# Differences between telomerase activation and ALT based on the G-Networks

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**The length of telomeres, protective structures at the end of chromosomes, positively correlates with the survival ability of carcinogenic cells. The length in human tumors is maintained by two known mechanisms, active telomerase and the alternative lengthening of telomeres (ALT). However it is known that compelled repression of telomerase-related genes may induce the cells to use ALT for immortalization. Using the Abnormal Pathway Detection Algorithm based on the theory of G-network, our analysis shows a distinguishable pattern of the hTERT down-regulation in the ALT cell lines compared to the normal cell lines. Moreover the algorithm detects a number of genes positively activated by c-Myc, which is found in many malignant tumors in a mutated form, have significantly reduced mRNA expression levels in the ALT cell lines.**

## I. Introduction

Telomeres, which are composed of TTAGGG repeats at the end of chromosomes (Blackburn, 2001), informs of replicative senescence as they are shortened per normal cell division (Harley, 1991). Maintaining telomere lengths, which is accomplished by the activation of telomerase or ALT, is positively associated with one of the hallmarks of cancers (Hirashima et al., 2013), which is resisting cell death (Hanahan and Weinberg, 2000). However hTERT, one of the most important protein components of telomerase, tends to be suppressed in the ALT-expressed cell lines (Atkinson et al., 2005), implying that deliberate repression of telomerase is a potential catalyst for cell immortalization by ALT [1]. Moreover, most genes positively interacting with c-Myc, which is found in many malignant tumors in a mutated form, are repressed in the ALT-expressed cell lines, suggesting that ALT may reduce the role of c-Myc.

G-network [2], one of the stochastic models motivated by queuing theory, introduces a new notion of *inhibition* to conventional queuing theory. It allows us to explore gene regulatory networks using queuing models. Based on interactions between known gene-regulation pathways (Metacore Analytical Suite), here we detect the significant abnormal pathways [3] among 29 genes present in the ALT-expressed cell lines. Furthermore, in order to uncover the roles of each targeted gene, we compare multiple gene regulatory networks with different combinations of genes.

## II. Methods

Identifying significant abnormal pathways using the G-network mainly focuses on estimation of transition probabilities ($p_{ij}^{+}$, $p_{ij}^{-}$), a probability that gene $i$ activates gene $j$ and a probability that gene $i$ inhibits gene $j$, respectively. We adopt and modify the algorithm illustrated in [3] for estimating the negative customer input rates under a normal condition, optimizing the transition probabilities in an ALT-expressed condition and determining the significant abnormal pathways under the steady state. Moreover the theory of Stochastic Automata Networks [4] and spectral gap are employed to explore the transient state using the global infinitesimal generator and the rate of convergence of the chain to its steady state for the last step of the analysis.

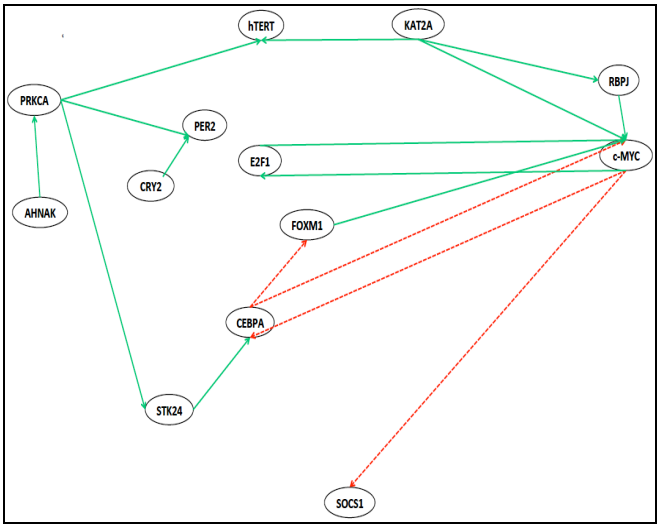


Figure 1. The significant gene regulatory pathways consisting 13 genes. From GSE14533 dataset in Gene Expression Omnibus, 4 normal and 18 ALT-expressed cell lines were analyzed. Green (solid) and red (dashed) lines represent positive and negative interactions between two genes, respectively. Consistent with the result from [1], E2F1, a known repressor of hTERT, maintains its pathways related to c-Myc in ALT-expressed cell lines, whereas the association between c-Myc and hTERT was identified as being insignificant.

## Selected References

[1] Lafferty-Whyte et al. "A gene expression signature classifying telomerase and ALT immortalization reveals an hTERT regulatory network and suggests a mesenchymal stem cell origin for ALT." *Oncogene* 28.43 (2009): 3765-3774.

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