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Understanding stem cell differentiation through self-organization theory.

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The mechanism underlying stem cells' key property, the ability to either divide into two replicate cells or a replicate and a differentiated daughter, still is not understood. We tested a hypothesis that stem cell asymmetric division/differentiation is spontaneously created by the coupling of processes within each daughter and the resulting biochemical feedbacks via the exchange of molecules between them during mitotic division. We developed a mathematical/biochemical model that accounts for dynamic processes accompanying division, including signaling initiation and transcriptional, translational and post-translational (TTP) reactions. Analysis of this model shows that it could explain how stem cells make the decision to divide symmetrically or asymmetrically under different microenvironmental conditions. The analysis also reveals that a stem cell can be induced externally to transition to an alternative state that does not have the potentiality to have the option to divide symmetrically or asymmetrically. With this model, we initiated a search of large databases of transcriptional regulatory network (TRN), protein-protein interaction, and cell signaling pathways. We found 12 subnetworks (motifs) that could support human stem cell asymmetric division. A prime example of the discoveries made possible by this tool, two groups of the genes in the genetic model are revealed to be strongly over-represented in a database of cancer-related genes.

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