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Mini Review

The Role of miRNAs in Downregulation of PTEN for Glioblastoma Multiforme

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Abstract

In this paper we show, in silico, the role of miRNAs in the post-transcriptional regulation of the onco suppressor gene PTEN by means of a (stochastic) competitive model including interactions with miRNAs and other concurrent genes. The model also covers protein formation and the mechanism going from the protein back to the miRNAs. The numerical simulations confirm the biologically observed situation that the increase of miRNAs concentration within the cell results in the lower expression of PTEN, thus suggesting severe implications in brain tumorigenesis.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and most aggressive malignant primary brain tumor in humans. Experimental evidences show that patients affected by GBM have a lower level of protein PTEN than usual. The issue of PTEN low expression in cancer has been addressed by researchers in different fields such as biological, biochemical and, more recently, mathematical.

PTEN (phosphatase and tensin homolog) is a tumor suppressor that acts as a phosphatase for the lipid signaling intermediate phosphatidylinositol-3,4,5- trisphosphate (PIP3), producing phosphatidylinositol-4,5- bisphosphate. PTEN gene, located on chromosome 10q23, is one of the most commonly mutated and deleted tumor suppressors in human cancer [3]. Loss of 10q, including PTEN gene, is the most common alteration associated with GBM (70% incidence) [11].

PTEN levels are frequently found down-regulated in cancer also in the absence of genetic loss or mutation. PTEN is heavily regulated by transcription factors, microRNAs, ceRNAs (competitive endogenous RNAs) and methylation, while the tumor suppressive activity of the PTEN protein can be altered at multiple levels through aberrant phosphorylation, ubiquitination and acetylation [3]. These regulatory cues are presumed to play a key role in tumorigenesis through the alteration of the appropriate levels, localization and activity of PTEN.

microRNAs (miRNAs) are 21-23 nucleotides long, endogenous, non coding RNA molecules, able to perform post-transcriptional regulation by specially binding target messenger RNAs (mRNAs), typically leading to a reduction in the levels of the corresponding proteins.

Despite the body of experimental evidences, a clear femph quantitative understanding of miRNA-mediated regulation is still lacking and this represents an unmet goal [4] A stochastic model for post-transcriptional regulation of PTEN.

It is known that the biochemical kinetics involving small numbers of molecules can be very different to kinetics described by the law of mass action and differential equations [10]. This effect is a consequence of the intrinsic noise of the system and is associated with the uncertainty of knowing when a reaction occurs and what reaction is that. When considering a collection of molecules, the intrinsic noise is accentuated when some chemical species have small numbers, as is often the case in genetic regulatory models where there are small numbers of key transcription factors that can bind to a limited number of operator regions on DNA.

We consider the chemical reactions model, say StochMod, represented in Figure (1) that describes the regulation of PTEN acting as a tumor suppressor. The model was first introduced in [1] where the authors focused in the mathematical treatment of chemical kinetics, the stochastic numerical algorithms necessary to simulate the solutions of the arising mathematical discrete system and the variants of codes used to implement such algorithms. In this paper, we focus in the capability of mathematical modeling of simulating really observable biological situations, such as the role of miRNAs in gliomagenesis, by targeting PTEN and other concurrent genes.

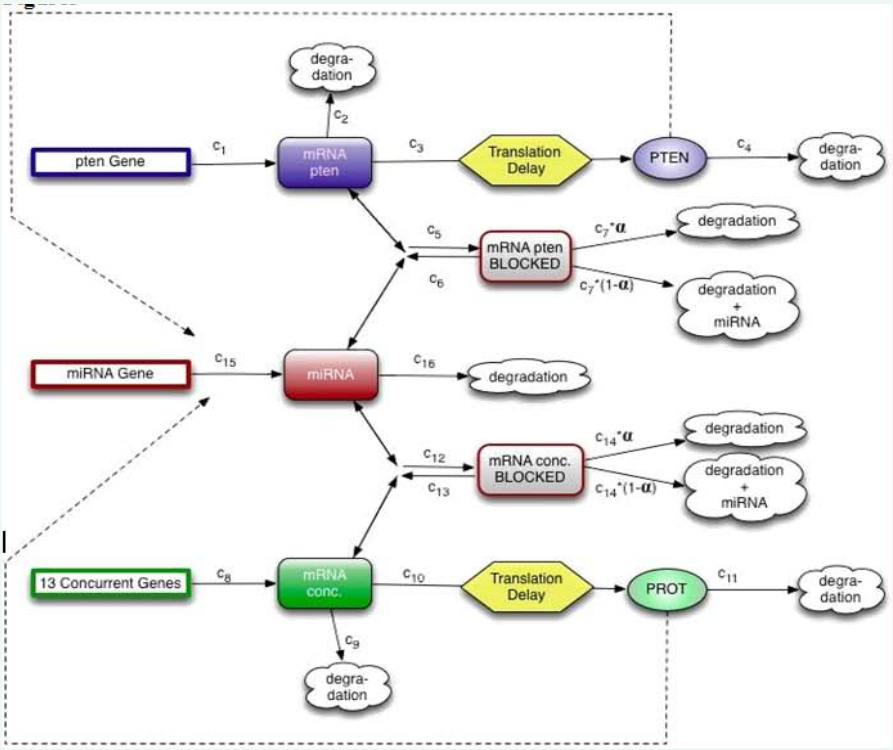

Figure 1 StochmMod model for posttranscriptional regulation of gene PTEN.

Gene PTEN is regulated by transcription factors and proteins that, in turn, can amplify or reduce the expression of protein PTEN. From the biological point of view, StochMod shows how miRNAs negatively influence the expression of mRNA, preventing the translation into protein. miRNAs act mainly after transcription, so that mRNA of PTEN, once blocked, degradates. miRNAs can also degradate without acting at RNA level. miRNAs can regulate the expression of almost all genes, thus plying a crucial role in the control of fundamental processes occurring within the cell, including differentiation, proliferation, angiogenesis, death and metabolism. In particular, there are evidences that show that miRNAs play an important role in tumor pathogenesis, from initiation to metastases. miRNAs that act on PTEN include those that present a single polycisteinic harp structure, such as miRNA-21, miRNA-22 and miRNA-214, and those with polycisteinic structure such as miRNA-17-92, miRNA-106b-25, miRNA-367-302b and miRNA-221-222. miRNA-21 is one of the most frequent miRNAs in human cancer. Its high expression is linked to the growth of metastases of specific tumors, such as lung tumor, colon-rectal carcinoma and ovaric tumour. miRNA-214 has been associated to bond sequence in 3'UTR of gene PTEN resulting in the lower expression of PTEN protein and the increase of AKT pathway [5]. miRNA-10a may promote cancer by targeting PTEN in non-small-cell-lung-cancer [7]. miRNA-26a and miRNA-1908 are associated with high-grade gliomas [6,8].

In Sumazin et al., 13 mPR (program-mediated regulatory interactions, using Hermes) regulators of PTEN with enriched locus deletions in PTEN intact tumors were selected (their names can be found in Figure (1) C in [9]. Accordingly, in StochMod we consider a pool" of genes coding for mRNA, concurrent in the transcriptional and translational processes of PTEN. These ceRNAs can promote miRNA synthesis; otherwise, once translated into protein, they can degradate, or else interact with the PTEN gene at a pre-transcriptional level.

We emphasize that the miRNAs we account for in our model target both PTEN and the concurrent genes.

StochMod does not account for factors acting at the pre-transcriptional level on the PTEN gene, although they have a specific role in the protein expression. Correspondingly to PTEN promoter, a number of possible interactions can happen, leading either to gene activation or repression. In particular, it is not clear the role of these repression factors yet and, consequently, there influence on Glioblastoma tumorigenesis.

At present, StochMod does not tell us what happens neither provides predictions in real clinical situations yet. These are the issues about which the authors are devoting their present job.

NUMERICAL SIMULATIONS

Through the dynamics of model StochMod, we can derive a set of chemical reactions that regulate the expression of PTEN that, in turn, give rise to a stochastic discrete mathematical system [1]. Such a stochastic system can be numerically simulated by suitable algorithms, such as SSA (Stochastic Simulation Algorithm) and DSSA (Delay Stochastic Simulation Algorithm), depending if delays are taken into account or not. In Genetic Regulatory Networks, both the transcriptional and translational processes take some time to be concluded, due to other processes being involved in the cell. Thus, from the

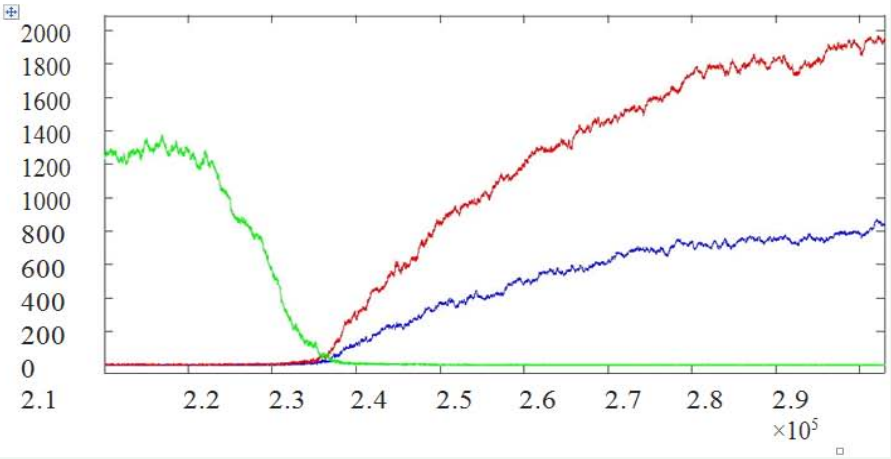

Figure 2 miRNAs (targeting both PTEN and ceRNA) and mRNA concentrations plotted vs time. The green line represents the miRNAs, the blue line mRNA of PTEN and the red line mRNA of ceRNA. The figure is an enlargement of the graphs of the evolutions along time of the above concentrations. It catches" the biological observation of simultaneous over expression of miRNAs and under expression of PTEN.

mathematical point of view, these time lags are appropriately modeled by the inclusion of delays", called transcriptional and translational delay. Transcriptional delays have little impact on the dynamical behavior of the system. Translational delays, i.e. the time lags between the mRNA production and the proteins formation, have much bigger effects since the model includes the feedback processes re ecting the interactions between the proteins and miRNAs, as we can see in Figure (1).

Simulations of the concentrations of reactants, either considering translational delays or not, are reported in [1].

Here we report the mathematical evidence of interconnection between the increase of miR-NAs concentration and down-regulation of PTEN. Figure (2) shows the effects of fluctuations of miRNAs on PTEN expression. The simulation is obtained by the Delay Stochastic Simulation Algorithm (DSSA) incorporating translational delay.

DISCUSSION

The study of post-transcriptional regulation in cancer is crucial, since cancer can be seen as the ultimate derangement of differentiation and proliferation control. Thus, investigation of the dysregulation of RNA processing in malignancy models can be a tool for identifying novel prognostic markers and therapeutic avenues. We considered a mathematical stochastic model for PTEN post-transcriptional regulation, whose low expression is known to affect Glioblastoma oncogenesis heavily. We took in account both the inward and backward interaction between the transcription factor and the miRNAs, including the sponge effect due to concurrent genes; the numerical simulations clearly show the inter-connection between the increase of miRNAs concentration and PTEN lower expression. The mechanisms of promotion and suppression that affect PTEN transcription process are the subject of a new paper in preparation.

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