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A Few of Modern Therapeutic Concepts in Oncology

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Even when cancer has many different phenotypic traits, each tumor cell "sick" genome drives all the malignant processes in its different evolutionary phases. In this way, cancer is mainly a targeted-genetic disease, perhaps the more complex one in nature, with the only teleonomic purpose of achieving its evolutive progression, a fate that invariably leads to patient death if not well treated.

Today, much is what we know in Cancer Science about: oncogenes, tumor suppressor genes, growth factors, transcription factors, kinase pathways, adhesion molecules, dynamics of the tumor microenvironment, etc. All of these elements may be "hacked" by the tumor to achieve selfsufficiency in growth signals, dedifferentiation, chromatin remodeling, anti-growth signal insensitivity, apoptosis evasion, limitless replicative potential, stemness heterogeneity, microenvironmental alterations, angiogenesis, immune evasion and metastases, among other malignant capabilities.

All the above-mentioned may be potential therapeutic onco-targets and many kinds of "bullets" have been designed to tackle the different oncogenic processes. Unfortunately, the "malignant foe" of tumor drug resistance makes it not impossible, but very difficult, to continue much time with the first therapeutic best-option for the patient. It must be noticed that second therapy lines of chemotherapy, applied mainly after a first tumor relapse, imply drugs that, in general and even used in combination, are less effective than the first line ones.

Nevertheless, it must also be said that some malignant tumors have the possibility to be cured with the administration of second line drugs, such as germinal cell tumors, choriocarcinoma, pediatric tumors, Ewing's sarcoma, blood cancers, and some cases of breast and ovarian cancer. With the rise of new therapeutic approaches coming so quickly into the clinical setting, as new emerging small molecules, immune-checkpoint inhibitors (large molecules-type), novel designed vaccines, gene therapies, CAR-T cell treatments and immunotherapies, some patients may be cured even after becoming refractory after frontlines of Chemo. This therapeutic concept works well in some leukemias and lymphomas and is in the way to prove its worth in solid tumors.

It is known that cancer cells and tissues are very complex and heterogeneous. This heterogeneity implies different gene mutations and cell kinetics with a great impact in clinics. Fast cell kinetics is related to better therapeutic responses as is the case in some testicular cancers, leukemias and lymphomas. There are also some "microanatomic" therapeutical targets not yet completely understood but very promissory, like mitochondria and its peculiar metabolic pathways (implying oncometabolites such as ketoglutarate); some glycolysis enzymes as potential targets, autophagy enhancement; aberrant Golgi apparatus glycosylation (important in the cell membrane maintenance); exosomes and other extracellular vesicles, that transport mainly micro-RNAs; ribosome integrity; etc. The future will make us learn about how to properly and selectively arrive pharmacodynamically to them.

Checkpoint inhibitors immunotherapy is an exceptional novel treatment in a huge expansion phase, as is the development of small molecules that are directed to abnormal genes and their derived proteins (proteomics). If we could block the main underlying mechanism of tumor progression, we could say we are in good shape to cope with the disease outcome, as we could cure it or at least make it a chronic disease prolonging the stable disease status (SDS) of the patient.

After the DNA becomes "ill", its altered translation message derives a great deal in protein kinases (PTKs) that phosphorylate other substrates that are also proteins, activating different cascades of cell signaling pathways. Interactions protein-protein are of vital importance (e.g., KRAS-RAF), conducting many different processes that make the cell grow and proceed in its malignant progression. This operative system can be compared to Tokyo's subway, where there are so many stations with the possibility to take a train (protein) to make the right combination. But if one or two of these trains that are central or neuralgic (drivers) suddenly stop, many others are affected. This can be homologated to the blockade of a mutant driver gene in a cell signaling pathway that leads to tumor cell growth.

Still blocking only one target is not enough, as there are probably many different malignant cell populations with other mutated drivers that finally lead to a pharmacodynamic resistance outcome. In Greek mythology, the Hydra of Lerma was an ancient aquatic monster in the form of a polycephalus serpent (whose number of heads ranges from three, five, seven or even more according to the source). The Hydra had the virtue of regenerating two heads for each one that was lost or amputated. Hercules oversaw the phenomenon (one head of the hydra he cut, other two heads appeared instead), teaching us in what sense tumorigenesis and tumor resistance may work.

Associated with the above-mentioned is the clonal expansion: as more tumor clones and subclones develop, higher is the probability of tumor drug resistance due to tumor heterogeneity. This opens research to the fascinating area of tumor cell dynamics. Here, aspects as to why different clones may compete or cooperate between each other are still partially unmet scientific questions that need to be answered. For the moment, we can speak about the "mood of the clone" and probably the growth factor involved.

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Inside the model that considers cancer as a disease of clonal evolution, an initially benign tumor accumulates mutations that confer malignant phenotypes of increasing aggressiveness. Clonal cell lineages may coexist and compete within a tumor, a phenomenon called clonal interference. Examples of this kind are tumor-associated mutations such as Myc gain-in-function, P53 point mutations or loss-of-function, loss of ribosomal genes, aneuploidy and RAS gain-in-function, just to mention some of the known ones. On the other hand, two different clones that evolved complementary traits may cooperate to render in higher tumor malignancy, even if each one by itself is not able to do so. In this sense the game theory, coming from computer science, may perhaps be useful in the study of cell clone fate.

In brief, even when advances in current cancer therapeutics are enormous, as they are able to tackle many different cellular targets and processes, future medicine must try to take advantage of growing knowledge about cell clone cooperation / competition in a tumor-specific way. In this sense, clonecompetition-based therapies are emerging as new potential avenues that can achieve the knock-out of the different underlying mechanisms of tumorigenesis and drug resistance. We are on this.