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Opinion

Cancer, with the Mirror on the Past

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Cancer Science has evolved in the last 2 decades in a geometric manner. It seems that in 2000, the term Molecular Medicine began to really impact in the basic knowledge, translational and clinical of neoplasms as in Medicine in general.

According to the before mentioned, oncogenes are better known of what their duties are in normal and tumoral cells, P53 acquired the term of "the guardian of the genome" and seemed to repair dangerous DNA damages to avoid cells malignant transformation, mechanisms of tumor resistance were better "dissected" (still an ongoing task for biologists) and all the organizational levels of DNA arriving to the nucleosomes of chromatin that derived in the epigenetic era. This is of course a very brief summary of what really happened.

Molecular biology is so vast today, that new proteins oncogene-derived appeared in the scenario, and these proteins are touched – blocked by specific partial agonists or antagonists' drugs. The new "era" of tumoral biomarkers" highlights here the process. The different names of these new proteins are sometimes difficult to remember as is their basic pathway within the cell and their cascade of interaction with other proteins (e.g., Janus transcription factors, Sox 2, Nectin 4, etc.).

Structure is a quite recent area of study, with new techniques such a cryo - electron microscopy that allows us to see the anatomy of the molecules and this will be a big niche for the new onco-medicines development. More than 20 years ago while working at the Gustave-Roussy, my mentor Dr Jean-Pierre Armand and me were with great enthusiasm, when we collaborated with Dr Fragu in a new imaging technique: ion- microscopy. We saw for e.g., how a novel anthracycline gets into the cell nucleus, the "lieu" where it interacts with DNA.

All the afore mentioned is parallel to the big efforts that the pharmaceutical industry makes in investments for new drugs development in Cancer medicine.

In the clinical setting, Small molecules are knocking Cancer cells (only we have to overcome some resistance mechanisms not well understood yet); Large molecules of the biotechnology such as monoclonal antibodies that work checking-inhibiting the "immobile" T-lymphocytes (checkpoint inhibitors that can also present with the non-attended tumor-resistance mechanisms that have to be solved); genetically modified T-lymphocytes that recognize cancer cells and destroy them with all type of cytokines (CAR-T therapy; just to mention that the literature describes a patient with refractory leukemia and disease-free since 10 years, so cured); gene therapy coming to age with new vector-genes and vaccines for the cancer-installed process, and other vaccines, working nowadays as cancer – preventing medicines.

I didn´t speak yet about the mirror on the past (my professor of Internal Medicine said always that pathologists "drive their cars looking the rear-view mirror", they diagnose illnesses after clinicians crash their minds thinking what the disease was). So, here we are going to be as pathologists.

The past shows the Skipper-Shabel model for leukemias kinetics; the Goldie-Coldman Model that was the birth of mathematical oncology, with equations it explains tumor growth and resistance; kinetic resistance related to dose response (adjuvant therapy of breast cancer, Bonadonna); the Gompertzian tumor growth model, a critical model for understanding mainly solid tumors growth; tumor cell kinetics with the different cell types of proliferative compartments with cells cycling's and tumor resistance in cases.

Finally tumor resistance with its different types : amplification of the copies of druggable enzymes (DHFR and methotrexate), apparent resistant due to the bad GI absorption of Melphalan, resistance due to low tumor cell membranes drugs penetration, this phenomenon was reversed wisely by the use of high chemotherapy doses, such as in Osteosarcoma, tumor model that can be cured in pretreated stage-settings by high-doses of methotrexate, and, finally the existence of outer-inner efflux pumps such as the "famous Glycoprotein - p 170". This intrinsic membrane protein makes that when a cytostatic enters the cell, the pump by an ATP-mediated mechanism, effluxes the drug outside the cell. Several drugs were tested "*in vitro*" for its reversal-inhibition, with no clinical success: the best in - class for this reversal was high verapamil doses but of course with the real danger of ventricular arrythmias (torsade's des pointes). No matter to use it clinically!

Where is briefly the nexus of the modern basic Oncology and the older one?

Clones with tumor cell kinetics and cell cycle progressions (old) as compared to tumor mutational burden (TMB) (new), an emerging and now stablished biomarker for immunotherapy success. The more TMB, the best response of the tumors to the checkpoint inhibitors. This TMB is related to the neoantigens that comports the cells and that their origin is parallel and constant with the different mutations of DNA during the tumorigenesis.

Tumor cell resistance by the amplification of the enzyme copies (old), can be compared to one of the mechanisms of HER2 resistance in breast cancer (neuralgic point of blockade that can comport the amplification of the protein in various copies, avoiding so, the "addiction" of effective medicines such as Trastuzumab) (new).

Clonal and sub clonal evolution, a cell population phenomenon, for e.g., in melanoma, explains its chemo-resistance but also some resistance aspects related to immunology. Clonal populations are very heterogeneous, and, in their evolution, this is more visible. Cancer heterogeneity is the clue marker of any type of tumor resistance. Clones are complex, they compete between them, but sometimes they can cooperate for the tumor growth.

Gompertzian growth have hidden traits angiogenesis – related. A tumor of 1 gr, has one million cells and 10 cc. This is an avascular state for the tumors. The nutrients and oxygen enter the cells by imbibition (as in the first stages of the embryonic period of the fetus). After that tumor volume, the neoplasm needs vessels to growth and the angiogenesis process begins.

Finally, the take-home message is of clinical relevance: all we cured with chemo, all what we treat with the novel anticancer agents and that sometimes the disease-free status homologates to cures, makes the "chemical mix combinations" of both a must for the better results of patients' outcomes. And we are doing this!

Surely, the more complex modalities, such as gene therapy and more complex vaccines will also enter at some time point in the same "combination era".

The mirror was clean and let us draw some interesting epoch's comparisons of kinetics, drugs and tumor resistance mechanisms, this last still is an elusive foe.