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REVIEWS

Spotlight

Making Mistakes Empowers Cancer Cells

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Lethal cancers have genomes that can reflect a jigsaw puzzle put together in a hurricane. The missing, misjoined, and extra pieces contribute to the driving forces behind the cancer phenotypes. But is this the only reason genomic instability is so prevalent in aggressive cancers? New findings support that the hurricane winds themselves, not just their aftermath, contribute to the cancer phenotype of metastasis.

The genomic scars of chromosomal instability are a hallmark of lethal cancers. Genomic and chromosomal instability are traditionally thought to enable cancer phenotypes through resultant changes in the DNA copy number levels of critical genes. Gain of strong oncogenes and loss of tumor suppressor genes are well understood examples, and more recently work has focused on more subtle, cumulative effects of changes in hundreds to thousands of genes along the genome or across functional pathways [1,2].

The potential relevance of genomic instability cannot be ignored. For example, in ovarian cancer the vast majority of cases are aggressive and have a high degree of aneuploidy [2]. Prostate cancer, by contrast, varies widely from indolent to lethal forms. In concordance, organ-confined prostate tumor cells are generally close to diploid while metastatic and therapy/castration-resistant prostate cancers (CRPCs) typically have high aneuploidy. Furthermore, in prostate cancer aneuploidy predicts outcome better than transcriptome signatures alone [3].

Despite its link to aggressiveness, there remains an incomplete understanding of how chromosomal instability contributes to cancer phenotypes. The inherent complexity of chromosomal instability and the reoptimization of the genome via selection for fitness advantages makes assessing the piecewise contributions of DNA copy number alterations (CNAs) challenging. In part due to this complexity, the role of chromosomal instability in tumorigenesis remains a chicken-and-egg-type conundrum, with it being difficult to prove whether chromosomal instability enables aggressive cancer phenotypes or whether aggressive cancer phenotypes result in cells with chromosomal instability [4].

Furthermore, once CNAs are established, is there any advantage to a cancer cell continuing to make chromosomal segregation and other types of DNA replication or maintenance errors? Chromosomal replication errors are likely to allow cancer cells to continue to sample the genomic landscape to provide fitness gains to selection barriers during subsequent tumorigenesis and to acquire resistance in response to therapies [5]. Also, experiments have revealed molecular details of how a cancer cell optimizes the rate of chromosomal instability [6]. Optimization is needed because excessive instability can be detrimental to the cancer cell [6].

Within this complexity it remains possible that optimally titered levels of chromosomal instability increase the fitness of cancer cells through mechanisms that are not related to resultant DNA copy number changes. For example, a cell responding to the stresses of chromosomal instability and the associated DNA damage and repair may be more primed to deal with other stresses. A recent report from Bakhoum, Ngo *et al.* [7] provides a striking example of how non-CNA based aspects of chromosomal instability enable the cancer phenotype of metastasis. Through a series of experiments founded on genetic approaches to alter the rate of chromosomal instability, the authors demonstrate that the activity of and errors associated with chromosomal instability (rate), as opposed to the genomic consequences of instability (state), contribute to the metastatic phenotype of cancer cells.

The investigators developed a system to alter the rate of chromosome missegregation by altering the activities of microtubule depolymerizing proteins involved in chromosome segregation. When these cells were used to generate tumors *in vivo*, the lines with higher chromosomal missegregation demonstrated an increased propensity for metastasis. To delineate the underlying mechanism, RNA-seq-based molecular profiling results pointed to a role for genes related to inflammation in the cells with higher chromosomal instability. These gene programs were reminiscent of those upregulated during viral infection due to viral DNA in the cytoplasm. This led to the hypothesis and experimental confirmation that chromosomal missegregation was resulting in cellular genomic DNA in the cell's cytoplasm. The authors then leveraged existing knowledge and a series of experiments to support a model in which lagging chromosomes from missegregation result in the formation of micronuclei that are prone to burst, thus releasing DNA into the cytoplasm.

The finding of errant cytoplasmic DNA brought into focus the expanding appreciation of the cGMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway. Studied for only 5 years, the cGAS cytosolic DNA-sensing pathway is motivating new understanding and therapeutic approaches across a range of diseases [8]. This includes a wealth of reports on genomic instability or DNA damage

leading to cytoplasmic DNA and cGAS–STING inflammation signaling (reviewed in [9]). The Bakhoum, Ngo *et al*. paper expands this advance in the field by providing evidence that the cytoplasmic DNA from chromosomal instability enhances tumor aggressiveness by increasing metastasis (Figure 1).

Activation of cGAS–STING signaling can result in inflammation signals that lead to growth suppression and senescence [9], but in chromosomally unstable cells the data are consistent with cells having a relatively low or rebalanced level of downstream signaling – predominantly noncanonical NF-κB signaling – that in sum is mild enough to allow proliferation. Importantly, the authors were able to demonstrate that the chromosomal instability-associated increase in metastatic potential was dependent on STING and noncanonical NF-κB signaling.

Ultimately, the authors hypothesize that the pathway from chromosomal segregation errors to increased metastasis represents cancer cells once again coopting a normal physiology cellular function, this time from the myeloid lineage (Box 1). The increased motility of and invasion by these cancer cells may mimic an immune cell that has picked up and sensed a pathogen in its cytoplasm and is then activated to home to the lymphatic system to participate in coordinating the systemic immune response.

This work provides a pioneering example of genomic instability leading to an aggressive cancer phenotype through a mechanism that is independent of

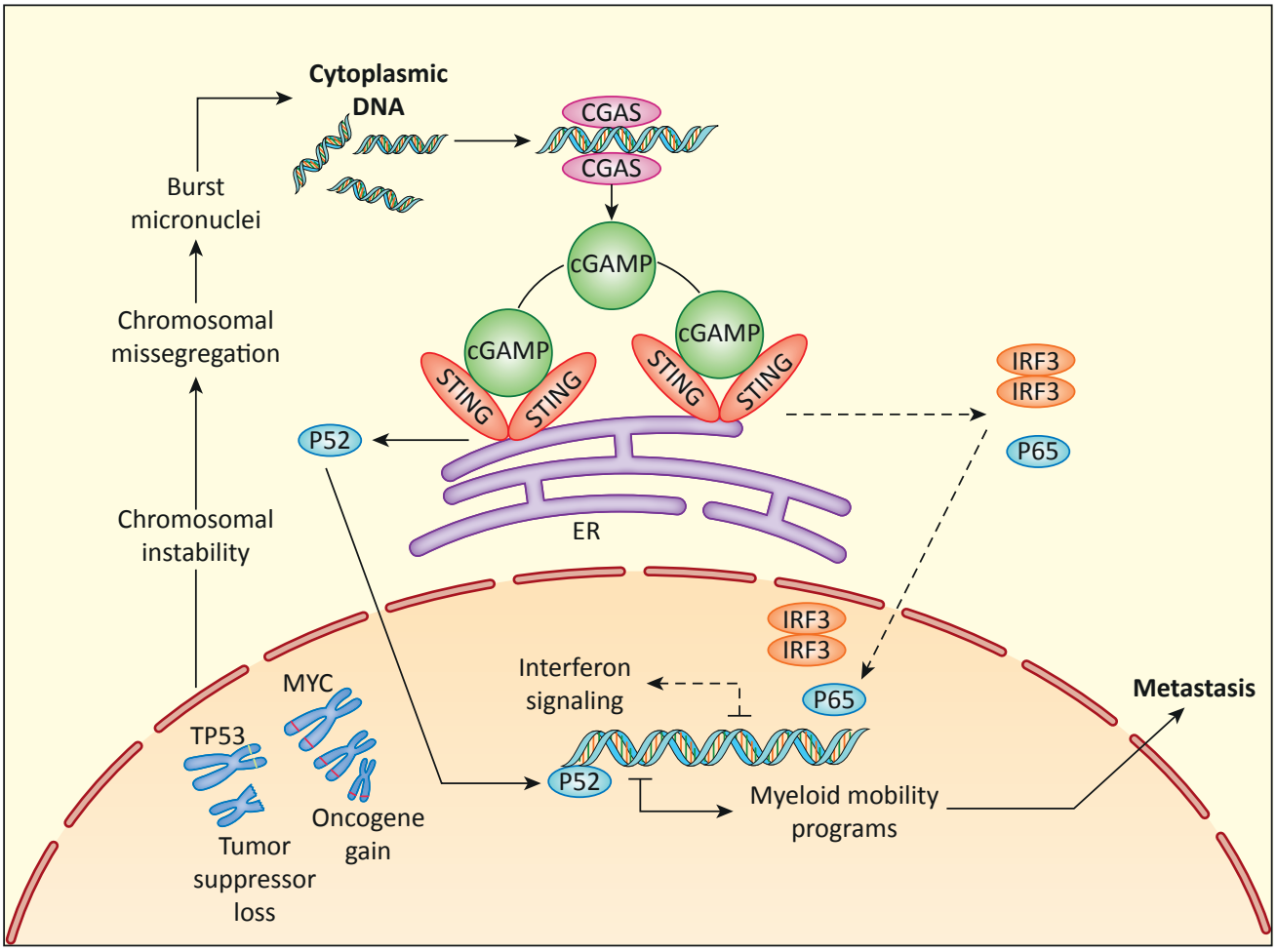

Figure 1. Enabling of the Metastatic Cancer Phenotype by Chromosomal Instability. Burst micronuclei from chromosomal missegregation result in cytoplasmic DNA, activating the cGMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway and preferentially noncanonical NF-κB signaling (P52; unbroken arrows) and inducing mobility programs that contribute to metastasis.

Box 1. Hypotheses for How Chromosomal Instability, Genomic Instability, Aneuploidy, and Copy Number Alterations Lead to Aggressive Cancers

- altered genomic states related to resultant DNA copy number alterations
  - strong oncogene amplifications
  - strong tumor suppressor gene deletions
  - more subtle and complex reoptimization of the genome
- altered phenotypes related to the rate of making genomic errors
  - plasticity to evolve further, in response to stresses and treatments
  - heightened stress state
    - e.g., elevated DNA repair mechanism
    - primed to respond to additional stresses
  - altered interaction with the immune system through, for example, effects on antigen presentation
  - altered signaling leading to metastatic potential
    - triggered by errant cytoplasmic DNA
    - cGAS–STING and noncanonical NF-κB signaling
    - coopting myeloid cell mobility programs

changes in genomic DNA copy number and aneuploidy and yields another potential example of tumor cells coopting programs from normal physiology. Thus, the work reveals a new angle for investigating why chromosomal instability is so frequent in tumors and so deadly.

The aneuploidy state is solidly associated with aggressive cancers and evidence supports that these cancers can retain the chromosomal instability activity that leads to their new genomes. Thus, identifying the vulnerabilities of these cells offers therapeutic opportunities that could have less effect on normal, diploid cells, thus providing a beneficial cancer-to-normal-cell therapeutic index. The work of Bakhoum, Ngo *et al*. provides one of the needed foundations to further rationally pursue these avenues. Such approaches will complement current efforts that, for example, target the aberrant mitosis of cancer cells [10].

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Forum

Mining Public Databases for Precision Oncology

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Millions of dollars have been spent on creating public databases. To date these data reside in isolated 'silos'. Real-world realization of precision oncology, the right drug for the right patient at the right time, may be possible only if the right data come to the right clinic at the right time.

Mining Public Databases: Unearthing the Gold Mines

Precision oncology implies that patients receive personalized therapy based on their molecular alterations. The clinical availability of next-generation sequencing technologies has opened new avenues for therapy. However, with the rapid rise in technologies we have a huge challenge to surmount to be able to use these large datasets for clinical translation. Oncogenes that are overexpressed, mutated, or altered in some other way are being targeted by pharmaceuticals developed specifically for a limited number of tumor types. However, matching patients to novel therapies is often a challenge, even when mutation and gene or protein expression data are available for the patient. The main reason for this is that it is often difficult to estimate the relevance of genomic data for specific genomic alterations that have only a limited literature.

One solution is to potentially integrate and leverage large public cancer databases that may be used to identify whether the tumor of the patient has an alteration that might be exploited by certain therapies. Using an integrated system of several cancers with data from a large number of patients, we might be able to identify oncogenic drivers and drug indications for certain alterations that are very rare in general. Although multiple next-generation sequencing databases have been created in the past years, their use in precision oncology remains limited. The Cancer Genome Atlas (TCGA)[i] [1] is currently the largest collection of