Pierre Hainaut, PhD

Pierre Hainaut, PhD, conducts research that spans basic molecular biology and molecular epidemiological studies related to the tumor suppressor gene p53, with an emphasis on its role in a variety of human cancers. His lab consistently generates important contributions on the molecular epidemiology and pathology of esophageal, breast, liver, and lung cancers.

The IARC center, in Lyon, France, is part of the World Health Organization. In January, Hainaut will take over the post of director at the International Center for Research and Training, Hospital AC Camargo, Sao Paulo, Brazil.

1

What role does p53 signaling play in normal cells?

p53 coordinates a number of antiproliferative programs in response to multiple forms of stress, including low oxygen, depletion of ribonucleotides, hyperactivation of growth signaling, and many forms of DNA damage. Among the antiproliferative programs induced by p53 are cell cycle arrest, cell differentiation, senescence, autophagy, increased DNA repair, and apoptosis. The type of program activated depends upon cell type, status (eg, stem, progenitor, or differentiated cell), and the type of stress. One interesting theory proposes that the *TP53* gene may have evolved as an adaptation of cells to enable them to handle oxidative damage caused by mitochondria.

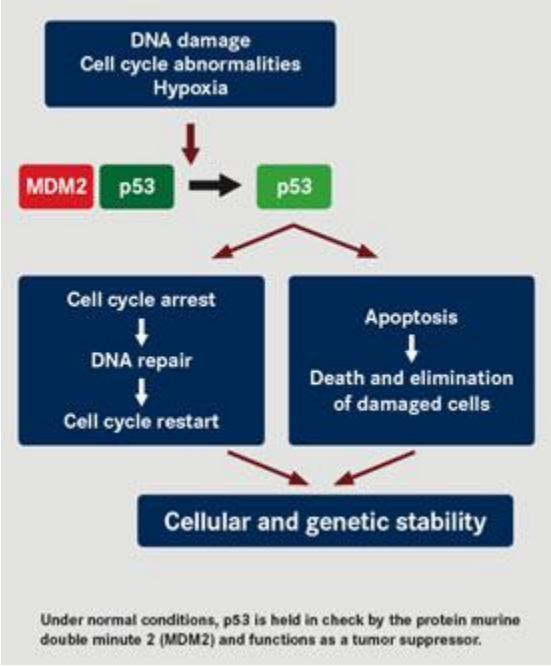
2

How important is it in the development of cancer?

It could be said that cancer cannot develop if p53 function and activity is intact and, in fact, all cancers may have altered p53 function. Many mechanisms of p53 inactivation have been identified. For example, inactivating mutations occur in around 50% of cancers, and loss of p53 alleles is detectable in 30% to 60%. Functional inactivation through interaction with inhibitory viral or cellular proteins is common in some cancers, and may account for another 5% to10% overall.

Other mechanisms include p53 promoter repression, competition with p53 homologues or with "inactive" p53 isoforms, and suppression of p53 expression by microRNA. The effects of these alterations may be very tumor-specific. In breast cancer, loss of p53 function is perhaps the most significant prognostic marker to date (with worse prognosis than ER/PR-, HER2-, or triple-negative). In lung cancer, *TP53* mutation has no prognostic effect, but it may alter tumor response to adjuvant therapy, thus exerting a form of gain-of-function.

Subjects who inherit a mutant *TP53* allele suffer from a familial syndrome of predisposition to multiple cancers: Li-Fraumeni syndrome (childhood solid tumors, early breast cancer, sarcomas). Long considered a rare disease, there is now evidence that it might be a much more common form of cancer predisposition.



Under normal conditions, p53 is held in check by the protein murine double minute 2 (MDM2) and functions as a tumor suppressor.

3

Are there any p53-targeted anticancer agents currently available or under development?

In fact, many conventional treatments (radiotherapy or chemotherapy) are at least partially p53-dependent. With respect to "targeted therapies," several approaches are in clinical trials: small drugs activating wild-type p53, small drugs "resuscitating" mutant p53, *TP53*-based gene therapy using viral vectors, and immunotherapy-targeting cells expressing p53 antigenic determinants. None are currently considered superior to standard treatments but there is significant hope that they may improve the effects of conventional therapy.

4

What has been the key discovery relating to p53 signaling in cancer in recent years?

The field is a goldmine for discoveries in molecular biology. In my view, the biggest recent advance is the identification of p53 as a key factor controlling oxidative metabolism (decreasing glycolysis, increasing oxidative phosphorylation in the mitochondria). Thus, loss of p53 function in cancer cells is one of the bases of the famous Warburg effect, the metabolic adaptation that allows cancer cells to thrive on glucose with no or little oxygen usage. There is now good evidence that p53 operates as a link between telomere shortening and changes in oxidative metabolism to control cellular senescence.

5

What is the future of research with regard to p53 signaling in helping our understanding of cancer or developing targeted treatments?

Firstly, monitoring p53 (mutations, loss of alleles, molecular signatures of expression of target genes) is already proving very important for prognosis and prediction (depending upon tumor type), and this type of application will become standard practice in the coming years. Secondly, although p53 might prove difficult to "repair" using small drugs, pathways upstream and downstream offer a huge number of potential targets. As these pathways have multiple entry and exit routes, combination therapy will be needed. This will take time but may well herald the next therapeutic revolution.