# An epigenetic switch involving a positive feedback loop linking inflammation to cancer effected by Myc and miRNA-17-92 microRNA cluster

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***Abstract*—Inflammation is a critical part of tumour progression. But the regulatory mechanisms linking inflammation and cells transformation was less understood. A pathway linking inflammation to cell transformation which is maintained by a positive feedback loop involving NF-$\kappa$B, Lin28, Let-7 and IL6 has been discovered. We extended the pathway,in which Myc and miR-17-92 microRNA cluster are added. Their roles are studied through the method of qualitative analysis. The result showed that both Myc and miR-17-92 microRNA cluster can promote the transformation. We have verified the the important elements of the pathway through sensitivity analysis.**

## I. Introduction

Cancer has been a huge threat to human health. It is estimated that more than one and half million new cancer cases and more than half million cancer deaths occur in US alone[1]. There are many factors causing cancer. The mutation of suppressor genes and the oncogenic genes may help cancer cells break the normal mechanisms controlling cell division, growth and survival [2], [3]. Furthermore, not all cancers are caused by gene mutation. The suppressor genes inactivated by DNA methylation, other proteins and microRNA may trigger the transformation of normal cells into cancer cells [4], [5]. The changing of the environment can also effect the suppressor genes and oncogenes.

Research shows that inflammation is a critical part of tumour progression [6], [7], [8], [9]. Inflammatory conditions are present before a malignant change occuring in some types of cancer. Many triggers of chronic inflammation are able to increase the risk of developing cancer. Such as microbial infections, autoimmune diseases and inflammatory conditions. However, the regulatory mechanisms linking inflammation and cells transformation were less understood.

Gene and microRNA may involve in the process from inflammation to cells transformation. The overexpression of inflammation cytokine IL6 facilitates malignant progression [8]. Low PTEN expression is related to diverse liver malignancies [10]. Members of the tumor suppressive Let-7 miRNA family are down regulated and the oncogene miR-17-92 microRNA cluster are overexpressed in lung cancers [17].

Some studies on the relationship between inflammation and cancer have made significant achievements. An inducible model of cellular transformation which linked inflammation and cancer was described by Iliopoulos and coworkers [11], [12]. The regulatory network is a positive feedback loop consisting of the NF-$\kappa$B transcription factor, the microRNA processing factor Lin28, Let-7 microRNA, and IL6 cytokine. They showed that the transformation can be triggered by transient activation of Src, which is a oncoprotein. After activation of this transformation, the STAT3 transcription factor and oncoprotein Ras will preserve the transformation state. As genes are not mutated in this precess, and both inflammatory state and cancer cells are seemed as stable cell, this change from a stable cell type to another stable cell type without any variation of DNA sequence is called epigenetic switch [11]. In addition to biological experiments, there are also theoretical studies about this regulatory network through a mathematical model [13].

The purpose of our study is to extend the regulatory network described by Iliopoulos and coworkers [11], [12]. We constructed and analysed a mathematical model based onproposition of Claude [13]. In our model, the oncogene Myc and miR-17-92 microRNA cluster are involved. We have revealed the roles of Myc and miR-17-92 microRNA cluster in the pathway by qualitative analysis.

## II. The model

In this work, we extend the immune regulatory network model on the basis of other researchers [11], [12], [13]. Experiments show that the positive feedback loop, involving NF-$\kappa$B, Lin28, Let-7 and IL6, is necessary for the transformation from inflammation to cancer(Figure 1A) [11]. The positive loop is activated by the Src oncoprotein which mediated by the inflammatory signal. Src activates NF-$\kappa$B and NF-$\kappa$B enhances the expression of Lin28. The synthesis of the Let-7 microRNA is inhibited by the microRNA binding protein Lin28. Once the Let-7 is inhibited by Lin28, the


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inhibition of transcription from Let-7 to IL6 will decrease, and IL6 will have a higher level of expression. After that, IL6 enhance the synthesis of NF-$\kappa$B. In this pathway, as the Src oncoprotein is meditated by the inflammatory signal, so for the convenience the study we refer Src as the inflammatory signal. The dynamic behavior of the network with change of inflammatory Src is shown in Figure 1B. The two red lines represent inflammation state and cancer state, the dotted line is unsteady state. The details about the two states will be described later.

Besides proteins NF-$\kappa$B, Lin28, IL6 and Let-7 microRNA, there are other elements involving in the transformation. Myc gene involved in the formation of many cancers [14], [15], [16]. And Myc expression is induced during the transformation process [12]. So Myc may be involved in the process and play an important role. In addition, Myc can be expressed by Let-7 microRNA and it can induces the expression of Lin28 [17]. Experiments have proved that Let-7 microRNA, miR-21 microRNA, and miR-181b-1 are important for the transformation process [11], [12]. Let-7 microRNA inhibits the transformation, while miR-21 and miR-181b-1 may switch on cell transformation[12], [13]. miR-17-92 microRNA cluster is oncogenic microRNA which encodes six individual miRNAs [17], [18], [19], [20]. The miR-17-92 microRNA cluster is a direct transcriptional target of Myc[14]. It is induced by Myc. The miR-17-92 microRNA cluster contains microRNAs repressing the expression of PTEN [14], [17], [18], [20]. Based on the relationship between miR-17-92 microRNA cluster and other miRNAs and proteins, we predict that miR-17-92 microRNA cluster may effect the transformation.

As the role of Ras oncoprotein, transcription factor STAT3 and miR-21 microRNA have clearly studied and they don't have direct action with Myc and miR-17-92. And our main idea is on the roles of Myc and miR-17-92. So they are not in our consideration. Comprehensive analysis described above, we construct a network model as shown in Figure 2.

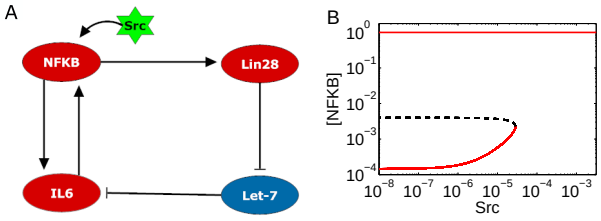


Fig. 1: **The core network and bifurcation diagram of the network.** (A) The core network. The inflammatory signal is mediated by the oncoprotein Src. Then Src triggers the inflammatory response and up-regulates the expression of NF-$\kappa$B. NF-$\kappa$B activates the expression of Lin28. Lin28 protein will suppress the synthesis of Let-7 microRNA. This response will reduce the inhibition of Let-7 to IL6. Since IL6 activates NF-$\kappa$B and NF-$\kappa$B which can promote the expression of IL6, both IL6 and NF-$\kappa$B will have a higher or a lower expression. (B) The bifurcation diagram of the core network with Src as the control parameter. The red line is steady state while the dotted line is unsteady state.

Mathematical models of the epigenetic switch linking inflammation to cell transformation including NF-$\kappa$B, Lin28, Let-7, IL6, STAT3, miR21, PTEN, Ras pathway have been proposed[14]. Based on Claude's mathematical model, we proposed our model contains NF-$\kappa$B, Lin28, Let-7, IL6, miR-17-92 microRNA cluster and oncogene Myc. In the present manuscript,we primarily explore the regulatory effects of Myc and miR-17-92 on transformation. According to Figure 2, the dynamical relations of the topology are characterized by the following nonlinear ordinary differential equations:

$$\begin{aligned}\frac{d[NFKB]}{dt} =&(K_{ASNF}\cdot Src + K_{AILNF}\cdot[IL6])\cdot \\ &(\frac{K_{IPTEN}}{K_{IPTEN}+[PTEN]})\cdot(\frac{[NFKB_i]}{K_{ANFKB}+[NFKB_i]}) \\ &- K_{DNFKB}\cdot(\frac{[NFKB]}{K_{INFKB}+[NFKB]})\end{aligned} \tag{1}$$

$$\begin{aligned}\frac{d[Lin28]}{dt} =&V_{SLin28}\cdot(\frac{[NFKB]}{K_{ANFLin}+[NFKB]}+ \\ &\frac{[Myc]}{K_{AMycLin+[Myc]}}) - K_{DLin28}\cdot[Lin28]\end{aligned} \tag{2}$$

$$\begin{aligned}\frac{d[Let7]}{dt} =&V_{SLet7}\cdot(\frac{K_{ILinLet}}{K_{ILinLet}+[Lin28]}) - k_1\cdot[mIL6]\cdot \\ &[Let7] + k_2\cdot[mIL6Let7] - k_3\cdot[mMyc]\cdot[Let7] \\ &+ k_4\cdot[mMycLet7] - K_{DLet7}\cdot[Let7]\end{aligned} \tag{3}$$

$$\begin{aligned}\frac{d[mIL6Let7]}{dt} =&k_1\cdot[mIL6]\cdot[Let7] - k_2\cdot[mIL6Let7] \\ &- K_{DILLet}\cdot[mIL6Let7]\end{aligned} \tag{4}$$

$$\frac{d[IL6]}{dt} = K_{SIL6}\cdot[mIL6] - K_{DIL6}\cdot[IL6] \tag{5}$$

$$\begin{aligned}\frac{d[mIL6]}{dt} =&V_{S1mIL6} + V_{S2mIL6}\cdot(\frac{[NFKB]}{K_{ANFIL}+[NFKB]}) \\ &- k_1\cdot[mIL6]\cdot[Let7] + k_2\cdot[mIL6Let7] \\ &- K_{DmIL6}\cdot[mIL6]\end{aligned} \tag{6}$$

$$\begin{aligned}\frac{d[mMyc]}{dt} =&V_{SmMyc} - k_3\cdot[mMyc]\cdot[Let7] + k_4\cdot[mMycLet7] \\ &- K_{DmMyc}\cdot[mMyc]\end{aligned} \tag{7}$$

$$\begin{aligned}\frac{d[mMycLet7]}{dt} =&k_3\cdot[mMyc]\cdot[Let7] - k_4\cdot[mMycLet7] \\ &- K_{DMycLet}\cdot[mMycLet7]\end{aligned} \tag{8}$$

$$\frac{d[Myc]}{dt} = K_{SMyc}\cdot[Myc] - K_{DMyc}\cdot[Myc] \tag{9}$$

$$\begin{aligned}\frac{d[miR17]}{dt} =&V_{SmiR17}\cdot(\frac{[Myc]}{K_{AMycmiR}+[Myc]}) - k_5\cdot[mPTEN]\cdot \\ &[miR17] + k_6\cdot[miRmPTEN] - K_{DmiR17}\cdot[miR17]\end{aligned} \tag{10}$$


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$$\frac{d[mPTEN]}{dt} = V_{SmPTEN} - k_5 \cdot [mPTEN] \cdot [miR17] + k_6 \cdot [miRmPTEN] - K_{DmPTEN} \cdot [mPTEN] \quad (11)$$

$$\frac{d[miRmPTEN]}{dt} = k_5 \cdot [mPTEN] \cdot [miR17] - k_6 \cdot [miRmPTEN] - K_{DmiRmPTEN} \cdot [miRmPTEN] \quad (12)$$

$$\frac{d[PTEN]}{dt} = K_{SPTEN} \cdot [mPTEN] - K_{DPTEN} \cdot [PTEN] \quad (13)$$

$$[NFKB_i] = [NFKB_T] - [NFKB] \quad (14)$$

where [NFKB], [Lin28], [Let7], [IL6], [Myc], [PTEN] and [miR17] represent the concentrations of NF-$\kappa$B, Lin28, Let-7, IL6, Myc, PTEN, miR17-92 microRNA cluster. [mIL6], [mMyc] and [mPTEN] are messenger RNAs of IL6, Myc and PTEN. [mIL6Let7], [mMycLet7] and [miRmPTEN] represent mIL6/Let-7 complex, mMyc/Let-7 complex and miR-17-92/mPTEN complex. Src is the inflammatory signal. $[NFKB_i]$ represents the inactivated NF-$\kappa$B. When compared with the model of Claude we don't consider STAT3, miR-21 and Ras. The relationship between Myc, miR-17-92 cluster and other genes and microRNA are included in our model. This mathematical model can be directly converted from the network which is shown in Figure 2. All the values of the parameters are shown in Table 1. Because many kinetic parameters are not determined from experimental data, we adopt the basal values of different parameter to be within the ranges given by Claude [13]. And the parameter values shown in Table 1 are used as standard values unless otherwise indicated. The concentration units are expressed in $\mu$M, while the time units for the parameters are expressed in minutes.

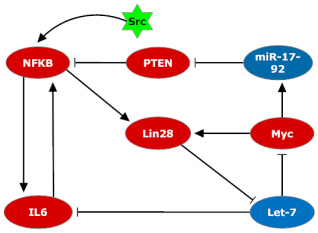


Fig. 2: **The network model.** The Let-7 microRNA represses the transcription of Myc. The latter promotes the synthesis of miR-17-92 microRNA,which reduces the inhibition of PTEN to NF-$\kappa$B. Moreover, Myc stimulates the expression of Lin28.

## III. Results

### A. States of the model

The state of the cell is determined by the expression level of the proteins. Protein expression level between different cell states vary widely. The expression of proteins and microRNAs are significantly different between normal and cancer cells. NF-$\kappa$B, Lin28, IL6 and Myc have a lower expression level while PTEN and Let-7 are expressed in a higher level when the cells are in inflammatory state(Figure 3A). Conversely, cancer cells have higher expression of NF-$\kappa$B, Lin28, IL6 and Myc , and lower expression of PTEN and Let-7 (Figure 3B).

The two different States can be inferred depending on the network structure. The transformation is triggered by inflammatory signal Src. When the signal level of Src is low enough to be smaller than the threshold (SN) (Figure 3C), it can not active the transformation. Then suppressor genes PTEN and Let-7 will repress the expression of other oncogenic genes and microRNAs under the initial conditions. The expression level of NF-$\kappa$B, IL6 , Lin28, Myc and miR-17-92 microRNA cluster will maintain at the low level (See as Figure 3A). Once the level of the signal Src is increased over the threshold, even for a short time, the transformation will be triggered. And the suppressor genes are inhibited by the oncogenic genes (Figure 3B). If the inflammatory signal is removed after transient activating the pathway, the expression of oncogenes will be still in a higher level while the suppressor genes in a lower level. So the cells can not converted from cancer to inflammation state. In other words, this transformation process is irreversible.

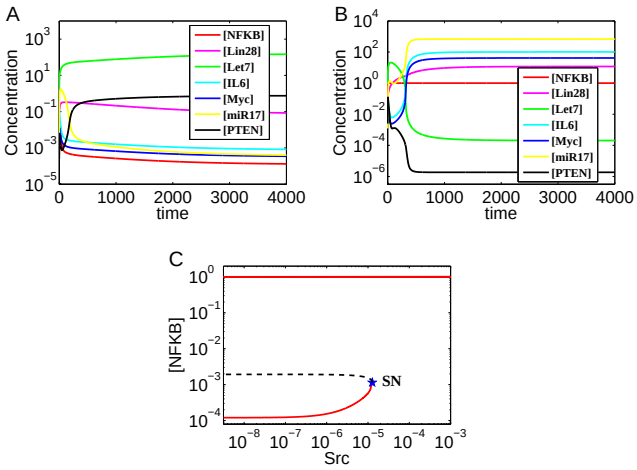


Fig. 3: **Two states of the model.** The initial values for the simulation are $[NFKB] = 0.1$, $[Lin28] = 0.1$, $[Let7] = 1$, $[mIL6] = 0.1$, $[IL6] = 0.1$, $mMyc = 0.1$, $[Myc] = 0$, $[mPTEN] = 1$. Other values are set to zero. (A) Inflammatory states. $Src = 10^{-9}$. (B) Cancer cell. $Src = 10^{-2}$. (C) Bifurcation diagram of [NFKB] with Src as a control parameter. Saddle note(SN) is the threshold of Src to trigger the transformation. The top red line means the cell is in cancer state. The bottom red line represents the inflammatory state.

### B. Effect of Myc

Myc is an oncogene with the ability to induce carcinogenesis [13]. It is required for cell cycle in normal cells but abnormal expression and function as the angiogenic switch in cancer cells [16]. Experimental results show that expression


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TABLE I: Parameters and value

| Parameter | Definition | Basal value | Ref |
|---|---|---|---|
| $NFKB_T$ | Total concentration of NFKB | 1 | [13] |
| $K_{ASDF}$ | Rate constant for the activation of NF-$\kappa$B by signal Src | 10 | [13] |
| $K_{AILNF}$ | Rate constant for the activation of NF-$\kappa$B by IL6 | 0.09 | [13] |
| $K_{IPTNF}$ | Michaelis constant for the inhibition of NF-$\kappa$B activation by PTEN | 5 | [13] |
| $K_{ANFKB}$ | Michaelis constant for the activation of NF-$\kappa$B | 0.01 | [13] |
| $V_{DNFKB}$ | Inactivation rate of NF-$\kappa$B | 0.01 | [13] |
| $K_{INFKB}$ | Michaelis constant of NF-$\kappa$B inhibition | 0.02 | [13] |
| $V_{SLin28}$ | Synthesis rate of Lin28 | 0.012 | [13] |
| $K_{ANFLin}$ | Michaelis constant for the activation of Lin28 synthesis by NF-$\kappa$B | 0.01 | [13] |
| $K_{AMycLin}$ | Michaelis constant for the activation of Lin28 synthesis by Myc | 1 | Estimate |
| $K_{DLin28}$ | Degradation rate of Lin28 | 0.002 | [13] |
| $V_{SLet7}$ | Synthesis rate of Let7 microRNA | 3 | [13] |
| $K_{ILinLet}$ | Michaelis constant for the repression of Let7 synthesis by Lin28 | 0.1 | [13] |
| $k_1$ | Associate rate of Let7 and mIL6 | 10 | [13] |
| $k_2$ | Dissociation rate of complex (mIL6Let7) between Let7 and mIL6 | 0.01 | [13] |
| $k_3$ | Associate rate of Let7 and mMyc | 10 | Estimate |
| $k_4$ | Dissociation rate of complex (mMycLet7) between Let7 and mMyc | 0.01 | Estimate |
| $k_5$ | Associate rate of miR17 and mPTEN | 12 | Estimate |
| $k_6$ | Dissociation rate of complex (miRmpten) between miR17 and mPTEN | 0.01 | Estimate |
| $K_{DLet7}$ | Degradation rate of Let7 microRNA | 0.01 | [13] |
| $K_{DILLet}$ | Degradation rate of the complex between Let7 and mIL6 | 0.5 | [13] |
| $K_{SIL6}$ | Synthesis rate of IL6 protein | 1.2 | [13] |
| $K_{DIL6}$ | Degradation rate of IL6 protein | 0.1 | [13] |
| $V_{S1mIL6}$ | Basal production rate of IL6 mRNA, mIL6 | 0.1 | [13] |
| $V_{S2mIL6}$ | Synthesis rate of IL6 mRNA promoted by NF-$\kappa$B | 0.01 | [13] |
| $K_{ANFIL}$ | Michaelis constant for the activation of mIL6 synthesis by NF-$\kappa$B | 5 | [13] |
| $K_{DmIL6}$ | Degradation rate of IL6 mRNA | 0.01 | [13] |
| $V_{SmMyc}$ | Synthesis rate of Myc mRNA, mMyc | 0.05 | Estimate |
| $K_{DmMyc}$ | Degradation rate of mMyc | 0.01 | Estimate |
| $K_{DMycLet}$ | Degradation rate of the complex between Let7 and mMyc | 0.5 | Estimate |
| $K_{SMyc}$ | Synthesis rate of Myc protein | 1 | Estimate |
| $K_{DMyc}$ | Degradation rate of Myc protein | 0.1 | Estimate |
| $V_{SmiR17}$ | Synthesis rate of miR17 microRNA | 14 | Estimate |
| $K_{AMycmiR}$ | Michaelis constant for the activation miR17-92 synthesis by Myc | 1 | Estimate |
| $K_{DmiR17}$ | Degradation rate of miR21 | 0.02 | Estimate |
| $V_{SmPTEN}$ | Rate of synthesis of PTEN mRNA, mPTEN | 0.02 | Estimate |
| $K_{DmPTEN}$ | Degradation rate of mPTEN | 0.01 | [13] |
| $K_{DmiRmPTEN}$ | Degradation rate of the complex between mPTEN and miR-17-92 | 0.02 | Estimate |
| $K_{SPTEN}$ | Synthesis rate of PTEN protein | 0.05 | [13] |
| $K_{DPTEN}$ | Degradation rate of PTEN protein | 0.1 | [13] |

of Myc is induced during the transformation process [12]. To investigate the role of Myc in the inflammatory pathway, we compare and analyse the dynamical behaviors of the pathway regulated by Myc.

We analyse the dynamical behaviors of the pathway via bifurcation analysis. We consider the influence of Myc on the epigenetic switch from the transcription level. The bifurcation results with different values of $V_{SmMyc}$ are shown in Figure 4. The bifurcation diagram can reflect feature of the model. The saddle node is able to explain the threshold of the transformation induced by the signal. The diagrams in Figure 4 show that the saddle note moves to left with the increasing $V_{SmMyc}$. In other words, Myc acts as an oncogene which can influence the threshold of the signal to epigenetic switch to a lower value. It makes the cell to be easily evolved into cancer cell. Figure 4F shows the two-parameter bifurcation with $V_{SmMyc}$ and inflammatory signal Src. The red dot line is the saddle note when Src and $V_{SmMyc}$ are at different values. The figure is divided into two subregions by the red dot line: subregion A and B. When the value of Src and $V_{SmMyc}$ are in subregion A. The cells will remain in cancer state under the initial conditions. Conversely, the cell will remain in the inflammatory state when in subregion B. The red dot line also shows that the threshold of signal Src decreases with the increasing of $V_{SmMyc}$.

Our research above is about the role of Myc which makes the transformation easier through effecting the threshold of inflammatory signal Src. Some researchers indicate that Myc provokes cancer[16]. When the transcription rate is large enough, the expression level of the elements in the pathway will be at one state, no matter what value of inflammatory signal Src is (Figure 4 A-E). The bifurcation diagram show that when $V_{smMyc} = 0.3$, the cell remains in the transformed state. In order to verify whether Myc can induce the transformation in this pathway, we analyse the bifurcation diagram of [NFKB] with $V_{SmMyc}$ as a control parameter with the condition that low level of inflammatory signal Src (Figure 5). We could get the following result from the bifurcation diagram(Figure 5): when $V_{SmMyc}$ is in a low rate the cell will remain in the normal cell state


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under the initial conditions; if $V_{SmMyc}$ increased but below the threshold, the transformation will not happen; once the value of $V_{SmMyc}$ was above the threshold, the switch will be triggered. This suggests that the role of Myc in this pathway is in accordance with its inducing effect in carcinogenesis.

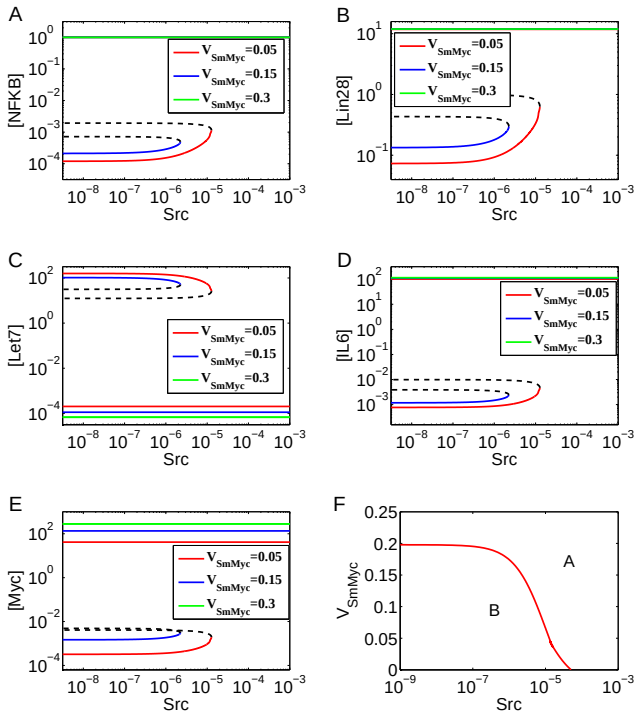


Fig. 4: **The effect of Myc.** (A)-(E) are the bifurcation of NFKB, Lin28, Let7, IL6, Myc with Src as the control parameter with different values of $V_{smMyc}$. The values of $V_{smMyc}$ are: 0.01, 0.05, 0.1, 0.15. (F) The two-parameter bifurcation diagram with inflammatory signal Src and $V_{smMyc}$ as the control parameters.

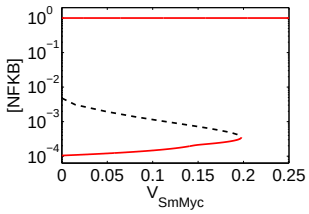


Fig. 5: **Bifurcation diagram of [NFKB] with $V_{SmMyc}$ as a control parameter at $Src = 10^{-8}$.**

## C. Effect of Myc and PTEN

PTEN is tumor suppressor and the pathway is negatively regulated by PTEN. When the transcription rate of PTEN, $V_{SmPTEN}$, increased, the threshold of signal Src will be improved to a higher levels [13]. And the expression level of PTEN is low in cancer cell. Myc as a tumor promoter is overexpressed in tumor. To study the joint action of PTEN and Myc, we regulate Myc and PTEN at the transcriptional level simultaneously. The transcription rate of Myc $V_{SmMyc}$ is changed from 0.3 to 0 while $V_{SmPTEN}$ changes from 0 to 0.3.

When $V_{SmMyc} = 0.3$ and $V_{SmPTEN} = 0$, IL6 is always in one state of high expression which means it is at the cancer state. If we reduce $V_{SmMyc}$ and enhance $V_{SmPTEN}$, the threshold of the transformation will have a substantial right moving(Figure 6).

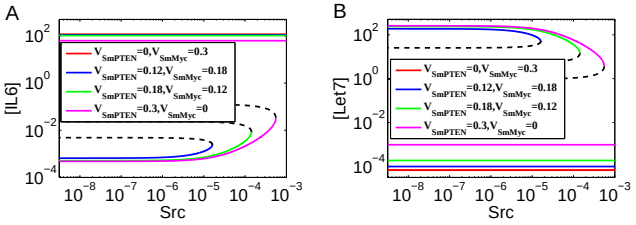


Fig. 6: **The dynamical behaviors of IL6 and Let7 with different $V_{SmMyc}$ and $V_{SmPTEN}$.** $V_{SmPTEN}$ changes from 0 to 0.3 while $V_{SmMyc}$ from 0.3 to 0. (A) Bifurcation of IL6. (B) Bifurcation of Let7.

## D. Effect of miR-17-92 microRNA cluster

miR-17-92 microRNA cluster is the target of Myc and Myc activates the expression of miR-17-92 [21]. Experiments confirmed that miR-17-92 is an oncogene [22]. It is overexpressed in many tumors such as lung tumors. And overexpression of miR-17-92 microRNA cluster promotes Myc to induce tumor [21]. To investigate the role of miR-17-92 in this pathway, we firstly knockout miR-17-92 from the network, and analyse the difference by comparing with the control condition. Figure 7 shows the difference between them. Obviously, the threshold of the signal Src to state transition is different. The threshold of signal Src is larger compared with control condition, which indicates that the carcinogenic of the pathway is reduced after knockout the miR-17-92 microRNA cluster.

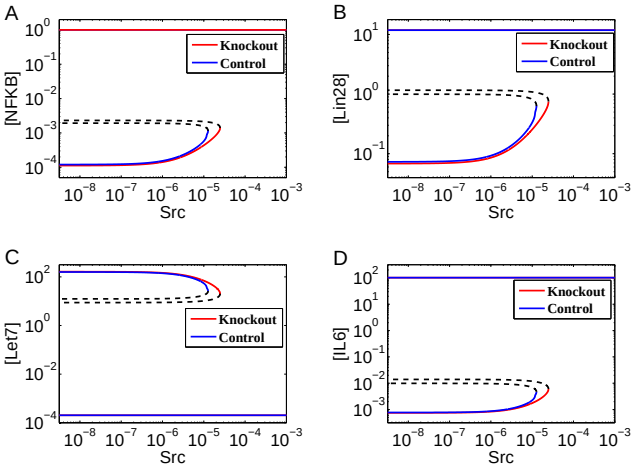


Fig. 7: **The dynamical behaviours of the pathway with and without miR-17-92 microRNA cluster.** The red dot line represents be without miR-17-92 and the blue triangle line represents be with miR-17-92.

Although miR-17-92 microRNA cluster is oncogene, it may not trigger the transformation from normal cell to cancer state. Figure 8C shows the bifurcation diagram of NFKB with $V_{SmiR17}$ as the control parameter. The basal value of $V_{SmiR17}$ is 14. From the bifurcation diagram, no matter decreasing or increasing of $V_{SmiR17}$, NF-$\kappa$B expression level will remain at a low level, which suggests the cell will remain in the normal state. This indicates that miR-17-92 can promote the transformation but can not trigger it.

To further investigate the role of miR-17-92, the difference between various values of synthesis rate of miR-17-92: $V_{SmiR17}$ was analysed(As shown in Figure 7A,7B). Figure 7 shows that the threshold of signal Src is positively related with the synthesis rate of miR-17-92, which means miR-17-92 can promote the conversion. But when $V_{SmiR17}$ varies significantly, there is only a relatively small changes in the magnitude of threshold. This suggests that although miR-17-92 microRNA cluster has cancer-promoting effect, its function actually is to enhance the induction of other oncogenes such as Myc but cannot trigger the transformation.

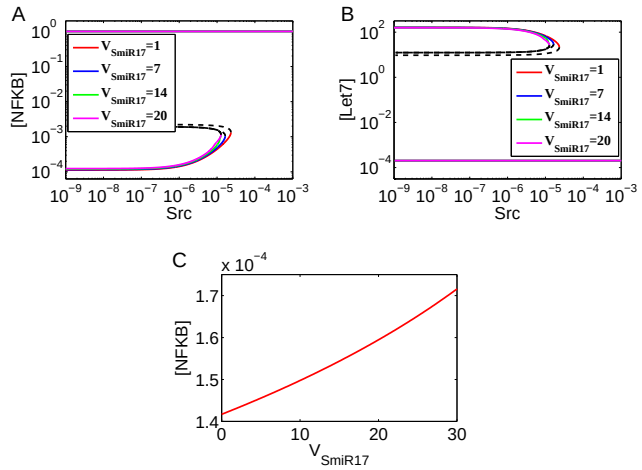


Fig. 8: **The dynamical behaviours of the pathway under the effect of miR-17-92.** The dynamical behaviour of NF-$\kappa$B and Let7 with different values of $V_{SmiR17}$. Where $V_{SmiR17} = 1, 7, 14, 20$.

### *E. Parameter Sensitivity Analysis*

Robustness is one of the important features of the network which can characterize the ability to maintain performance in response to any disturbance of the system parameter. The qualitative behavior of the network is significantly affected by changes in control parameters, which may dramatically affect the steady state and the bifurcation points. The effect of parameter changes on the steady state and the bifurcation points is not evenly distributed: some parameters have significantly impact on the steady state and the bifurcation points, while other do not. The genes belong to the former category may play important roles in the transformation.

Based on the mathematical model, we conduct bifurcation analysis to identify which parameters have a major impact on the steady state and the bifurcation points. We consider the transcription rate, translation rate and the binding rate of microRNA and mRNA as the control parameters in the pathway. To perform the state sensitivity and the saddle node sensitivity, each value of the parameter increased and decreased 20% off its base value. And we study 13 parameters.

Parameter sensitivities of the steady state and saddle node of each parameter are shown in Figure 9. The most sensitive parameters are $V_{Slin28}$, $V_{Slet}$, $k_1$, $V_{Smil6}$ and $K_{Sil6}$. They respectively represent the synthesis rate of Lin28, the synthesis rate of Let-7, the binding rate of Let-7 and mIL6, the transcription rate and the translation rate of IL6. The rest parameters have minor influence on the steady state and the saddle node. The most sensitive 5 parameters are related to Lin28, Let-7 and IL6, which indicate these three elements are important for the pathway. This result consistents with the experimental results that the positive feedback loop involving NF-$\kappa$B, Lin28, Let-7 and IL6 maintains the epigenetic transformed state [11], [12].

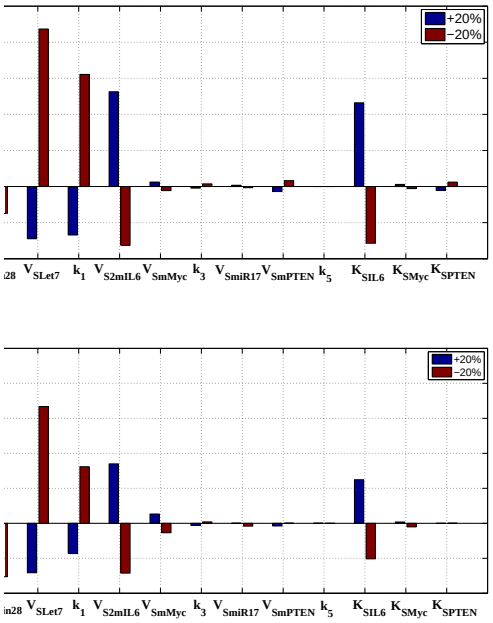


Fig. 9: **Parameter sensitivity analysis.** (A) The change in the steady state of IL6 in response to a 20% increased and decreased value of each parameter.(B) The change of the saddle node bifurcation point in response to a 20% increased and decreased value of each parameter.

## IV. Discussion

There are many mechanisms can induce cancer. Among these mechanisms, the inflammation is an important part in the process of tumor evolution. However, the regulatory mechanisms linking inflammation and cells transformation was less understood. Iliopoulos and coworkers described a model which linked inflammation and cancer [11], [12]. The model is mediated by a positive feedback loop including NF-$\kappa$B, Lin28, Let-7 and IL6. The transformation can be triggered by inflammatory signal Src. Based on the experiment


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results, a theoretical study of this regulatory network through a mathematical model is implemented in our research.

In this paper, we extend the regulatory network and construct a computational model of the network based on Claude's work [13]. Besides the positive feedback loop, we consider two other factors: Myc oncoprotein and miR-17-92 microRNA cluster. The model shows two different states with the change of inflammatory signal Src. When Src is at a low level, the cell will remain in the inflammatory state under the initial conditions. After the level of Src crossing the threshold, the switch will be triggered and the cells transform into cancer state.

The transformation from inflammation to cancer is mediated by the positive feedback loop. The two added factors can effect the performance of the transformation. By bifurcation analysis, we show that Myc act as cancer-promoting gene. It decreases the threshold of inflammatory signal Src which make the transformation trigger more easier (Figure 4A-4E). Furthermore, we predicate that the Myc may trigger the transformation if the transcription rate increased to a certain level (Figure 5). PTEN act as tumor suppressor which increases the threshold of inflammatory signal. The joint action of Myc and PTEN have more significant effect on the performance of the transformation (Figure 6).

miR-17-92 microRNA cluster is an oncogene, the dynamical behavior of the model is different between the pathway with miR-17-92 and without miR-17-92(Figure 7). Although miR-17-92 plays a role in tumor promotion, it is not so significant as Myc. Even though the transcription rate of miR-17-92 have substantial changes, the threshold of the inflammation signal shows small variation (Figure 8). So we predicate that miR-17-92 acts as oncogene which enhance the induction of oncogene Myc and can not trigger the switch.

To identify which parameter have major effect on the pathway, we conduct bifurcation analysis. The result shows that the parameters are related to the positive feedback loop are most sensitive. So we verify the importance of the positive feedback loop in another way. Although we have only a qualitative analysis of the model, not all of the parameters of the model is got from the experimental data. However, our work still reflect the main characteristics of the inflammatory regulatory network. We believe that our work is of certain significance to figure out the relationship between inflammation and cancer.

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