Genetic instability and darwinian selection in tumours

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Genetic instability has long been hypothesized to be a cardinal feature of cancer. Recent work has strengthened the proposal that mutational alterations conferring instability occur early during tumour formation. The ensuing genetic instability drives tumour progression by generating mutations in oncogenes and tumour-suppressor genes. These mutant genes provide cancer cells with a selective growth advantage, thereby leading to the clonal outgrowth of a tumour. Here, we discuss the role of genetic instability in tumour formation and outline future work necessary to substantiate the genetic instability hypothesis.

The past two decades have witnessed the explosive growth of cancer genetics. Up until then, the cancer cell genome was virtually a black box. In the time since, numerous genetic alterations have been found in cancers – discoveries that have advanced our basic understanding of tumour formation and have led to a revolution in the care of patients afflicted with this disease[1,2]. We are at a crossroads at the turn of the century: the molecular detail of an entire cancer cell genome seems to be within our reach. Knowledge of these extensive genetic changes informs our strategies for cancer treatment and prevention, but it also highlights fundamental questions about tumour formation. How can a tumour accumulate so many genetic changes? Are all tumour cell genomes intrinsically different because they are more plastic than those of normal cells? Does the presence of these numerous genetic alterations imply that all tumours are genetically unstable?

The role of genetic instability in tumour formation has been debated for nearly 100 years[3–5]. It is now well established that all tumours contain genetic alterations, including subtle changes in DNA sequence as well as cytogenetically visible changes such as chromosome losses, gains and translocations. It is clear that one cannot determine the level of genetic instability of a tumour merely by scoring the presence of these alterations as instability refers to a dynamic rate of change[6,7]. For example, the unavoidable basal rate of endogenous DNA damage could, in principle, account for these alterations accumulating over the many rounds of tumour cell division. Recent data, however, have strongly suggested that an abnormally elevated level of genetic instability can be found in many tumours[8]. This instability is reflected in the heterogeneity seen within individual tumours and among tumours of the same type. Such heterogeneity underlies the histological, karyotypic, molecular, physiological and biochemical differences that can be observed by simply examining different parts of the same tumour.

Instability – cause and effect?

Recent studies of tumour instability have led to the realization that there are several, completely distinct, forms of genetic instability. One of the best understood is that arising from inactivation of DNA mismatch repair (MMR) genes such as *MSH2* or *MLH1*[9]. The inactivation of MMR genes in tumours gives rise to instability at the nucleotide sequence level as naturally occurring replication errors cannot be repaired effectively. This instability is most easily observed at short sequences of DNA repeats scattered throughout the genome, called microsatellites, thus generating the characteristic microsatellite instability (MIN) seen in these tumours[10–12]. MIN tumours have nucleotide mutation rates two to three orders of magnitude higher than normal cells or mismatch-repair-proficient cancers of the same cell type[13–15].

Strikingly, unlike the vast majority of solid tumours, MIN cancers have a normal complement of chromosomes. These cancers retain a diploid karyotype – one pair of each of the chromosomes. This observation is impressive because of its stark contrast with other solid tumours. Non-MIN tumours have a wide variation in chromosome number – their karyotypes are aneuploid[12]. Such observations have led to the suggestion that cancers develop instability either at the sequence level (MIN) or at the chromosomal level, but not generally at both levels. In this view, the aneuploid karyotype is the readout of an underlying chromosomal instability (CIN). Because these instabilities are rarely found to coexist in tumours, it would seem that one form of instability is sufficient to drive tumorigenesis[8].

The causes of chromosomal instability are just beginning to be investigated[7]. One theory posits that CIN in cancer is a natural side-effect of the malignant transformation process driven by preceding mutations in growth-controlling oncogenes and tumour-suppressor genes such as *ras* and *TP53* (encoding p53). This theory is supported by evidence that the introduction of *ras* or *myc* oncogenes into cells can cause an increase in genomic aberrations[16,17]. Similarly, alterations of the tumour-suppressor gene *TP53* can exacerbate genetic instability[18].

However, several arguments suggest that these well-known oncogenes and tumour suppressors are not responsible for initiating the CIN phenotype. The very existence of karyotypically stable MIN tumours argues against a causal role for these genes in CIN. These tumours have mutations in the same oncogenes and tumour-suppressor genes as CIN tumours and have similar stage-specific growth and progression characteristics – but are not aneuploid. Additionally, the continued chromosomal stability of stable diploid human cells after targeted deletion of *TP53*[19] suggests that other genetic alterations are necessary to initiate genomic instability. These cases prove that the mutant genes driving advanced tumour progression do not inevitability generate or require aneuploidy.

Another theory postulates that aneuploidy is not determined by genetic alterations but instead results from the altered cellular architecture that ensues whenever an abnormal chromosome complement is present within cells[20]. In this scenario, a chance abnormal division in an otherwise normal cell gives rise to a karyotypically abnormal daughter cell with a selective growth advantage compared with that of its neighbours. The abnormal number of chromosomes in this cell destabilizes the segregation machinery, autocatalysing chromosome missegregation and further aneuploidy[21].

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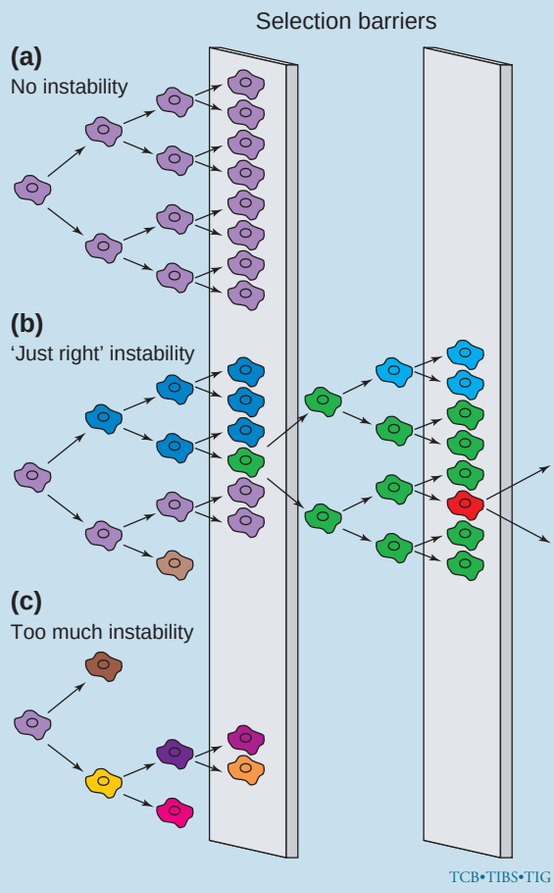

FIGURE 1. Overcoming selection barriers in the race to tumorigenesis. In normal cells (a), the intrinsic rate of instability is low. Correspondingly, when cells reach the first selection barrier on the road to cancer, the diversity of the cellular population is low. Because none of the cells contains the genetic alteration required to overcome this selection barrier, tumour progression is blocked. In tumour cell precursors (b), there is an increased level of genetic instability. In this case, the broad heterogeneity of the cell mass facing the first selection barrier virtually guarantees that at least one of the cells contains the requisite genetic alteration to overcome this hurdle and continue the process of tumour progression. Genetic instability is observed in the final tumour because the instability mutation propels progression and is carried along as a passenger with the clonally selected alterations. If the level of genetic instability is too high (c), the accumulated damage from cell division rapidly rises above the threshold for viability – apoptotic pathways are activated and cell death ensues. At the level of the cellular population, this leads to extinction. Not enough cells reach the first selection barrier to select a malignant clone effectively.

An alternative to these hypotheses draws from the lessons of microsatellite instability. Perhaps, aneuploid tumours arise in the same way as MIN tumours: they sustain an early mutational event in a chromosome-stability gene (instead of a mismatch repair gene) that drives chromosomal instability (instead of microsatellite instability). Mutations in CIN genes are just beginning to be described[22], and experiments are still needed to prove their role in the molecular mechanisms of aneuploidy.

Selection – driving tumour formation

Tumours initiate as a result of mutations in a single gene in a single progenitor cell. Subsequent mutations in the offspring of this cell and waves of clonal expansion give rise to daughter cells that have the growth advantage typical of cancer. Clonal selection drives this process[23]. The mutational targets of this multistep progression are oncogenes and tumour-suppressor genes – genes that are mutated and then directly affect the rate of cell growth or cell death[24].

There is accumulating evidence that another class of genes can be targeted during this clonal-selection process. These include genes such as the nucleotide excision repair genes[25], the Bloom's syndrome gene *BLM*[26] and the mismatch repairs genes *MSH2* and *MLH1*[9]. In each of these cases, an important role for the wild-type gene products is to maintain genome stability. Alteration of these genes in cancers increases the effective mutation rate in tumour cells, providing variation for the forces of selection to act upon.

Different types of genomic instability lead to different modes of inactivation of tumour-suppressor genes and oncogenes, but the recurring theme is the same – targeting of crucial growth-controlling pathways. A good example involves the APC–β-catenin pathway, which must be inactivated to initiate colorectal tumour growth[27]. This pathway is thought to restrain cell growth through the cytoplasmic sequestration of β-catenin; when translocated to the nucleus, β-catenin drives transcription of genes that promote cell survival[2]. Alteration of this pathway, either through loss of wild-type APC or dominant 'escape' mutations in β-catenin, lead to aberrant survival gene transcription and provide cancer cells with a growth advantage compared with their neighbours.

In CIN tumours, where the chromosome loss rate is elevated compared with that in normal cells, the APC–β-catenin pathway is often targeted through direct intragenic mutation of one allele of the APC gene combined with loss of the wild-type gene as a consequence of chromosomal loss[28,29]. A small percentage of CIN tumours sustain an intragenic activating mutation in β-catenin, which disrupts its interaction with APC and allows it to drive transcription in the nucleus – a pathway equivalent to lesion-induced inactivation of APC[30,31].

In MIN tumours, the rate of point mutation is elevated relative to that in normal cells. Thus, in some MIN tumours, inactivation of the APC–β-catenin axis occurs through direct intragenic mutations of the APC gene in both alleles, preferentially within small stretches of repeated sequences (e.g. homopolymeric runs) of the kind that are particularly mutatable in MMR-deficient states[32]. In many other MIN tumours, pathway inactivation is through point mutation of β-catenin. Regardless of the type of genetic instability driving mutation in these cancers, the same functional result is achieved – a crucial growth-controlling pathway is targeted, providing a growth advantage to cells with the mutation.

This growth advantage in cancer cells can be observed experimentally. Reintroduction of a wild-type gene encoding p53 or APC into the cancer cell containing a mutant copy is a fatal event[33,34]. Analogously, loss of a mutant c-Ki-*ras* gene, but not a normal *ras* gene, completely abrogates the ability of cell lines to form tumours *in vivo*[35]. Thus, the unrestrained growth of a tumour is dependent upon the continued inactivation of tumour-suppressor genes and activation of oncogenes. Instability genes are different. When a cell inactivates an instability gene such as *MLH1*, there is no immediate growth advantage to that cell. Reintroduction of wild-type *MLH1*, expressed at physiologic levels, into a tumour cell containing a mutated *MLH1* gene is not a fatal event[36].

With this in mind, a mutational cause for genetic instability seems to fly in the face of clonal-selection theory. Increasing genomic instability should not increase the growth advantage of an individual cell; rather, it should decrease the fitness of that cell compared with a cell with intact genome surveillance. Too much genomic instability would be fatal to a cell. In fact, many cellular mechanisms have been identified that monitor genome damage and direct cells towards a programmed cell-death pathway if this damage is too great[37]. We are then left with a conflict

at the interface of the genetic-instability and clonal-selection theories: how do cancer cells select for mutations that not only have no direct growth advantage but might even carry a significant growth disadvantage?

Instability — a selective paradox?

To understand how mutations in instability genes can be selected during tumour evolution, we can look to basic studies of mutation rate and cellular fitness in bacteria[38]. In *Escherichia coli*, the total fitness of a population results from the balance between the positive effects of mutational variation, which can promote selection under new environmental pressures, and the deleterious effects of mutation, which can lead to population-wide 'mutational meltdown'[39,40]. Instability genes become selected because they hitchhike along with positively selected mutations. Cells with drastic mutations in an instability pathway never become the predominant cell type in a population – their levels of instability exceed the threshold for viability by leading to too many deleterious mutations. However, in stressful environments, bacteria with higher overall levels of genomic instability eventually dominate the population because their progeny are more likely to develop mutations that later provide a selective growth advantage[41–43]. In these rapidly changing environments, 'mutators' have an edge[44]. These principles, applied to tumour cell populations, are illustrated in Fig. 1.

The model in Fig. 1 also provides an understanding of how genetic heterogeneity can exist within the 'clonal' process of tumorigenesis. The tumour is clonal only in the sense that all cells within a tumour are derived from the same stem cell precursor (among the millions of stem cells present in the normal colorectal epithelium, for example). Genetic instability makes the tumour itself a population under change – a huge collection of coexisting subclones, each with the potential for future changes in the face of selective pressures[45].

What are these selective barriers? Highly abnormal microenvironments exist in tumours, which are subjected to periods of anoxia, malnutrition, fluctuating hormonal influences and potential attack by numerous arms of the immune system. It is difficult to think of a more fertile breeding ground for a mutator phenotype. Indeed, the wide prevalence of both aneuploidy and karyotypic heterogeneity in tumours is compatible with the idea that an early mutational event causing genomic instability might actually be necessary for cancers to progress beyond the initial benign stages.

Back to the future

Much hard work lies ahead. The most definitive proof for a genetic basis of genetic instability in tumours will come from the discovery of the instability genes that are actually mutated in cancers. To date, the number of cancers with known mutations in genes that initiate instability is small. In addition to the discovery of more causative genes and mutations, the hypothesis outlined above suggests that these genes should be mutated early in the neoplastic process (such as MMR genes in MIN tumours). Work with non-human organisms cannot only identify potential instability gene candidates but also can provide powerful ways to explore their biochemical and physiological mechanisms of action. We also predict that some of the genes that can cause CIN will be found to be altered in the germline of families predisposed to cancer.

The genetic-instability hypothesis can be viewed as a pessimistic one. If the cells within a tumour are really so heterogeneous and so ready to form variants in the face of challenge, do we have a realistic chance of ever curing advanced cancers? The answer, surprisingly, is 'yes'. Moreover, our best chance of cure might actually be a result of the instability of the tumour. Normal cells respond to stressful conditions by activating their genome-stability genes, allowing them time to repair damage and eventually recover. By contrast, the stability pathways of tumour cells are defective, theoretically making the cancer cells more sensitive to stress-inducing agents. This unique feature of cancer could provide a target for direct attack by instability drugs. Indeed, such drugs have been instrumental in identifying instability genes in yeast[46,47]. If these agents kill genetically unstable yeast cells better than normal cells, why shouldn't similar drugs kill genetically unstable human cancer cells better than their normal counterparts?

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Pattern formation in single cells

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Single-cell patterning begins with an asymmetric cue that orients the axis of polarity. Despite great diversity in the types of cues, common mechanisms appear to mediate the polarizing response. Rho-family GTPases initially process and reinforce polarity cues by remodelling cortical actin, and these local asymmetries are subsequently propagated to the microtubules, membrane and secretory pathway to generate the final pattern. Homologues of the yeast polarity genes fulfil similar functions in higher eukaryotes, revealing a fundamental conservation in how polarity arises. Unlike yeast, however, more complex eukaryotic cells can manifest multiple axes of polarity, suggesting that additional mechanisms have evolved to generate more elaborate patterns.

Although developmental biologists normally think of pattern formation in the context of how the appropriate cell types are specified in the right place in an organism, single cells can also generate complex patterns (Fig. 1). Eukaryotic cells adopt a vast range of morphologies, and these forms are usually essential for their function. Even unremarkably shaped cells often possess elaborate asymmetries in subcellular organization. For example, motile cells could not move without polarizing their actin and microtubule cytoskeletons, and intestinal epithelia require a polarized vesicle-trafficking system to absorb nutrients from the gut and transport them to the bloodstream. Like embryonic patterning, which begins with the polarization of the body axes, patterning at the single-cell level starts with the specification of an axis of cell polarity, and, in some cases, these two processes are identical: in organisms such as *Caenorhabditis elegans*, *Drosophila* and *Xenopus*, the main body axis of the animal is defined by the polarity of the single-cell zygote. Thus, cell polarity presents cell biologists with many of the same conceptual challenges as developmental patterning – but on a much smaller scale. Given that the first eukaryotes are thought to have evolved about two billion years before multicellular organisms[1], patterning at the single-cell level is probably a very ancient process, and it is difficult, if not impossible, to think of an example of a cell *in vivo* that is not polarized in some way.

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Cues

It is important that cells not only polarize but that they polarize in the right direction, and therefore they must respond to asymmetric cues, which can be either intrinsic or extrinsic to the cell. Much of our understanding of how cells polarize comes from the study of the unicellular budding yeast *Saccharomyces cerevisiae*, where cell polarity is manifest in the pattern of budding: haploid cells choose axial bud sites, whereas diploids bud in a bipolar fashion, and each polarity is intrinsically specified by asymmetries at the cell cortex[2]. In both cases, the Rsr1p GTPase links cortical cues to the downstream polarity-establishment proteins, raising the question of how cells choose the correct spatial signal for the appropriate stage of their life cycle. When axial cues are defective, haploid yeast bud at bipolar sites, revealing a hierarchy in which axial cues take precedence. Mutant yeast that cannot interpret either axial or bipolar cues still bud, but do so at random locations. Thus, yeast cells can still polarize in the absence of cues, and therefore these signals function specifically to orient the polarization machinery.

In *S. cerevisiae*, cortical signals for bud-site selection are reinforced at each cytokinesis, thereby reprogramming the mother and daughter cells with intrinsic asymmetries for the next round of division. The rod-shaped fission yeast *Schizosaccharomyces pombe* also relies on intrinsic signals for polarizing growth; unlike budding yeast, however, these cues are thought to arise *de novo* during each cell cycle from asymmetries inherent in microtubules and from their dynamics of self-assembly[3]. Microtubule disruption or mutations in the *tea1* gene result in abnormal cell branching owing to growth at ectopic sites[4]. Tea1p protein localizes to the ends of microtubules, suggesting a model in which microtubules 'discover' the cell poles by maximizing their length, and Tea1p then marks these as the sites for polarized growth.

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