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Mathematical modeling of the cells repair regulations in Nasopharyngeal carcinoma

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ABSTRACT

Nasopharyngeal Carcinoma (NPC) is a malignant cancer which is caused by the activation of *Epstein-Barr* Virus (EBV) via some external factors. In the cells repair regulations, the *p*53 gene mutation can be used as the early indication of the NPC growth. The NPC growth is due to the DNA damage accumulation caused by the EBV infection. In this paper we construct the cells repair regulations model to characterize the NPC growth. The model is a 15 dimensional of first order ODE system and consists the proteins and enzymes reactions. We do some numerical simulations to show the inactivation of the phosphorylated and acetylated *p*53, and the chromosomal instability of *p*53 gene, which can be used as the earlier stage detection of NPC.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a tumor on the epithelial cells which covers the nasopharynx surface and its channel [1]. It is mainly caused by *Epstein Barr Virus* (EBV) which can be activated by some external factors, such as cigarette, salted fish, alcohol, etc [2]. The endemicity of the NPC covers several regions in the world such as the Southern of China, South East Asia, Japan, North Africa, and the Middle East. The highest case happened in Southern of China whose the case ratio 15 to 50 cases in 100,000 inhabitant [3].

The EBV is classified as a human gamma-herpes virus which is strongly causes lymphomas and carcinomas. An EBV protein which can be expressed by all latent form in the proliferating cells and exists in all EBV-associated tumor is called*Epstein-Barr Nuclear Antigen* (EBNA1), [4].

The common problems for the NPC treatment process is that the disease is usually detected in the latest stage. It is due to the unspecific symptoms of the disease, such as otitis media effusion, Eustachian tube dysfunction, conductive hearing loss, and ear pain on the early stages [3].

The Mathematical model for cell repair regulation as the response of DNA Double Strand Breaks (DSB) which is one of the important protein in the regulation, has been conducted in [5,6]. However, the model is not specific for the NPC. In this paper, we develop the model by adding the *p*53 mutation process which is indicated by the existence of EBNA1 and *Latent Membrane Protein* (LMP1) as the causal factor of NPC. The expression of the LMP1 protein is represented by its molecules in NPC tumor cell related to $\beta - actin$ as its loading control, [7–9]. The un-repaired or mis-repaired of DNA DSB which leads the mutation of *p*53 and the malfunction of those proteins, are the early indication of NPC. We use Michaelis–Menten and Hill equations to express the chemical reactions among the proteins in our model.

This paper is organized as follows. We start with the introduction of the cell-repair regulation process for NPC and the role of some proteins which are involved in the process. After that, a mathematical model which show the chemical reactions among proteins in the cells repair regulations of NPC will be constructed. The model which is a 13 dimensional system of ODE contains the important proteins which play an important role for the NPC disease. In this case, we will use numerical simulation to show the variables which trigger the gene mutation to activate the

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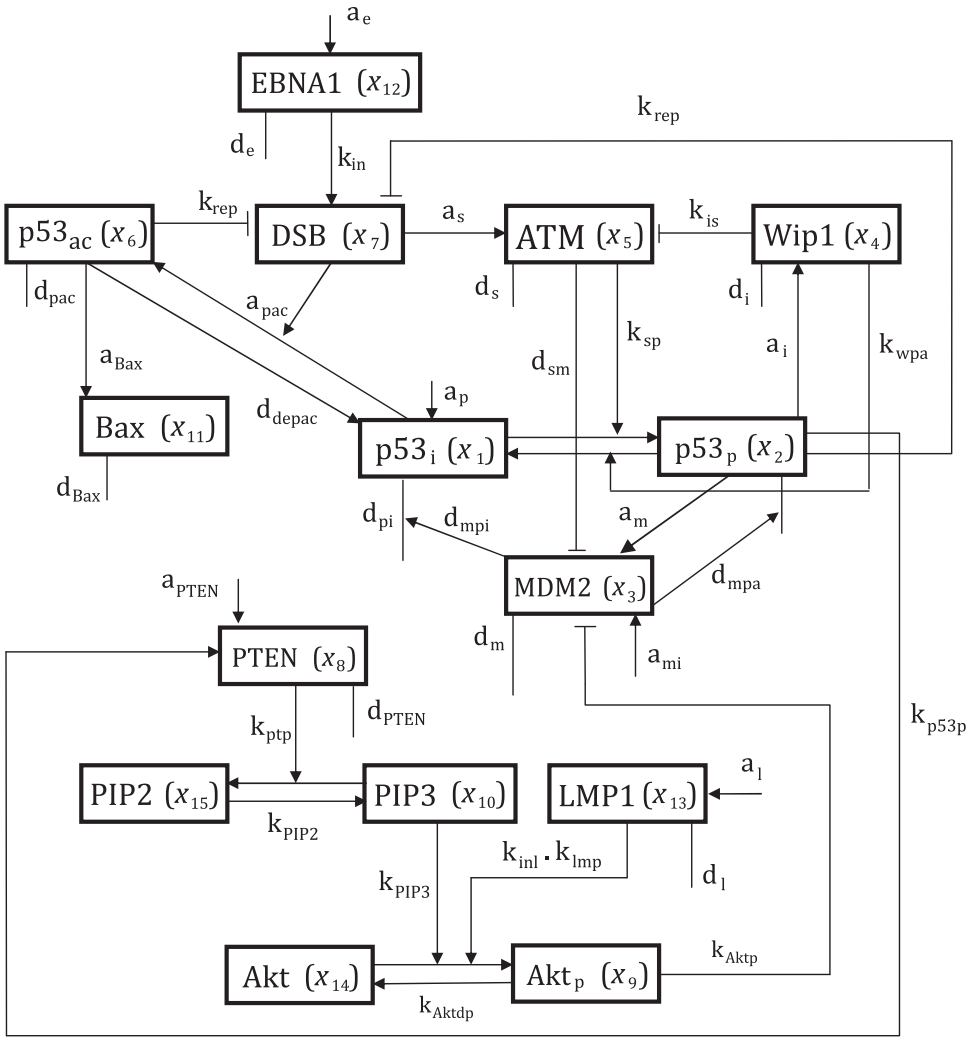

Fig. 1. The transfer diagram of cell repair regulation. The transcription and the activation are denoted as arrow headed line. The suppression is denoted as blunt arrow, and the degradation is denoted as dotted line.

NPC disease. Furthermore, we will close this paper with some concluding remarks.

2. Model formulation

The DNA damage regulations and the gene mutation which trigger the chromosomal instability are very important in the activation of NPC. The chromosomal aberration, DNA DSB, and the engagement of the DNA Damage Response (DDR) as parts of the DNA damage regulation can be induced by the EBNA1. The unrepaired or mis-repaired DNA DSB can cause the gene mutation which leads the malfunction of the proteins and many genomic alterations [10,11]. It provides the cells repair regulations on the human body as the response of DNA damage [5,6,12].

The gene mutation can trigger the chromosomal instability occurrence which causes the tumor growth and cancer progression. A tumor suppressor-oncoprotein which includes in majority cancer development is $p53$. The mutation of $p53$ can cause the chromosomal instability on cultured cell [13–15]. So, this mutation can be used as the early indication of the NPC.

There are some other cell proteins which are included in this regulation, such as Ataxia Telangiectasia Mutated (ATM), Murine Double Minute (MDM2), Wild-type $p53$ inducible protein 1 (Wip1), Phosphatase and Tensin Homolog (PTEN), Akt, Phosphatidylinositol 4,5-biphosphate (PIP2), Phosphatidylinositol 3,4,5-triphosphate (PIP3), and Bcl-2-associated X (Bax) [5,6,16]. These proteins affect the growth and the progression of the cancer.

The first signal to respond DNA DSB as the main protein in cell response coordination is represented by the ATM protein. After being activated, this protein mediates the $p53$ phosphorylation process that activates $p53$, [5,12]. The $p53$ transactivation process is inhibited by the MDM2 protein. The MDM2 protein controls the $p53$ protein expression through ubiquitination and degradation of the $p53$ protein [17].

The phosphorylated $p53$ protein ($p53_p$) induces the Wip1 and the MDM2 proteins to stabilize the regulation process. The protein transcription which involves the Wip1 and MDM2 proteins need some time to finish the process. So, in our model we provide a delay time parameter for this case, [5]. The $p53_p$ also induces the PTEN protein transcription. The protein transcription is assumed to follow Hill's equation with coefficient 4. This is from the fact that the $p53_p$ protein is in tetramer form [6].

When the DNA DSB surpasses a certain level, the acetylation of the inactive $p53$ protein ($p53_i$) start to be held. The acetylated $p53$ protein ($p53_{ac}$) which protects the $p53$ protein from its degradation by the MDM2 protein will induce the Bax protein expression as pro-apoptotic gene which has a role as a pro-apoptotic marker. However, the $p53_{ac}$ protein can also be deacetylated to get the $p53_i$ protein [5].

The other important protein in cell repair regulation is the Akt protein. It is a protein kinase which exists in two forms, i.e. the