Perspective

Cancer Research

The Continuum Model of Selection in Human Tumors: General Paradigm or Niche Product?

Simon Leedham and Ian Tomlinson

Abstract

Berger and colleagues recently proposed a continuum model of how somatic mutations cause tumors to grow, thus supplementing the established binary models, such as oncogene activation and "two hits" at tumor suppressor loci. In the basic continuum model, decreases or increases in gene function, short of full inactivation or activation, impact linearly on cancer development. An extension, called the fail-safe model, envisaged an optimum level of gene derangement for tumor growth, but proposed that the cell gained protection from tumorigenesis because additional mutations caused excessive derangement. Most of the evidence in support of the continuum model came from *Pten* mutant mice rather than humans. In this article, we assess the validity and applicability of the continuum and fail-safe models. We suggest that the latter is of limited use: In part, it restates the existing "just right" of optimum intermediate gene derangement in tumorigenesis, and in part it is inherently implausible that a cell should avoid becoming cancerous only when it is some way down the road to that state. In contrast, the basic continuum model is a very useful addition to the other genetic models of tumorigenesis, especially in certain scenarios. Fittingly for a quantitative model, we propose that the continuum model is most likely to apply where multiple, cancer-promoting mutations have relatively small, additive effects, either through the well-established case of additive germline predisposition alleles or in a largely hypothetical situation where cancers may have acquired several somatic "mini-driver" mutations, each with weaker effects than classical tumor suppressors or fully activated oncogenes. *Cancer Res; 72(13); 3131–4. ©2012 AACR.*

Introduction

The basic equation of natural selection taught to students is genotype + environment = phenotype (1). In tumorigenesis, selection acts on genotypes generated by mutation to produce a phenotype. The selective advantage of any genotype may sometimes be independent of environment, and sometimes the role of environment is forgotten or ignored. However, simple observations, such as the organ- or tissue-specificity of many mutations in cancer, show that environment must be very important in determining which genotypes are selected and hence which phenotypes occur (2). It is simply necessary to define environment broadly to include the normal intracellular milieu, the effects of nearby cells (whether cancer or normal) and existing abnormalities within that cell, including mutations that have already provided a selective advantage.

Several different types of mutation occur in tumors and are selected depending on the environmental context. In a recent article, Berger and colleagues (3) proposed a new continuum model of how somatic mutations caused tumors of epithelial origin to grow. In the basic continuum model, decreases or increases in gene function, short of full inactivation or activation, impact on cancer development (Fig. 1). The degree of loss or gain of gene function is monotonically associated with increasing cancer risk. The authors contrasted the continuum model with the existing oncogene and tumor suppressor (two hit) models (4, 5) in which full gain or loss of function is required (Fig. 1). Instead, they viewed the continuum model as an extension or generalization of well-established models of cancer mutation in which full gain or loss of function is not found, including haploinsufficiency and dominant-negatives (6, 7). However, haploinsufficiency and dominant-negative models lack the critical monotonic effect of the continuum model, and we shall regard these 3 models as distinct from one another (Fig. 1).

The continuum model is implicitly designed to apply to somatic mutations in tumorigenesis. Most of the evidence in its favor comes from mice that carry mutations that are partially or fully defective for the function of genes such as *Pten* (3).

Critique of the Model

An initial reflection on the continuum model is that it does not diverge fully from the oncogene and tumor suppressor models, because in most continuum scenarios, tumorigenesis is still most strongly favored by full gene activation or inactivation. This begs the question of why a cancer genome would work its way gradually toward the selective optimum when it could reach it as easily by acquiring mutations with strong effects on function. The most plausible explanation under a

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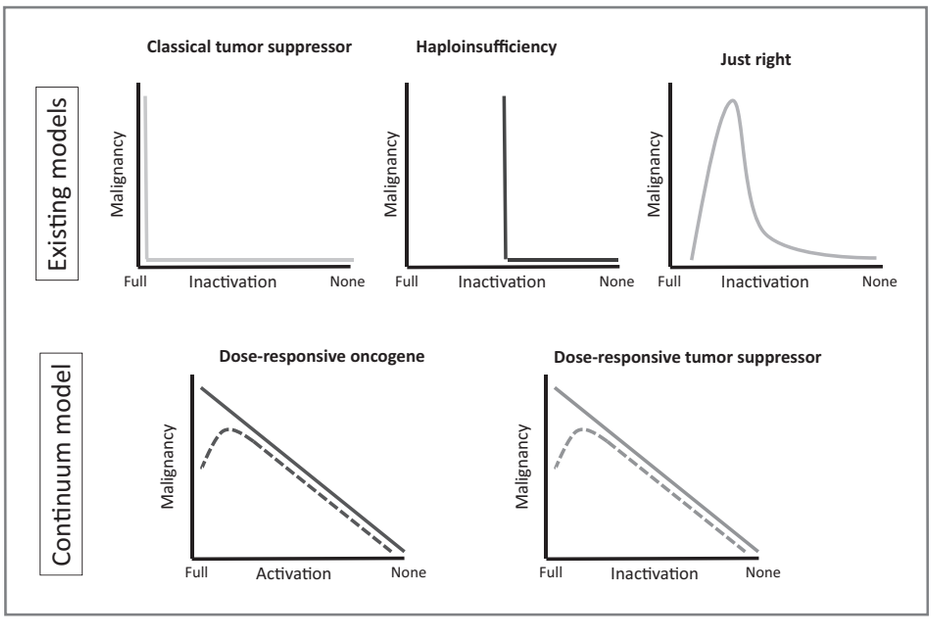

Figure 1. Existing models compared with the continuum model, including the fail-safe variant (dashed lines). Diagram style replicates that used by Berger and colleagues (3) to provide direct comparison. Note that the haploinsufficiency model shown is the classical one and differs from that originally provided by Berger and colleagues, which resembled a stepwise tumor suppressor model. The classical oncogene model is not shown, but is essentially the inverse of the classical tumor suppressor model.

continuum model is that mutational constraints prevent this from occurring.

For a gain-of-function model in which very specific mutations activate an oncogene, the continuum model is unlikely to apply. Thus, we would expect few atypical or partially activating mutations in proteins activated by missense changes, such as K-ras or B-raf. However, one particular scenario that is attractive for a continuum model is for oncogenes activated by amplification, where relatively severe mutational constraints do exist. Here, a gene is much more likely to be an effective driver of tumorigenesis if low-level copy number gain provides a selective advantage before the full advantage is conferred by true amplification.

In a similar fashion, tumor suppressors are more likely to drive tumorigenesis if the heterozygous mutant genotype has some tumorigenic effect. This is clearly a stepwise rather than a true continuum of effect and it has been hard to find good evidence of this in humans, perhaps because of evolutionary pressure for dosage compensation in critical genes. More generally, for a tumor suppressor (unlike an amplified oncogene), there is no evidence to show that totally inactivating mutations are especially difficult to acquire compared with partially inactivating mutations. Therefore, a continuum model seems somewhat implausible for a tumor suppressor, given that the fastest-growing tumors (that is, those that come to clinical attention) will usually have the optimal mutations, namely those that properly inactivate the protein.

The second issue with the continuum model is its reliance on mutant mice, either carrying germline variants or variants induced by highly efficient Cre-mediated recombination. *Pten* is the exemplar. There is little doubt that tumor susceptibility does vary with the degree of mouse Pten dysfunction—in general the greater the dysfunction, the greater the tumor burden of a particular mouse (with the exception of obligate *Pten* haploinsufficiency for prostate tumorigenesis). There is little doubt that insights provided by such models continue to be very important. However, it is less clear that they provide a firm basis for how mutations arise and are selected in sporadic human tumorigenesis. Not only may short-lived animals such as mice have been under less selection pressure to avoid cancer, but also the very efficiency of Cre means that these mouse models actually most closely resemble a human that is mosaic for a germline mutation. If, for example, *Pten* function is partially inactivated in a mouse by induced somatic recombination, many cells will be affected, leading to a microenvironmental change. Although human tumor microenvironments are not phenotypically normal, they are generally genetically near normal, and sudden, widespread microenvironmental changes like those induced by Cre simply do not occur in spontaneous tumors. In the usually accepted model of sporadic, stepwise tumorigenesis, a single stem cell acquires mutations and becomes a cancer by waves of clonal expansion after acquisition of advantageous mutations. In this scenario, we argue, the mutations selected are more likely to have relatively profound, cell-autonomous effects.

An interesting issue, and a potentially fertile ground for the continuum model is the multitude of mutations uncovered by cancer genome sequencing that do not seem to be drivers, yet might not in all cases be simple passengers (8). While the continuum model was proposed to apply to single genes, it could apply to a set of genes for which individual mutations have small effects on tumor promotion, but where the acquisition of large numbers of such mutations could provide a combined driver of tumorigenesis, that drive being roughly proportional to the number of mutations acquired. Here, both mutational and selective constraints might favor this polygenic continuum model of tumorigenesis in which somatic mutations may have a large effect on a gene's function, but a correspondingly small selective effect and hence a strong possibility of loss through drift or gain through new mutation.

An interesting issue is how many of these "mini-driver" mutations might a cancer possess. Given the technical and

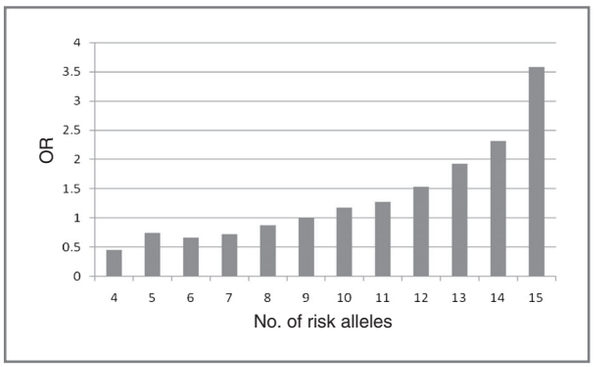

Figure 2. Monotonic increase in risk of colorectal cancer as number of risk alleles increases. The odds ratio (OR) of colorectal carcinoma is calculated for groups of individuals who have different numbers of risk alleles at 14 colorectal cancer single-nucleotide polymorphisms (SNP) from a set of 7,849 individuals from the United Kingdom. In this simplified situation, effect sizes of each SNP are ignored. Owing to low frequencies, individuals with $\leq$4 or $\geq$15 risk alleles are grouped.

statistical difficulties in distinguishing between mini-driver and neutral (passenger) mutations, any suggestion must currently be speculative. However, we believe it reasonable that each cancer could possess tens or more mini-driver changes, especially if it has acquired some form of genomic instability. For example, there is ongoing debate about the functional consequences of the multiple aneusomies often found in carcinomas; such large-scale copy number variants might easily have subtle, yet nontrivial effects on tumor growth.

Although the continuum model was primarily proposed to explain somatic mutations, one scenario to which it might well apply is to cancer susceptibility polymorphisms. Here, individual germline variants—whether common or rare alleles—have small or modest effects on cancer risk, but the combined effects of many variants may be large. Again, this can be regarded as a polygenic form of genetic control. This risk is likely to be modulated in most cases through subtle effects on transcript levels. Importantly, the effects of most predisposition alleles appear to be log-additive, an effect that encompasses allelic dosage at a single single-nucleotide polymorphism, multiple independent polymorphisms at one risk locus, and variants at distinct risk loci. Overall, the existing data (9) show that cancer risk is a monotonically increasing function of activation or inactivation per gene, and, as far as can be discerned, for the overall set of genes (Fig. 2).

Berger and colleagues (3) further developed the continuum model to cover a scenario that they term fail-safe. Here, the optimal level of gene derangement for tumorigenesis lies short of full gain or loss of function. For some genes, the notion that full gene activation or inactivation is suboptimal for tumorigenesis is entirely plausible, and it has been described previously as the "just-right" model (Fig. 1; refs. 10, 11). In the just right model, the tumorigenic optimum may vary with microenvironment, such as tumor location or the stage of tumorigenesis, and in the case of adenomatous polyposis coli (*APC*) there is substantial experimental evidence to support this (12, 13). The fail-safe nomenclature implies the existence of an inherent antitumor component. While we believe that an optimum level of derangement may exist for several cancer genes and pathways, we believe that this is more likely to reflect underlying cell biology rather than the existence of an endogenous cancer prevention mechanism.

In conclusion, the continuum model is a very useful addition to the expanding variety of models of the selective advantages provided by different types of mutation during tumorigenesis. The fail-safe version of the continuum model, in contrast, partly restates the just right model and partly places a somewhat implausible emphasis on adaptive avoidance of tumorigenesis. The central question for the continuum model is, of course, when does it apply and to which genes does it apply? There must be some doubt as to whether tumorigenesis in *Pten* mutant mice, on which the continuum model is based, provides a truly representative model of human carcinogenesis, and it is even questionable whether mutant *APC* follows a continuum over more than a small part of its range. Our testable view is that a continuum model is most likely to apply to a situation where multiple, cancer-promoting mutations have relatively small, additive effects, either through germline predisposition or through mini-driver somatic mutations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S. Leedham, I. Tomlinson
Development of methodology: I. Tomlinson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I. Tomlinson
Writing, review, and/or revision of the manuscript: S. Leedham, I. Tomlinson

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