A MATHEMATHICAL MODEL OF TRANSFERRIN UPTAKE BY A CELL: NEW MODE OF TFR2-DEPENDENT IRON DEPOSITION UNDER OXIDATIVE STRESS CONDITIONS

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Iron (Fe) ions are necessary for cell proliferation, metabolism and many other cellular functions. Cells uptake Fe in a complex with transferrin (Tf) via two receptors TfR1 and TfR2. TfR1 mediates a well-known way whereas the role of TfR2 is poorly known. TfR2 demonstrates some exclusive abilities: stabilization by holotransferrin molecules and biphasic Tf uptake. In oxidative stress and inflammation the increase of Fe level (both free and bound by Tf) is often observed, while the level of free Tf is decreased. We assumed that the reason of this phenomenon is the elevated Tf uptake by cells specialized for Fe deposition and/or transport mediated by specific properties of TfR2. To check this hypothesis we build mathematical model of Fe and Tf uptake by TfR2(+)-cells and investigated its dynamical properties.

For formal description and simulation of model of transferring uptake by a cell we used BioUML workbench (http://www.biouml.org). Fe homeostasis system was divided into several interacting modules: (1) Fe uptake regulation (including TfR1- and TfR2-induced endocytosis of different forms of Tf, vesicular transport, endosomal sorting and Fe transport from endosomes to cytoplasm; (2) ferroportin-dependent Fe export from a cell; (3) Fe deposition in a complex with ferritin; (4) regulation of Fe regulatory proteins (IRP); (5) posttranscriptional regulation by IRP system; (6) regulation of TfR2 expression; (7) regulation of ferritin expression. For description of molecular interactions we used chemical kinetics equations, for description of gene expression the Hill equation was applied. Some model parameters were extracted from literature other was fitted on the base of obtained by authors experimental data. Corresponding system of differential equations was solved using BioUML workbench.

The results of modeling demonstrated that Tf concentration may decrease due to biphasic uptake of Tf by TfR2(+)-cells. Increased saturation of Tf with Fe as a consequence of high level of Fe and low level of free Tf may lead to forcing of TfR1-dependent transport of Fe as a result of higher TfR1 to Tf:2Fe affinity (in comparison with free Tf and Tf:1Fe) and activation of TfR2-dependent uptake of Tf:2Fe due to stabilization of TfR2 receptor.