

Modeling the Interaction of Growth Factor and Apoptosis Subsystems in Cancer

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Cancer research to date has largely focused on individual cellular subsystems, and the specific malfunction of the regulatory mechanisms (so-called *dysregulation*) associated with each one. In an influential review, Hanahan and Weinberg [7] identified a set of six distinct acquired functional capabilities—called "hallmarks"—that are common to virtually all types of human cancers, namely: (1) self-sufficiency in growth signals, (2) insensitivity to antigrowth signals, (3) evasion of apoptosis, (4) limitless replicative potential, (5) sustained angiogenesis, and (6) tissue invasion and metastasis. Such a categorization then suggests a systematic approach to studying and analyzing the mechanism of occurrence of an otherwise bewildering array of cancer types and tumor subtypes within specific organs. A detailed understanding of the molecular, biochemical and cellular mechanisms by which each *hallmark* trait is acquired should then provide a rational basis for developing efficacious protocols of targeted therapy for cancer treatment or tumor prevention.

It is clear, however, from Hanahan and Weinberg's review, and several other works as well (for example [4]), that (i) the emergence (or suppression) of any particular hallmark involves interactions between various associated cellular subsystems, and (ii) the dysfunction of a single subsystem can contribute to the emergence of several hallmarks simultaneously. For example, it is known that the dysregulation of the growth factor signaling protein Ras can lead to self-sufficiency in growth signals [9], the evasion of apoptosis [3], and angiogenesis [8]. It has also been noted that the tumor necrosis factor, (TNF) signaling pathway interacts significantly with many others, including apoptosis and NF- κ B (a transcription factor that regulates several genes that mediate tumorigenesis and metastasis) [2]. Specifically, it is known that enforced activation of NF- κ B protects against apoptosis, while susceptibility to TNF-induced apoptosis increases in the absence of NF- κ B. Similarly, the investigation reported in [12], shows how the single ligand TNF can elicit the activation of both apoptotic and pro-growth subsystems, noting, among other things, that TNF binding to TNF receptor 1 (TNFR1) (as opposed to TNFR2) can activate apoptosis through cytochrome C release and also antiapoptotic cellular responses. Thus, without accounting for potential modulating effects (synergistic or otherwise) caused by connectivities and interactions, isolated subsystem analysis may be inadequate and misleading.

It is becoming increasingly accepted that mathematical modeling provides an efficient way of obtaining truly quantitative insight into the behavior of these subsystems and their interactions. As a starting point for quantitative characterization of the dynamic behavior of cellular subsystems and the effect of known interactions on the emergence of cancer, we have focused first on the interaction between the growth factor and apoptotic signaling pathways, specifically via PI3-kinase (PI3K). It is known that PI3K, when activated by EGF (epidermal growth factor) binding to the EGF receptor (EGFR), activates protein

kinase B (PKB), which phosphorylates and thereby inactivates the pro-apoptotic protein BAD [4]. We have developed a model of this connected ensemble as follows: we modeled the connections between PI3K and PKB and between PKB and BAD by combining reasonable mechanistic assumptions and available literature data [5]; we then used this to link a published model of EGFR signaling that included activation of PI3K [10] with our modified and updated version of an apoptosis model that incorporates the pro-apoptotic effects of BAD [6]. Our presentation will highlight the model development and how we have used the resulting ensemble model to explore quantitatively how anti-apoptotic EGFR signaling may potentially interact with pro-apoptotic stress signals. We will discuss how this model provides a quantitative understanding of how other factors outside of the obvious apoptotic subsystem is implicated in acquiring the *evasion of apoptosis* trait. For example, our model predictions suggest, among other things, the somewhat surprising result that it might be possible for EGFR signaling to disrupt the apoptotic pathway, possibly as much as an hour after the initiation of stress signals.

Our future efforts will be directed towards further mechanistic refinement of the apoptosis model and the PI3K–PKB–BAD links. We will also begin modeling interactions between EGFR and the apoptotic signaling occurring further downstream, particularly through the signaling proteins Ras and ERK. Several models of EGFR signaling that include Ras activation have already been published [1, 11], leaving the majority of the modeling to the interaction of Ras and ERK with the apoptotic pathway. These models will then be used to explore the interaction of these pathways during normal function and during the dysfunction of specific signaling components. Our ultimate goal is to use these models to generate experimentally testable hypotheses regarding novel therapeutic approaches that may not have been conceivable had the subsystems been studied in isolation.

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