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Cancer onset and progression: A genome-wide, nonlinear dynamical systems perspective on onconetworks

K. Qu, A. Abi Haidar, J. Fan, L. Ensman, K. Tuncay, M. Jolly, P. Ortoleva*

Center for Cell and Virus Theory, Department of Chemistry, Indiana University, Bloomington, IN 47405–7102, USA

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Abstract

It is hypothesized that the many human cell types corresponding to multiple states is supported by an underlying nonlinear dynamical system (NDS) of transcriptional regulatory network (TRN) processes. This hypothesis is validated for epithelial cells whose TRN is found to support an extremely complex array of states that we term a "bifurcation nexus", for which we introduce a quantitative measure of complexity. The TRN used is constructed and analyzed by integrating a database of TRN information, cDNA microarray data analyzers, bioinformatics modules, a transcription/translation/post-translation kinetic model, and NDS analysis software.

Results of this genome-wide approach suggest that a cell can be induced to persist in one state or to transition between distinct states; apparently irreversible transitions can be reversed when the high dimensional space of extracellular and intracellular parameters is understood. As conditions change, certain cellular states (cell lines) are no longer supported, new ones emerge, and transitions (cell differentiation or death) occur. The accumulation of simulated point mutations (minor changes which individually are insignificant) lead to occasional dramatic transitions. The genome-wide scope of many of these transitions is shown to arise from the cross-linked TRN structure. These notions imply that studying individual oncogenes may not be sufficient to understand cancer; rather, "onconetworks" (subsets of strongly coupled genes supporting multiple cell states) should be considered. Our approach reveals several epithelial onconetworks, each involving oncogenes and anti-tumor and supporting genes.

Keywords: Bifurcation nexus; Cell differentiation; Onconetwork; Microarray data; Gene ontology; Nonlinear dynamical system; Regulatory network

1. Introduction

Classic work in cancer genomics has focused on the discovery of oncogenes and tumor suppressor genes (Sassone-Crosi et al., 1988 and Table 1). These are the elements on which much of our understanding of cancer is built. The importance of oncogenes as initiators of directional signaling pathways has been suggested (Vogt et al., 1999). Models of small sub-networks constructed around some of these "key" genes have yielded insights into cancer onset and progression (Obeyesekere et al., 2004; Hervagault et al., 1991). However, cell transformation can be genome-wide in scope due to extensive gene–gene cross-linking in the structure of the human transcription regulatory network (TRN), and these restricted models overlook many important effects, as evidenced by unforeseen drug side-effects and acquired drug resistance. It is even more difficult for these models to answer fundamental questions such as why the transition to cancer may occur without dramatic changes in chromosomal sequence; why microbes make dramatic yet reversible changes in metabolism or physiology in response to environmental variations; and why multi-cellular organisms develop a myriad of differentiated cell types displaying major differences in cell behavior with the same DNA sequence. In this paper, we propose that these diverse phenomena can be described using one model, and we will demonstrate this using a genome-wide human TRN.

Equations describing cellular reaction-transport processes are nonlinear in concentrations, membrane potentials, etc., therefore, a cell can be considered to be a nonlinear dynamical system (NDS). Attempts to analyze cellular NDS problems date back to Turing (1952) who

*Corresponding author. Tel.: +1 812 855 2717; fax: +1 812 855 8300.
E-mail address: ortoleva@indiana.edu (P. Ortoleva).

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Table 1
Most important genes (up to 35) for each of the four zones seen in Fig. 3

	Zone 1		*Zone* 2		*Zone* 3		*Zone* 4	
1	STAT1	44	MYBL1*	20	NFE2L1	807	HIF1A	1693
2	TP73+	27	SMAD3	5	FOXO3A	546	NFE2L1	1609
3	FOXO3A	25	POU2AF1	3	TBP	285	STAT3	311
4	NR3C1	25	NR3C1	3	GATA1	267	GLUR	294
5	BRCA1+	25	POU2F2	2	ATF4	190	TBP	285
6	TP53+	24	CEBPB	1	NR3C1	143	STAT5B	163
7	STAT5B	19	ZNF148	1	USF2	139	STAT5A	147
8	RELA	18	TFEB	1	JUND	132	STAT2	147
9	NFKB1	17	BRCA1+	1	DBP	132	CEBPD	83
10	STAT2	16			TCF4	127	USF2	81
11	STAT5A	16			TBX2	108	JUND	79
12	P63	14			KLF2	105	TCF4	79
13	TNFRSF25	14			JUNB	83	TBX2	73
14	ZNF148	13			ZNF148	82	FOXO3A	70
15	POU2AF1	10			NFKB1	68	KLF2	65
16	FOSL2+	8			FOSL1+	59	JUNB	55
17	RBL2	8			RUNX1	49	ZNF148	42
18	PAX3	7			TFEB	45	NR3C1	30
19	JUN*	6			MYBL1*	33	FOXA3	23
20	ZNFN1A1	6			FOXA3	32	RUNX1	23
21	SP4	6			BRCA1+	25	NFKB1	21
22	RXRA	6			ELF1	23	FOSL1+	18
23	g_+)	6			NFYB	23	BRCA1+	14
24	g_-)	6			FOXA1	21	RXRA	11
25	g_AGE2	6			RXRA	17	MYC*	10
26	g_AP-3_(1)	6			TFAP4	13	ELF1	9
27	g_ATF-6	6			VDR	12	TFEB	9
28	g_BAP	6			ATF1	10	NFYB	9
29	g_BCL-9	6			YY1	10	MYBL1*	9
30	g_BRCA2+	6			SPI1*	9	SRF	9
31	g_CARG	6			STAT1	9	FOXA1	8
32	g_CBF1	6			PAX3	8	DBP	8
33	g_CDK4+	6			PGR	8	ATF4	7
34	g_CLIF	6			HSF1	7	VDR	6
35	g_COUP-TF1	6			TP53+	7	TFAP4	6

The importance factor is the shaded area shown in Fig. 4 as described in Section 2. Here g_xyz represents the gene that encodes protein xyz. Oncogenes (*) and tumor suppressor genes (+) are from http://embryology.med.unsw.edu.au/DNA/DNA10.htm.

proposed the concept of self-organized patterns in interacting cells. Reshevsky emphasized the role of nonlinearity in biological systems (Rashevsky, 1960) while Kauffman studied multiple cellular states based on a boolean model (Kauffman, 1969); these authors suggested that the distinct steady states supported by an NDS might be distinguishable cell lines or types (some normal, some cancerous), and transitions between these states are associated cell transformations. Later Prigogine and coworkers systematically described self-organization, demonstrating the importance of far-from-equilibrium conditions in supporting NDS phenomena (Nicolis and Prigogine, 1977). Recent research has focused on cell differentiation (Ortoleva and Ross, 1973a, b), cell modeling (Ortoleva et al, 2003; Novak and Tyson, 1993), and multiple steady-states analysis (Hannsgen and Tyson, 1985; Mochizuki, 2005). Presently, there is a great interest in delineation gene regulatory networks and deriving their implications for cell differentiation based on the integration of genomic, proteomic, metabolic and other data. Our objective here is to relate the biological phenomena of distinct cell types to the properties of the TRN and the NDS effects it supports.

Transitions associated with nonlinear cellular dynamics are frequently assumed to be caused by mutations that change the structure of the TRN. For example, cancer may occur after months or years, leaving the impression that it is a result of such a rare dramatic mutation. Yet minor mutations at the local sequence level may leave the structure of the TRN intact, instead altering, for example, transcription factor (TF)/gene binding or transcription rate constants. In the cell system, a minor sequence change can move a key physicochemical parameter, but no dramatic change in behavior will occur until a critical state is reached. At this point, a dramatic transition in RNA expression and other key cell activity is suddenly triggered (without changing the basic structure of the TRN). In this process, no individual point mutation is actually responsible; rather, it is a cumulative effect. It may take years for