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News and Commentary

Tell me about your stemness. I'll give your cancer risk!

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An essential and almost existential question regarding cancer development has been a matter of intense debate in the past year. Environmental insults such as ultraviolet radiation, smoking or others were recently proposed to account for only a small portion of cancer risk, and we were offered an alternative 'bad luck' hypothesis.[1] Bad luck was more likely to occur in highly replicative and long-lived cells that could maintain and propagate a given mutation. This question is of utmost importance and at the centre of preventive efforts against cancer.

In a recent publication, Zhu *et al.* addressed this issue through genetic labelling and tracking of cells with either high or low stem cell potential.[2] Indeed lineage tracing is one of the main tools in determining cell fate or the cell of origin of cancer.[3,4] It has been used in a variety of cancer types to specifically label or induce an oncogenic event in a precise candidate cell population to be followed. Zhu *et al.* decided to target a CD133+ population that admittedly would play different roles in different organs. From the lack of tissue or stem cell specificity of this marker emerges the actual originality of this study. Indeed, in a first series of experiments they characterized how important the CD133+ population was in contributing to the homeostasis and development of the tissue of interest. This was performed through lineage tracing and labelling of CD133+ cells in the neonatal or adult period and following their fate over time to find whether they've formed part or most of the tissue. From this first experiment the authors concluded that CD133+ cells were acting as stem cells in some tissues but as differentiated cells without stem cell properties or 'generative capacity' in others. This apparent heterogeneity in function among CD133+ cells was then used to interrogate the potential of CD133+ cells to generate tumours by genetically introducing a wide range of potential activated oncogenes or inactive tumour suppressors.

The authors made two essential observations after careful multivariate analyses by taking into account important parameters such as the generative capacity, but also the proportion of CD133+ cells in a given organ at induction and the proliferative potential of CD133+ cells in homeostasis: tumours from CD133+ cells could mostly be found in tissues where they had generative potential. This was interpreted as follows: tissue stem cells and not differentiated cells are more susceptible to develop tumours if they harbour oncogenic mutations. Of course the initiating mutations in part explained the organ specificity of the tumours that developed. But it was not as strongly linked to tumour formation as the generative capacity. The second observation was the difference in tumour incidence in neonates versus adults. In general terms for the same mutations and the same generative capacity of mutated cells, neonates were more resistant to tumour development and displayed a lower tumour incidence. This second observation remains to be further explored.

Finally, the authors, suspicious of the relevance of the homeostatic conditions where all these experiments were performed, nicely demonstrated that, if an injury changes the generative capacity of the cells harbouring mutations, it strongly affects their tumour-forming potential.

Overall, these findings bring the authors to propose a model where a cell-intrinsic factor, defined as the generative capacity in a tissue, can greatly influence tumour formation. These cell-intrinsic factors are influenced by external factors inducing an injury response that can modify the generative repair of the cells. This argues in favour of the model proposed by Tomasetti and Vogelstein,[1] arguing that most cancers are related to the life-long replicative activity of a given tissue's stem cells. However, these recent data add additional complexity to this model by introducing the notion of tissue repair, which can affect this replicative activity.

As in all good studies, the work by Zhu *et al.* also triggers new questions.[2] At the technical level, it would have been important to evaluate the tumour-forming potential of stem cells and non-stem cells from the same tissues, whereas the choice of CD133, although elegant, allows comparing tissues where CD133+ cells are stem cells to other tissues where CD133+ cells are not stem cells. Conceptually, it is also becoming essential to test this hypothesis in tissues with more complex homeostasis or regeneration. For example, epidermal cancers of the skin are the most frequent human malignancy. The epidermis is however a highly compartmentalized tissue, with each compartment having its own stem cells, some being quiescent and some actively cycling.[5] So far, lineage-tracing studies trying to determine the cell of origin have mainly focused on homeostatic conditions.[6] It would be important to test the principles identified in this work to these

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more complex stem cell environments such as the skin and the breast.[7] Most importantly, this work also prompts us to review our understanding of the role of carcinogens. Most carcinogens, beyond inducing DNA mutations, also trigger a proliferative response that amplifies the risk of cancer development. Deciphering these two effects will prove important and may lead to effective primary prevention strategies as well as pharmacological or nutritional interventions.

Conflict of Interest

The authors declare no conflict of interest.

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