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Poster presentation

DNA interaction with sperm cells: ODE model

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Introduction

A computer simulation concerning initial events in the sperm/DNA interaction was performed. DNA binding with MHCII and CD4 proteins, DNA internalization into spermatozoa, and DNase activity in sperm were described by first order differential equations (ODE). The dynamics of the system depended on the parameters of the model. The simulation could explain controversial results in sperm mediated gene transfer research and posed this phenomenon to an unknown form of biological evolution.

Background

The phenomenon of foreign gene transfer with sperm was first observed in lab conditions in 1971 [1]. Since 1989 [2,3], when sperm mediated gene transfer (SMGT) was rediscovered, some unusual molecular mechanisms in spermatozoa were described, such as the ability of sperm cells to capture exogenous DNA [4] and RNA [5] molecules, the reverse transcriptase activity in sperm cells [6], the insertion of foreign nucleic acids into sperm chromatin [7] and an apoptosis-like response to the high concentration of internalized DNA [8]. SMGT has been seen as a mechanism for genome destabilization [9] and evolution [10]. In this work the dynamics of sperm/DNA interaction was investigated by computer simulation.

Method

The structural model of sperm/DNA interaction (Figure 1) was used to describe the problem. I assumed free foreign DNA, complexes of DNA with MHCII and CD4 proteins, DNA compartmentalization in the sperm cell, DNase activities in the seminal fluid and in the spermatozoon. The DNA flow between nodes was described by the first order differential equations: See Figure 1.

where, variable S1 is free DNA, S2 is MHCII bound DNA, S3 is CD4 bound DNA, S4 is foreign DNA in the sperm cell, variables S5 and S6 are DNAs cleaved by DNases outside and inside sperm cells respectively. Ratios of parameters $k_{-1} = k_4 = 0.1$ were not varied; values of parameters k_5 and k_6 were changed during 'physiological' experiments with DNase activities: $k_5 = \{0, 1\}$, $k_6 = \{0, 0.1, 1\}$; the coefficients k_1, k_2, k_{12}, k_3 were changed in 'genetic' experiments and in the simulation of IF-1 block: $k_1 = \{0, 1\}$, $k_2 = k_{12} = k_3 = \{0, 0.1\}$. The initial conditions were 1 for input DNA (S1 = 1) and 0 for all DNA binding contents, {S2,...,S6} = 0. Combinations of parameter values were investigated by the simulation.

Results

I speculated about an interaction between MHCII and CD4 molecules and about the release of a part of the DNA from spermatozoa by CD4 recycling. However, the model of foreign DNA stream in spermatozoa was in good agreement with experiments for sperm/DNA interaction. The modeling described some stages of DNA penetration into a sperm cell: delay phase, DNA internalization, plateau, and decrease of internal DNA content. I obtained the fast MHCII/DNA interaction by simulation, because the high value of $k_1 = 1$ was used, which corresponded to a strong chemical binding. In addition, the fine dynamics of DNA

$$dS1/dt = k_{-1}*S2 - (k_1 + k_5 + k_{12})*S1 + k_4*S4$$
$$dS2/dt = k_1*S1 - (k_{-1} + k_2)*S2$$
$$dS3/dt = k_{12}*S1 + k_2*S2 - k_3*S3$$
$$dS4/dt = k_3*S3 - (k_4 + k_6)*S4$$
$$dS5/dt = k_5*S1$$
$$dS6/dt = k_6*S4$$

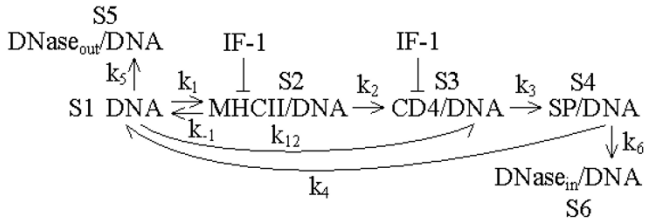

Figure 1
Flow diagram of protein/DNA interactions in sperm cell

distribution between the participants-MHCII and CD4 proteins-in the course of sperm/DNA interaction was shown. This hidden mechanism was not revealed in biochemical investigations. Modeling with DNase activities demonstrated their significance in SMGT. The simulation showed that DNases in seminal fluid did not fully prevent the penetration of foreign DNA into spermatozoa. According to the model, the IF-1 protection leads to a significant decline of foreign DNA in sperm cells. I achieved a total suppression of sperm/DNA interaction in the case of both IF-1 presence and DNase activity in the seminal fluid. In addition, the internal DNase activities evoked degradation of captured DNA. Artificial elimination of components from SP/DNA transport pathway in the virtual knockout experiments demonstrated the sufficient role of MHCII molecules in sperm/DNA interaction, as well as the participation of CD4 receptors in the internalization of DNA into spermatozoa. Surprisingly, the disconnection of MHCII and CD4 proteins ($k_2 = 0$) had a more significant effect on DNA internalization than simple MHCII block ($k_1 = 0$); the amounts of DNA in sperm cells at steady states were 0.08 and 0.33 respectively.

Conclusion

I suppose the equilibrium state, which corresponds to sperm/DNA block, is a special case that might easily be disturbed and have unusual consequences. A large set of variations for parameters in the SMGT model caused 'leaky' states, where a part of exogenous DNA could penetrate sperm cells. These events could have taken place in nature and might have led to the foreign DNA penetration into spermatozoa. This kind of lateral gene transfer could be one of mechanisms for the compositional evolution of Eukaryotes [11].

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