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How tumour cell identity is established?

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The enormous increase in our understanding of the biology of tumour cells in the last four decades did not have a proportional impact in our capacity of controlling the development of the disease. We do not know how to stop a pre-cancer cell developing into a cancer yet, mainly due to the fact that the early events that determine the fate and lineage commitment of cancerinitiated cells remain largely unknown. The consequences of this lack of knowledge about the initiation of cancer is well illustrated by women carrying a BRCA1 or BRCA2 mutation who choose to undergo prophylactic bilateral total mastectomy for reducing the risk of breast cancer. Clearly, the most critical point of cancer development is the transition from a normal target cell to a cancer cell. However, the mechanisms establishing tumour cellular identity, which play an essential role in allowing cancers to arise, have received little attention. From this perspective, at least three are the key questions for understanding the cancer initiation process. What are the leads instructing a target cell carrying an oncogene to switch from a normal to a cancerous identity fate? What is the molecular nature of the cancer cell switch? When, during normal cell development, does this switch take place? This last question is critical because, to find the players of the normal/cancer switch mechanism, one has to know when/where to look. The mechanisms initiating cancer must integrate developmental cues (different between cancer types) with the universal requirements for the creation of a tumour mass. Although it is generally believed that the decision to become a cancer cell must be made once the normal cell has adopted a cell identity fate compromise in the majority of cancers, recent data suggest that this timing of cancer initiation is not a universal feature shared by many oncogenes. Actually, several recent papers have found that oncogenes contribute to cancer development not only by inducing proliferation, but mainly via developmental reprogramming of the epigenome of the tumour target cell. Indeed, using stemcell restricted transgenic expression systems, it has been shown that the expression of the oncogene in the reprogramming-prone stem/progenitor cells is capable of programming the development of all the cells that compose the tumour mass. Overall, these results not only highlight a previously unrecognized role for oncogenes in cancer, but also provide evidence for a previously unmodeled process for tumourigenesis in which the programming of the malignant tumour cell identity has already taken place at the stem cell stage,thus uncovering a new role for oncogenes in the timing of cancer initiation. In this context, mutations that activate oncogenes would have a driving role in the reprogramming process, but may act as passenger mutations (or have a secondary, different role) thereafter. These findings open new questions. First, is the decision to initiate cancer made at one time point during the differentiation process, or are a series of consecutive decisions required to switch to a cancer-cell fate? and, are all these decisions cell-autonomous? What is the nature of the (epi)genetic pathway downstream from the cancer-specific initiation gene defect(s)? If we learn how to stop cancer development by manipulating the cancer-initiation programme then, someday, understanding the initiation of cancer will also be useful for cancer therapy. It is our task not only to address these and other questions, but to determine their relative importance for each stage and type of cancer.

Furthermore, the biology of cancer cell commitment is relevant not only to understand stem cell properties of cancers and in developing cancer treatment strategies but also to regenerative medicine, as it is clearly imperative that regenerative medicine gains full control over reprogrammed cell fates. This issue of Seminars in Cancer Biology presents a series of chapters illustrating current knowledge, unusual perspectives and novel interpretations on how reprogrammed tumour cell fates influence the carcinogenic sequence. The reader can easily verify thatthe views expressed in this issue of Seminars in Cancer Biology, including those ofthe Guest-Editor, are by no means homogeneous. In fact,they offer a representative cross section of different research orientations currently present in the field. I feel that a better definition of the specific subjects related to the “tumour stem cell reprogramming” would help in integrating these different views and in coordinating research efforts towards the common of understanding how tumour cell identity is established. The coming years will show whether this optimism is well founded, or whether the immense complexity of this disease will continue to confound our best endeavours to tackle cancer.