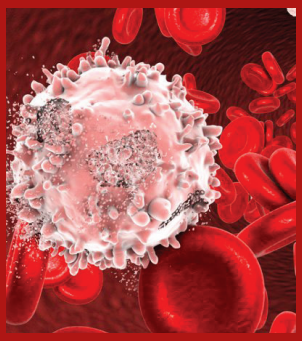
RAS ONCOLOGY & THERAPY

# Short Communication: The Basic Science of Oncology



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## Introduction

The title of this breviary corresponds to Professor Tannock´s Manual of Oncology. He is one of the pioneers in Cancer Science, its translation into the clinics and a key main defender of Randomized Trials in Oncology.

Thalassemia molecular dissection in 1949, made Molecular Medicine appears in scene (Pauling), and oncology basic basis were waiting for the DNA structure and function discovery (Watson, Crick and Franklin). This last was an enormous Science breakthrough that helped us to understand the pathogeny of several diseases including Cancer as the more relevant one.

Today Genomics and its sisters´ Transcriptomics and Proteomics are clue in Cancer Medicine. We know the gene maps of the tumors which are relevant in Precision-Medicine- Oncology.

Many protein-cellular pathways are abnormally expressed in tumors (mainly kinases), but DNA is somewhat the backbone of the process, and is "very sick" in Cancer presenting with many genetic and epigenetic abnormalities.

Probably, a few genes are the "brained ones" who manage the cancer process (drivers). And I said probably, for some new discovered are putative ones and finally they don´t drive tumors and are only the bystander passengers.

I consider two essential DNA derivative molecules as the subdirectors of the Cancer process development. They are the growth factors and the transcription factors, this last one called the "master regulators" (Califano).

The first ones are mutations of their counterparts present in the normal cells. They are proteins that make cells growth and divide, probably giving cancer a quantitative characteristic and not a qualitative one. The more growth factors quantity the more dividing cells.

Biochemically speaking, they can mutate in structure: dimerize obtaining similar proteins subunits and achieve a more complex structure. They can also make many similar copies of them (hyperexpression). They derived sometimes from oncogenes and others from simply DNA mutations.

At the Clinical Setting, many blocker drugs have been and are in development (e.g. HER 2 blocked by Trastuzumab and Pertuzumab; EGFR tackled by Cetuximab, etc.).

On the other hand, we have the transcription factors, that are proteins focus of intensive research today. They also derived from mutant DNA and intervene in many cellular processes (e.g. E2F).

The drug development transcription factors-directed is ongoing mainly in early development phases, but some anti-transcription factors compounds are gaining later development phases.

These are molecules difficult to block, but when possible, outstanding clinical results are obtained (Ruxolitinib).

Transcription Factors are the proteins that run the operation room of the Cancer Cell and they are rarely mutated. Blocking one of them could arrest aberrant cellular activity resulting from many mutations at once.

Ruxolitinib, an anticancer blood drug, inhibit an important master regulator, and hold promise for the future treatment of solid tumors.

The cell cytoplasm gives us many proteins that traffic within it and sometimes in the cell nucleus and are globally named protein kinases. They mainly phosphorylate the amino acid tyrosine and secondarily serine. This "switch on" the other cellular oncogenic related pathways, finally concluding with apoptosis inhibition, cell growth maintenance and cancer phenotype differentiation.

The tyrosine kinases and other inhibitors are today more than fifty in the clinical setting and many before-difficult-to-treat cancers are currently tackled such kidney, Lung, melanoma mainly with drugs such as Sunitinib, Pazopanib, Sorafenib, Axitinib, Vemurafenib.

Considering first, Cancer as a one-cell-disease in origin, we can follow its development as a tissue disease one.

Its phenotype is essential for it can comport different tumor populations growing, namely clones and subclones. The more different clones the more aggressive disease. Clones cooperate within them; they also can present competition for substrates and some amounts of oxygen. This is the real Cancer dynamics, being like this, Cancer "a disease of cell populations".

At this organization level of the tumor or its distant metastatic niches, we consider some types of tumors resistant to the therapies due to the presence of different clones.

We have "more peripheric ally located", the tumor microenvironment (TME), this stroma tissue constantly interacting with the epithelia. The pharmacological control of the TME is going to become a reality in the forthcoming years.

In this location, we have different immune cell populations that regulate how tumors work in this sense.

Well is known about proteins that "cover" the tumor cells, hiding them from the T lymphocytes surveillance and making them, somewhat invisible to these cells.

Immune Medicine has developed smart molecules called check-point inhibitors (CPI) (Pembrolizumab) who can deblock those "hidden cells" for the immune system. Now lymphocytes can "eat tumors".

Impressive clinical results with cures in advanced disease settings, has been obtained with CPI (melanoma and renal tumors).

The medical spectrum of tumors to be treated by them is many.

All the before-mentioned, only wants to summarize the role of some cancer proteins in the different cell-tumoral tissue compartments.

The future will show us a bigger number of them, but we must take into account the lesson learned from the master regulators: one of them is blocked, and the result is the arrest of aberrant cellular activity at many mutations at once.

Like this, to target "the protein" is easier than to target the complex diseased Cancer DNA.