B-Raf and C-Raf proteins turn mouse white

October 5 2012

Mice with black fur that turns white? Specialist cancer researchers from Inserm, CNRS, the Institut Curie and the Université Paris-Sud have taken steps to better understand the development of skin cells responsible for pigmentation (known as melanocytes). By genetically manipulating mice with black fur, the researchers identified two key players: B-Raf and C-Raf proteins.

These proteins are required for melanocyte stem cell self-maintenance and, as such, correct pigmentation throughout the mice's life span. Without these two proteins, the mice's fur turns white. Their research is published in the review *Cell Reports* and paves the way for serious possibilities in terms of stopping the formation of melanomas, tumours that originate from melanocyte cells.

Melanocytes are cells in the organism used for skin, fur and hair pigment. This pigmentation function provides protection from the sun and lends organisms their colour. Malfunctions in these cells may lead to skin cancer known as melanoma. Melanomas are highly aggressive cancers that become very difficult to treat as they develop and metastases occur.

A few years ago, researchers discovered that, in humans, the B-Raf gene (coding gene for protein of the same name) is mutated in more than 50% of melanoma. Spectacular progress has been made in recent years in the treatment of this cancer, thanks to the development of pharmacological inhibitors that target an enzyme: the B-Raf kinase. However, despite this treatment, cancer returns in several patients, indicating that not all

cancerous cells have been eliminated. This led researchers to believe that B-Raf is not the only element driving the cancer process.

In this new research, scientists have tried to understand how melanocytes function normally, to then understand their specific role in cancer. To this end B-Raf protein expression, then, in turn, C-Raf protein expression, were removed from mice with black fur (ideal to clearly see any changes in pigmentation).

No changes in pigmentation were observed for mice that only had their B-Raf or C-Raf expression removed by researchers from the line of cells producing melanocytes. Mice that had both coding genes for B-Raf and C-Raf removed simultaneously had a normal colour at birth. However, they progressively lost their pigmentation as they grew. They turned grey from black, before becoming increasingly white.

For Alain Eychène, the research team leader, "these observations represent a fault in melanocyte renewal. Since the colour black is present at birth, the pigment cells clearly exist. However, the progressive whitening of the fur, once B-Raf and C-Raf have been removed from the cell line, proves that both these proteins are required for melanocyte renewal".

As is the case for all cells, melanocytes originate from stem cells; the latter are responsible for renewal during moulting. This research shows that it is specifically this population of stem cells alone that disappears progressively in mutant mice. For Alain Eychène, "This is the first in vivo demonstration of the role of RAF proteins in the self-renewal of stem cells".

The fact that B-Raf and C-Raf are both involved in controlling and renewing pigment stem cells represents another step towards understanding and treating melanoma. By blocking these proteins (using

inhibitors) in patients undergoing treatment, it is possible that in time researchers will succeed in eliminating all cancerous stem cells, i.e. the likely cause behind cases of cancer reoccurrence.

More information: *Cell Reports*, dx.doi.org/10.1016/j.celrep.2012.08.020

Provided by Institut National de la Sante et de la Recherche Medicale