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Revealing the role of SGK1 in the dynamics of medulloblastoma using a mathematical model

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HIGHLIGHTS

- We propose a model of intracellular signaling related to monosomy and trisomy of chromosome 6q.
- The model is calibrated based on the gene expression microarray data for the two types of medulloblastoma.
- Model simulations indicate the importance of SGK1 gene in the development of medulloblastoma.
- The model suggests a strong correlation between the cMyc protein level data and cancer prognosis.

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ABSTRACT

Deregulation of signaling pathways and subsequent abnormal interactions of downstream genes very often results in carcinogenesis. In this paper, we propose a two-compartment model describing intricate dynamics of the target genes of the Wnt signaling pathway in medulloblastoma. The system of nine nonlinear ordinary differential equations accounts for the formation and dissociation of complexes as well as for the transcription, translation and transport between the cytoplasm and the nucleus. We focus on the interplay between *MYC* and *SGK1* (serum and glucocorticoid-inducible kinase 1), which are the products of Wnt/β-catenin signaling pathway, and *GSK3β* (glycogen synthase kinase). Numerical simulations of the model solutions yield a better understanding of the process and indicate the importance of the *SGK1* gene in the development of medulloblastoma, which has been confirmed in our recent experiments. The model is calibrated based on the gene expression microarray data for two types of medulloblastoma, characterized by monosomy and trisomy of chromosome 6q to highlight the difference between diagnoses.

1. Introduction

Medulloblastoma is a malignant brain tumor that mainly affects children. 85% of all medulloblastoma cases are below the age of 18 (Korshunov et al., 2010). The mortality during the first two years after diagnosis oscillates between 10% and 15% (Pfister et al., 2009). Treatment involves resection of the tumor and then, depending on the patient's stage and molecular aberration, radiotherapy or chemotherapy (Pomeroy and Sturla, 2000; Rossi et al., 2008). Medulloblastoma is attributed to several mutations, such as 17q gain, i(17q), *MYC*/*MYCN* amplification, 6q gain, 6q loss and Wnt pathway activation (Pfister et al., 2009). Importantly, prognosis depends on the type of mutation causing the disease. In general, tumors can be either non-invasive or metastasize through the cerebrospinal fluid.

Our research is devoted to understanding the role of signaling pathways in two types of medulloblastoma, monosomy and trisomy of the long arm of chromosome 6q (monosomy is loss of one chromosome copy and trisomy is gain of one chromosome copy), which are characterized by radically different prognosis. The trisomy 6 case is found to have a poor prognosis, while the monosomy 6 case has a good prognosis following the medical treatment (Pfister et al., 2009). Monosomy 6 is always found in combination with the β-catenin mutation, leading to constitutive Wnt signaling activation. It was discovered that mutation of β-catenin in medulloblastoma was associated with a good prognosis in a pediatric patient (Ellison et al., 2005).

The 6q loss and 6q gain appear to induce the deregulation of the expression of *MYC* and *SGK1* in the mutated cells (for biological notation, see Table 3). *MYC* is a transcription factor that regulates

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expression of a number of genes and is involved in biological processes such as cell growth and proliferation (Dang, 1999). *SGK1* is responsible for the intracellular transport and cell survival (Simon et al., 2007). Both genes seem to play an important role in the cell's homeostasis and their deregulation can affect cellular processes finally resulting in carcinogenesis.

In the case of monosomy of chromosome 6q we observe the downregulation of the mRNA level of *SGK1*, whereas its upregulation is detected in the case of trisomy 6. Interestingly, the *SGK1* gene is located on chromosome 6q, which suggests that a disruption in the chromosome balance alters the mRNA level of *SGK1*. However, the mechanism has not yet been explained. The concomitant upregulation of the mRNA level of *MYC* is found in both types of medulloblastoma. Since pediatric monosomy 6 of medulloblastoma is always related to the β-catenin mutation, the increase of the β-catenin translocation to the nucleus may explain upregulation of its target gene *MYC* (Korshunov et al., 2010). On the other hand, the reason for the *MYC* mRNA upregulation in trisomy 6 is not understood.

Observations of the mRNA levels are based on the data from the microarray analysis at the cancer clinics in Heidelberg, Boston and Amsterdam (see Appendix C). We employ these mRNA experimental data to define the control variables, i.e., independent variables that can be manipulated or controlled in an experimental design to understand how they affect the dependent variables of the model.

Our goal is to find the corresponding protein level by modeling the particular interactions between the crucial components of the signaling pathway. We aim to check how the differences in the control variables influence the level of the SGK1 and cMyc protein depending on the type of medulloblastoma, and we compare the results to the clinical data on the cancer dynamics. Consistently, we investigate to what extent the prognosis is related to the *SGK1*/*MYC* gene dynamics. Behavior of both genes may shed light on the patient prognosis and provide clues as to how adjust the treatment. To model the system, we reduce it to its main components. This enables obtaining a clear and comprehensible model, which still describes the complex system. Based on the simulation studies, we present new hypotheses concerning the discrepancy in dynamics of the two types of medulloblastoma based on the interactions between *SGK1*, *GSK3*β and *MYC*.

2. Biological background

The Wnt/β-catenin signaling pathway is one of the most important pathways in human cells. The Wnt gene was discovered already 30 years ago (Klaus and Birchmeier, 2008). The knowledge of its function and role in the cell increased during the recent years. The so-called *canonical Wnt pathway* describes a cascade of reactions regulating embryonal development and adult tissue maintenance (Wang and Wynshaw-Boris, 2004). Substantially, destabilization of the Wnt pathway leads to tumorigenesis and was found in many types of cancers (Logan and Nusse, 2004; Kolligs et al., 2000). In medulloblastoma the mutation influences directly β-catenin, causing its resistance to degradation. Consecutive accumulation in the cytoplasm triggers β-catenin translocation to the nucleus, which results in abundant transcription of the downstream target genes of the pathway (Zurawel et al., 1998; Fodde and Brabletz, 2007). This, together with β-catenin mutation, is always found in pediatric monosomy 6. The corresponding medulloblastoma subtype is called WNT subgroup MBs.

In cells that are not deregulated, the presence of β-catenin in the nucleus leads to the transcription of *MYC* (Lee et al., 2006) and *SGK1* (Dehner et al., 2008) at a normal level. Then the translation of their mRNA is observed in the cytoplasm. After translation each protein is transported to an appropriate cellular compartment depending on the role in the cell. The SGK1 protein remains in the cytoplasm if no additional signal is activated (Firestone et al., 2000), and the cMyc protein moves to the nucleus, where it functions as a transcription factor. SGK1 in the cytoplasm can bind to GSK3β and phosphorylate it, marking it for degradation (Arteaga et al., 2007). GSK3β is a protein that can shuttle between the cytoplasm and the nucleus, and when it is in the cytoplasm, it can be degraded via an interaction with SGK1 (Wang et al., 2010; Arteaga et al., 2007). On the other hand, when GSK3β is shifted to the nucleus, it may bind to cMyc and phosphorylate this protein targeting it for degradation (Gregory et al., 2003). SGK1 and GSK3β return to the previous states after their phosphorylating activity, ready for new binding.

Since the transport between the cytoplasm and the nucleus is an essential process in the cell, it is necessary to take into consideration the transport rate as well as the difference of the volumes of the two compartments. Additionally, some substrates may exist in different compartments of the cell and in the framework of ordinary differential equation modeling they have to be considered as separate variables. In Fig. 1 we depict the modeled system and in Fig. 2 we present the simplified diagram of the system dynamics, in which we outline the positive and negative coupling between discussed proteins.

In this work, we use subscripts t and p to distinguish between the transcripts and the proteins, respectively. We do the same for

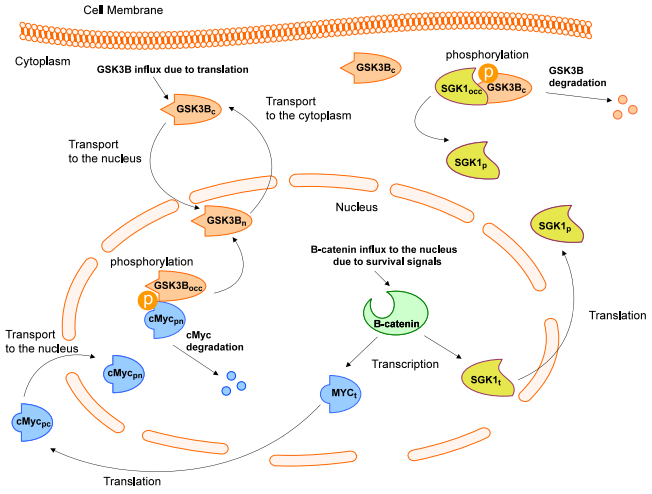

Fig. 1. Schematic diagram of the modeled system. *Abbreviations*: $SGK1_t$ – concentration of the *SGK1* mRNA (transcript), $SGK1_p$ – cytoplasmic concentration of the SGK1 protein, MYC_t – concentration of the *MYC* mRNA (transcript), $cMyc_{pc}$ – cytoplasmic concentration of the cMyc protein, $cMyc_{pn}$ – nuclear concentration of the cMyc protein, $GSK3\beta_c$ – cytoplasmic concentration of the GSK3β protein, $GSK3\beta_n$ – nuclear concentration of the GSK3β protein, $GSK3\beta_{occ}$ – occupied GSK3β in a complex with cMyc, $SGK1_{occ}$ – occupied SGK1 in a complex with GSK3β.

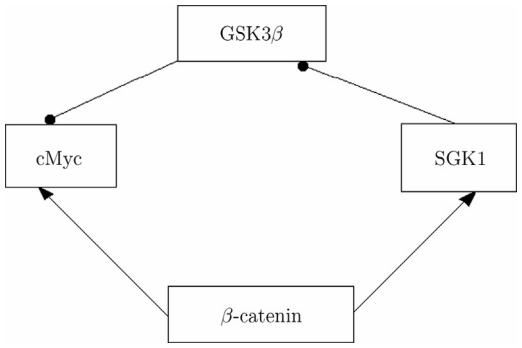

Fig. 2. Simplified diagram of the system dynamics, where the arrow-ended and dot-ended lines denote positive and negative influences, respectively. We observe positive (double negative) coupling between the proteins SGK1 and cMyc.