Mutation, selection and metastasis

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Mutation and selection are important concepts in cancer biology. One well-known example is hereditary colon cancer. Patients with mutations in the DNA mismatch repair genes MLH1 or MSH2 develop colon cancer because of an increased rate of mutations. And tumors in patients with familial polyposis coli have a growth advantage because of a mutation in the tumor suppressor gene APC. Mutations and selection also help to explain the process of metastasis, the formation of secondary tumor foci at distant sites in the body. Understanding metastasis is important, because it is often this spread of the tumor that makes a previously localized cancer an incurable disease.

In 1977 a landmark paper in Science by Isaiah Fidler and Margaret Kripke (Fidler 1977) described a mouse model of lung metastasis using the syngeneic B16 mouse melanoma cell line. This melanoma cell line originated spontaneously in a C57BL/6 mouse in 1954 and is known to metastasize to the lung. They produced several clones of the B16 cells, each clone originating from a single cell and therefore genetically identical. Cells from these clones were then injected into the tail vein of C57BL/6 mice. The number of lung metastases in these mice varied dramatically between clones and was also different from the parental cell line. Fidler and Kripke concluded that a subpopulation of highly metastatic cells preexists in the parent population and is selected during the metastatic process.

In 1994 I started to work on a research project that tried to identify molecules responsible for the selection process in this B16 lung metastasis model. This was before microarrays and the sequencing of the mouse genome, and we used a technique called differential display to identify differentially expressed genes in two variant B16 cell lines that created low and high numbers of lung metastases. We identified a novel gene that turned out to be a transcriptional regulator (Shioda 1996) but probably is not that critical for the metastatic process.

In 2009 we have learned a lot more about the metastatic process, but we still know much more about genes involved in tumor cell proliferation, apoptosis, etc. than the genes critical for the metastatic process. And we still have not come up with a clever way to specifically treat that malignant subpopulation of tumor cells that will later produce metastatic disease.

References

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