A progression puzzle

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Most, if not all, human tumours develop through a succession of genetic and epigenetic changes that confer increasingly neoplastic (cancer-like) characteristics on cells. Indeed, this multistep process has been likened to darwinian evolution within the microcosm of living tissues, in which the units of selection are individual cells. A cell that possesses advantageous characteristics (ones that favour survival and proliferation) is selected to become the progenitor of a successor cell population that eventually dominates the tumour mass. A rare variant that arises among the many successor cells will, in turn, initiate the next round of clonal succession. Between six and ten such clonal successions may be required to generate highly malignant human cancer cells.

According to the prevailing reasoning, this process of tumour progression gives rise initially to cells that have acquired the ability to form primary tumour masses of substantial size. Genetic changes, acquired by cells during the initial phases of tumour progression, that provide some type of proliferative advantage enable the cells carrying these mutant alleles to spawn large descendant populations within the primary tumour mass. Among these advantageous phenotypes are the acquisition of constitutive mitogenic signals, the ability to resist growth-inhibiting signals, to avoid programmed cell death (apoptosis) and to induce blood-vessel growth (angiogenesis). Subsequently, individual cells in these large cell populations acquire yet more mutant alleles that enable them to metastasize to seed new colonies at anatomical sites that may be far removed from the primary tumour mass.

This model of tumour progression carries with it a striking conceptual inconsistency: the genes that specify the final step in tumour progression — metastasis — would not seem to confer increased proliferative benefit at the primary site. That is, there is no reason to think that a metastatic phenotype enables cells to proliferate more effectively within the primary tumour mass, thereby increasing their representation in the overall tumour-cell population. Hence, rare cells in the primary tumour mass that happen to acquire metastatic capability will remain rare. As the success rate of individual cells undertaking metastasis is extraordinarily low, this makes it difficult to imagine how metastasis can ever proceed.

Reasoning like this drives us to consider a quite different mechanistic model: namely, that the tendency to metastasize is largely determined by the identities of mutant alleles that are acquired relatively early during multistep tumorigenesis. It is already apparent that there are several alternative genetic paths that cells can take en route to forming a primary tumour. Thus, a particular phenotype required early in tumorigenesis by an evolving tumour cell can be acquired through the mutation of any one of several alternative growth-controlling genes. We suggest that a subset of the mutant alleles acquired by incipient tumour cells early in tumorigenesis confer not only the selected replicative advantage, but also, later in tumorigenesis, the proclivity to metastasize. This proclivity will become manifest only much later in tumour progression, in the context of yet other mutations that have struck the genomes of descendant cells.

This type of thinking has three implications. First, the tendency of a tumour eventually to metastasize is already preordained by the spectrum of mutations that progenitor cells acquire relatively early in tumorigenesis; that is, some cancers start out 'on the wrong foot'. Second, genes and genetic changes specifically and exclusively involved in orchestrating the process of metastasis do not exist. Instead, the genes for metastasis are largely those that cancer biologists have been studying intensively for a generation: the oncogenes and tumour-suppressor genes. Third, because important components of the genotype of metastasis are already implanted in cells relatively early in tumorigenesis, even relatively small primary tumour cell populations may already have the ability to dispatch metastatic pioneers to distant sites in the body.

Several independent lines of evidence seem to support these ideas. In some small, well-localized primary human breast cancers, individual carcinoma cells are clearly detectable in the bone marrow. Furthermore, DNA-microarray analysis reveals that the gene-expression pattern of metastatic tumour cells is often strikingly similar to that of the cells confined to the primary tumour mass from which they were derived, implying that the dominant cell population in the primary tumour mass is phenotypically and possibly genotypically (almost) identical to the cells in the metastases.

Equally relevant are other studies in which the gene-expression profiles of the dominant populations of breast-cancer cells within a primary tumour mass have been used to predict, with 90% accuracy, whether the tumour will remain localized or whether the patient will experience metastases and disease relapse. Here, once again, the metastatic behaviour of these cancer cells seems to be determined relatively early in tumorigenesis. (The implications for the usefulness of early clinical detection of breast cancer are unsettling.) Finally, several well-studied oncogenes, including *ras* and *myc*, the proliferative powers of which are well documented, can function in certain mouse models of tumorigenesis to enable cancer cells to metastasize.

These ideas have implications for our eventual understanding of the genetic and biochemical bases of metastasis. Some researchers have searched far and wide in the genomes of advanced, highly aggressive tumour cells for the genes responsible for inducing metastatic capability. Perhaps the culprits have been staring us in the face for a long time — the mutant genes that are known to confer darwinian selective advantages early on may be the same genes that, further down the line, empower metastasis. ■

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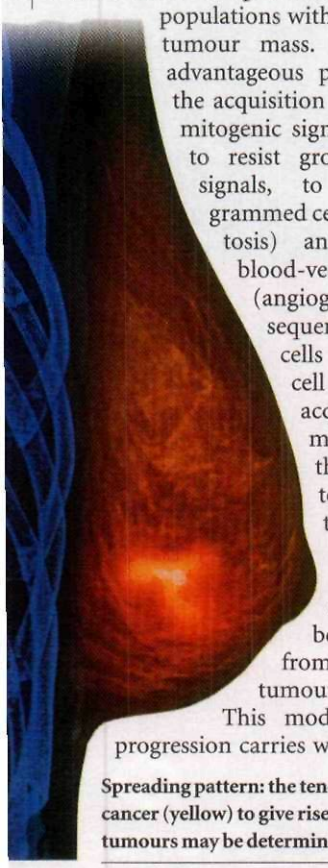

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Spreading pattern: the tendency of a breast cancer (yellow) to give rise to secondary tumours may be determined early in its life.

Metastasis genes

The prevailing model of tumour progression carries with it a striking conceptual inconsistency.

FURTHER READING
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