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Cancer escape

by Professor Alain Puisieux

Alain Puisieux is the Manager of the Lyon Cancer Research Centre (CRCL), a research structure wholly dedicated to cancerology.

"Much of the CRCL's work is dedicated to fundamental research: understanding the mechanisms that lead a normal cell to become cancerous; how this transformation, known as malignant transformation, occurs; determining the consequences, and thus how cancerous diseases develop.
The cells of our organism are constantly subjected to different stresses stemming from our environment (for example, ultraviolet rays from the sun that damage our skin cells), and to stresses that come from our own metabolism. As we have evolved our cells have developed highly efficient systems that combat these stresses and prevent the occurrence of mutations which could trigger alterations in the genome of each of our cells, leading to abnormal proliferation and the onset of cancer.
How do these systems function? They are complex, rather like a car speed regulator. Each cell has its own speed regulator. When it divides too often, it can either cause the car, i.e. the cell, to stop definitively, or amount to a death sentence for the driver, meaning that the cell will commit suicide. The system is very coercive but it obviously protects the entire organism against this abnormal proliferation.
To become cancerous, this cell must bypass these protection systems: the death sentence for the cell or the definitive arrest of proliferation.
What interests the teams of the CRCL is to understand how these cancerous cells succeed in escaping these protection systems.

There is a protein called P53 that plays an absolutely crucial role in the smooth functioning of these protection systems. For a cancer to develop, it is necessary to prevent the activity of P53 at one moment or another in the steps of its progression.
The cell in the process of transformation uses different means to inhibit P53.
The guardian P53 can be subjected to direct attack to alter it and prevent its function, by example, through a mutation.
The CRCL's teams have been able to demonstrate the reactivation of processes normally confined to the embryo during the progression of many cancers. These are embryonic processes.
Two very important processes occur during the development of the embryo:

1. A large number of cell divisions, since we obviously start with a very small number of cells before the formation of an embryo, then, later that of the adult organism;
2. These cells must be highly mobile so that they can form the different tissues of the embryo's organs.

We have highlighted an aberrant and abnormal reactivation of these embryonic processes during the development of cancer. On the one hand, this aberrant reactivation provides the capacities for abnormal proliferation by deactivating the safeguard and protection processes, while, on the other,

it permits pre-cancerous and cancerous cells to acquire abnormal mobility capable of triggering metastatic dissemination and the formation of another tumor (metastasis) at another location in the organism.

The ultimate aim of our teams is to use our better understanding to propose new tools at the service of patients with cancer.
There are different ways of doing this, but it is first necessary to understand what happens. From the moment we understand the different elements underlying cancer escape, we can try to target them by conceptualizing molecules capable of inhibiting these systems that prevent cell protection processes from functioning in order to restore them.

The CRCL's teams have developed different mechanisms that permit cancer cells to escape protection systems.
The progress achieved by these works has led us to reach different steps of the process leading to the production of new drugs. Some of these works have reached relatively early stages of understanding and identifying the best possible target for restoring our protection.
In other works we have reached more advanced stages of developing an anti-cancer molecule and some are at preclinical level, meaning that we use different models to test the molecules identified previously.
Lastly, one of these projects is at an even more advanced stage, since we now have molecules that function well in different preclinical models that can be tested, so we have reached the point where this new drug will have to be tested on patients with cancer.