made a comparison of the two alternative hypotheses [APProSI (Figure 5 (c-d)) and APProSII (Figure 5 (e-f))]. It suggests that a proposed interaction of beta secretase with SORLA does not impact on APP processing.

Outlook

- Extension of mathematical models by inclusion of additional factors and cellular compartments.
- Validation of models through experimental data in cells and mouse models *in vivo*.

Tet-Off inducible APP gene expression - methodology

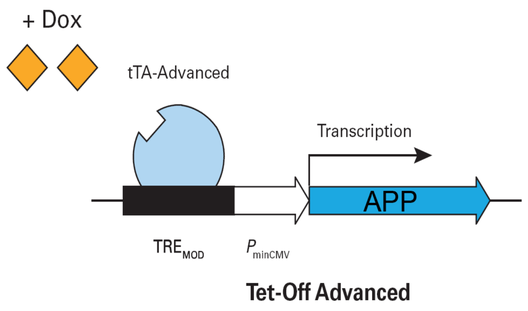


Figure 3. Binding of the Tet-controlled transactivator (tTA) to the tetracycline response element (TRE) induces APP expression. In the presence of doxycyline binding of tTA to TRE is reduced and APP expression is impaired in a dose-dependent manner. (Clontech Laboratories, modified)

HELMHOLTZ ASSOCIATION
Alliance on Systems Biology

Universität Rostock
Traditio et Innovatio
www.sbi.uni-rostock.de

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN BERLIN-BUCH
IN DER HELMHOLTZ-GEMEINSCHAFT e.V.

Contact Information:
http://msbn.mdc-berlin.de/project_alzheimer
[1] Systems Biology and Bioinformatics Group, University of Rostock (www.sbi.uni-rostock.de)
[2] Max-Delbrück-Center for Molecular Medicine Berlin-Buch

The project started June 2008. Further information can be found on our website.