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Chromosomal instability and cancer: not just one CINgle mechanism

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INTRODUCTION TO ANEUPLOIDY

One of the most impressive undertakings in the life of a somatic cell occurs when it divides into two daughter cells. Nearly 3 billion base pairs of nucleotides packed into 23 pairs of chromosomes are duplicated, line up on a mitotic plate, and are pulled away from their identical sisters, tethered to mitotic spindles. This almost always results in a perfectly symmetrical division of the duplicated genome. Anyone who has dealt with fishing line along the shore of a stream knows how daunting it can be to keep a few metres of monofilament from becoming lethally tangled. Yet, the cell does this nearly every time with ineffable ease and, moreover, detects when the process is misbehaving, and halts progress. When a cell undergoes an unbalanced mitosis, this leads to the creation of aneuploid cells. In spite of the number of mitoses that occur each day, one is hard-pressed to find aneuploid cells in normal tissues.

ANEUPLOIDY AND CANCER

Cancer cells have survival advantages over their normal progenitors, but they tolerate some degree of malfunction in mitotic homeostasis, and are frequently aneuploid. Perhaps even more surprising, the more aneuploidy one finds in a colorectal cancer (CRC) the more deadly the tumour.[1] One might anticipate from first principles that a derangement in orderly cell division would be difficult to tolerate, would confer a deficit in fitness, and that mitotic instability would lead to its own demise. However, this is not the case, and understanding this paradox might provide some insight into how cancers develop, and how we might find its Achilles heel.

The conceptual challenge for understanding aneuploidy is not in finding putative causes of chromosomal instability (CIN). The real problem is that there are multiple genetic alterations that can lead to this problem, and most are supported by solid evidence. Some are mechanistically obvious. Mutations or loss of expression of mitotic spindle genes (*Bub1*, *Mad2*), mutations in genes encoding centromeric proteins, amplifications of cell cycle checkpoint genes (*cyclin E*, *Cdc4*) and other genes involved in the mitotic process (*Eg5*, *APC*, *Mcm4*, *Aurora A kinase*, etc.) have been linked to CIN. Other genetic aberrations associated with CIN, such as K-*RAS* mutations or *DNMT* knockouts, must work indirectly,

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and it is less apparent how this works. Furthermore, in aneuploid yeast, the presence of extra genetic material has an antiproliferative effect.[2] The problem is complex.

INCREASED AND DECREASED FITNESS ASSOCIATED WITH CIN

Mathematical modelling has been applied to the issue of cancer to help deal with the two-edged sword of genomic instability. How does a process that intrinsically interferes with an essential cellular process lead to cancer? Nuclear mayhem can suppress cellular growth by imposing a death toll on dividing cells and, at the same time, the generation of genetic diversity offers a chance for evolutionary selection. Each time a novel mechanism for CIN is proposed, there is an unavoidable conflict between changes that reduce cellular fitness and those that provide an opportunity for the evolution to cancer.

This problem is explored in this issue of *Gut* (***see page 249***), where it is reported that downregulation of the *hSgo1* gene is associated with CIN in CRC.[3] *hSgo1*-negative cell lines exhibited aneuploidy, and had prolonged periods of mitotic arrest, aberrant cell divisions, mitotic slippage and mitotic catastrophes. These are all problems that would be expected to reduce cellular fitness. Interestingly, the authors did not find mutations in the *hSgo1* gene, which has several possible interpretations. The *hSgo1* gene may be a specific target of downregulation by some other primary process involved in carcinogenesis, such as an oncomir or an abnormally expressed transcription factor. *hSgo1* could be part of an elaborate signalling cascade, in which this is just one manifestation. However, the authors enhanced their argument that *hSgo1* is mechanistically involved in aneuploidy by downregulating the gene in the near-diploid human colorectal cancer cell line HCT116, and inducing the morphological signatures of CIN.

In spite of the challenges for survival caused by CIN, this process can be advantageous for cancerous growth.[4] Chromosomal rearrangements can lead to the formation of chimeric fusion genes (such as the *Bcr–Abl* in some leukaemias) or deregulation of gene expression. Genomic gains can amplify oncogenes, whereas chromosomal losses can lead to the deletion of tumour suppressor genes. In CRC, there have not been examples of activating oncogenes through chromosomal rearrangements such as are common in leukaemias, and it is assumed that the principal mechanism enhancing cellular fitness is the loss of tumour suppressor genes.

CHANGES IN THE LANDSCAPE DURING THE EVOLUTION OF A TUMOUR

Whether CIN drives cancer progression or inhibits it may depend on the amount of instability in the cellular colony. It has been proposed that moderate degrees of aneuploidy are associated with tumourigenesis, while massive CIN is suppressive.[5] A colony of cells probably requires a certain amount of instability to overcome selection barriers, whereas too much genomic instability may be chaotic and lethal.[6] The optimal amount of genetic instability in the context of CIN has been estimated theoretically,[7] and coincides with experimental measurements of the rate of chromosomal loss.

As cancer progresses, the optimal balance of the competing pressures may change. If we view CIN as the cancer cell's strategy in its struggle for survival, the changing microenvironment may affect the choice of an optimal strategy. What might have been a successful strategy at the beginning of the growth may be detrimental for the colony later on. For example, as a colony goes through a sequence of adaptations, further changes to the genome may undo what has been achieved in terms of the accumulation of necessary mutations, and halt or even reverse tumour progression. This reasoning finds experimental support in that the level of genetic instability in breast cancers initially increases, reaches a peak, and then decreases in later stages.[8] A mathematical analysis suggests that the optimal

strategy for cancer consists of a high level of CIN at the beginning followed by stabilization at later stages.[9]

VIRAL ONCOGENESIS AND CIN: ANOTHER PROPOSAL

The big question that remains to be answered is what initiates CIN. Many of the proposed mechanisms of CIN involve allelic imbalance of the gene implicated in causation,[10] which creates a seemingly circular conundrum about the ultimate provenance of this process. However, it has long been known that oncogenic viruses, such as Epstein–Barr virus, human papilloma virus (HPV), human T cell leukaemia virus 1 and others, typically induce CIN as they induce neoplastic transformation. In most instances, the virus is involved early in transformation and, in some instances, is lost later in the life of the tumour, in a process called “hit and run”. The human polyomavirus JC virus is an oncogenic virus that is present in most CRCs.[11] Interestingly, introduction of this virus into cultured diploid CRC cells induces CIN, but it is quickly lost from the cell genome.[12] One could speculate that a transforming virus could initiate CIN, which would generate diverse populations of cells with rearranged genomes and, eventually, a clone with the most advantageous group of mutations and rearrangements would emerge, and overgrow its ancestors. Once this stage is reached, cells with the virus (and ongoing CIN) might be selected against. There is no direct evidence for this scenario, but whatever accounts for CIN in cancer is certainly complex, and still remains to be completely resolved.

CONCLUSION

Thus, we are left with a complex observation. Most CRCs have CIN, and the cancer cell appears to have made a Faustian bargain in which it tolerates a malevolent process that kills many in the colony, but later leads to a dramatic advantage for growth and survival. This paradox offers an opportunity to exploit the weaknesses imposed by CIN. Moreover, in the case of viral oncogenesis, it is tempting to speculate that preventing exposure to the virus—as has already been shown for HPV and cervical cancer—could have a major impact on public health.

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