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Editorial

Cancer stem cells: differentiation block or developmental back-tracking?

It is a well known curiosity that only a minority of cells within a tumour are typically responsible for tumour growth and development. Over the last few years it has become possible to isolate and characterise these tumour-maintaining cells, first from haematological malignancies [1] and recently also from a number of solid tumours. The fact that many of the isolated tumour-maintaining cells share surface markers with somatic stem cells and have capacities of both self-renewal and differentiation have popularly rendered them the name “cancer stem cells”. Processes for isolation of such cells are complex and to some extent also controversial as described by several authors in this issue of *Seminars in Cancer Biology*, e.g. Park et al. and Fan et al. As further illustrated by the article by Loda, the identification of such cells also depends on understanding normal cell differentiation and the hierarchal relationships between tissue cells.

More than a century ago, it was suggested that cancer cells originate from embryonic cell rests [2, 3]. The concept of cancer stem cells reintroduces this connection between carcinogenesis and ontogenesis, suggesting that different histological tumour subtypes reflect different stages along a normal differentiation lineage. One example of such a model is the relationship between subtypes of thyroid carcinoma and normal thyroid development proposed here by Takano. The stem cell theory of cancer also harmonises well with the classical model of multi-step carcinogenesis [4]. Somatic stem cells have a longer life span than their differentiated progeny and could thus, over many years, accumulate somatic mutations and undergo step-wise selection and clonal expansion as outlined by Bapat in this issue. The accumulation of mutations in normal precursor/progenitor cells implies transmission of these mutations to their mature descendants. As further described by Höglund,

this scenario could partly explain the field cancerization effect reported particularly in bladder cancer and head and neck carcinomas. The concept of cancer stem cells finally underscores the importance of targeting the correct cells for cancer therapy. Eliminating only the higher differentiated, rapidly dividing cells by chemo- or radiotherapy is not likely to result in successful long-term remission if less differentiated and slower proliferating cells remain to repopulate the tumour. On the other hand, the potential of stem cells to differentiate into more mature cells opens up attractive venues for treatment by agents that specifically induce differentiation. For some tumours, such as neuroblastoma, several differentiating agents have already been identified and thoroughly studied *in vitro* as summarised in the articles by Ross and Spengler, and by Pählman et al. in this issue.

Although it is an attractive hypothesis that most tumours are derived from normal somatic stem cells, there are some valid arguments against it. For example, the idea that mutational multi-step carcinogenesis is restricted to long-lived, somatic stem cells is difficult to reconcile with the panorama of sometimes very complex genetic alterations observed in infant tumours. Furthermore, many of the childhood tumours which are known to derive from immature embryonal cells, such as nephroblastomas and teratomas, typically exhibit a bi- or triphasic histopathological pattern sometimes with concurrent epithelial, mesenchymal and blastemal elements. Such an overtly diverse histology is rarely seen in adult tumours from which “cancer stem cells” have been isolated such as breast cancer and glioma. It cannot yet be excluded that more or less terminally differentiated cells could acquire stem cell-like features (dedifferentiate) through acquisition of genetic and/or epigenetic changes. An alternative, and highly interesting mechanism described by Houghton et al. in this issue is the transdifferentiation of bone marrow stem cells to epithelial neoplastic cells after migrating to inflammatory lesions.

From the vast amount of data accumulated on cytogenetic and molecular genetic alterations in tumours, it has been concluded that specific somatic mutations at the DNA or chromosome levels are only capable of promoting tumourigenesis if they occur at a certain physiological state, *i.e.* in a permissive context of cellular differentiation. This could explain why most of the well known gene fusions in leukaemias and soft tissue tumours are highly specific for certain histopathological subtypes, as only a limited number of cells would offer the right context for the radical alterations in transcription and growth signalling brought about by these genetic alterations. Bearing the cancer stem cell theory in mind, it is tempting to suggest that the number of genetic alterations necessary for transformation is dependent on the degree of differentiation of the host cell. In such a threshold model of carcinogenesis, normal stem cells inherently share some features with neoplastic cells including the capabilities of self-renewal, migration and invasion. Thus, a limited number of genetic alterations, leading to differentiation block, might be sufficient for neoplastic transformation. For example, in nephroblastomas originating from immature blastemal cells through inactivating *WT1* mutations, none or few gross chromosomal abnormalities are typically observed [5]. A similar pattern of very few gross chromosomal alterations is seen in many leukaemias, where gene fusions have convincingly been shown to result in differentiation block at various levels of the haematopoietic hierarchy [3]. In contrast, the transformation of more mature cells could require a sequential accumulation of discrete genetic or epigenetic alterations, each insufficient for neoplastic transformation on its own. The end-result in this process would be the complex pattern of oncogene activation and tumour suppressor gene deletion observed in many epithelial tumours. Histologically, such a slow process would be reflected by the gradual transition from dysplasia to carcinoma in situ to invasive carcinoma. However, gene fusions may occur also in tumours with a gradual accumulation of complex genetic lesions, as exemplified by the *TMPRSS2/ETS* fusion gene present in prostate cancers,

typically having highly complex karyotypes [6]. It is beyond doubt that additional data will be needed to resolve whether differentiation block through single radical genetic alterations, dedifferentiation through an accumulation of several genetic hits, or a combination of these two is the main pathway for transformation in common cancers. This issue of *Seminars in Cancer Biology* is an attempt to provide an overview of the currently most burning issues regarding tumour cell differentiation and cancer stem cells.

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