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Opinion

Molecules and Clonality in Cancer

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Cancer is without doubt, one of the most important Internal Medicine diseases.

The advances in the clinical setting treatment of this disease are huge, with the advantage, that many Basic Science disciplines, such as Molecular Biology, Biochemistry and Pharmacology positively impact in the understanding of this process.

We discover permanently new basic Cancer cell issues, such as modifications of normal biochemical pathways that the cell uses for its metabolism and growth, but when Cancer is present, the alterations are many and may not be all countable yet.

A "brain cell driver", KRAS is an old known oncogene, that promotes the abnormal cell division and tumor growth. Its basic biochemistry is very well known today and showed us where topologically KRAS can be druggable.

Two emerging drugs are with worth now in the clinical setting and successfully treating some Lung adenocarcinomas and colorectal cancer patients. Anyway, it´s noteworthy that being KRAS the second most prevalent molecular signature in lung cancer, it is still somewhat drug orphan and for the moment it demonstrates little drug addict ability in contrast to other less prevalent molecular markers (ALK, ROS1 for e.g.) which have many ongoing and potential drug-blockers.

The above-mentioned shows us a complex KRAS kinetics druggability.

The other molecular anatomy part of a cancer cell is the low-down functions or absence of the principal tumor suppressor gene, P53, the genome guardian, another essential process regulator. The drug developments here are complex for, enhancing the activity of something that is nearly absent comports a big challenge. At least we have the chance to target it when partially mutated.

Both KRAS and P53 are extremely old, be of note that P53 born 800 million years ago, so it was originated in our ancestors the dinosaurs who presented with Cancer also.

In the middle of these 2 molecules, are the Transcription Factors (TF), proteins that finally perform the task that oncogenes asked for, they finally enter the cell nucleus, bind to DNA, and stimulate the cell proliferation and other cancer-related programs, such as the absence of apoptosis. The TF are considered the master's regulators, they run the operator cell room, working after receiving an oncogene signal.

It is noteworthy, that the TF are rarely mutated and are less in number as compared with oncogenes. Many current – in -development drugs that block their activity are trying to prove their clinical worth. In relation to the before- mentioned, at the time are needed the development of different drugs to target the different oncogenes and their pathways, in the case of the TF´s, a less amount of compounds are required : TF´s are really bottle necks of oncogenes, with one TF being druggable and posteriorly several pathways are tackled.

The reflection on Cancer has not to be only that of a molecular disease-one, but also of a clonal cell one.

Clonality and tumor cell growth are the stems of the final paradigmatic process in Cancer: the metastases.

Beginning the seventies, we reached the mentors such as Goldie, Skipper, Norton (for mentioning some of them) explaining us the

importance of tumor cell populations kinetics, cell growth, response to Chemo and tumor resistance.

It was early clear, that blood cancer populations were different from solid tumor ones. In the first ones, we can cite leukemias which comport a high cell proliferation phase of nearly "the all", all cells are cell cycle cycling. They also present with a peculiar pattern of extremely high initial tumor chemosensitivity. Preclinical leukemia models have elegantly explained this issue (Leukemia 1210) and the success in the treatment of some acute leukemias and Lymphomas, clearly are the clinical counterpart of those preclinical basic models.

In solid tumors, many populations are not constantly cell cycling (in S phase dividing and growing) and a mathematical model named Gompertzian curve (described by Gompertz) describes this.

Initially there´s a growing exponential phase, and the curve is linear like in bacteria cultures, the clones have an exponential growth. Here, Chemo sensitivity is high. Then, the tumor growths more slowly and if the tumor can growth for a long enough period, a plateau phase will be reached, with a doubling time so long that further increases in volume will not be discernible. Some tumors at this plateau reach 1 kg and all the phenomena of Chemo- resistance is switched on, leading to an ominous patient outcome.

It is interesting, that some solid tumors at this final growth phase, grow not by cell duplications, but by the absence of tumor cell loss.

Of course, that all the afore mentioned, covers different patterns in the different tumor models. For e.g. a tumor can grow slower in its primary tumor site than in its lung metastases.

Bizarre is the fact that, in the beginning of the new millennium, the impact of molecular Medicine appeared and made us for a little time, "orphan" on the concept of clonality.

Today is known that there´s also clonal expansion in normal tissue populations of different organs, and that is related to aging processes and inflammatory-immune events. Many things from these last processes will impact with more knowledge in the subject.

If we don´t consider the current new anti-Cancer avenues, the last mentioned paragraph regarding expansion of normal clonality probably explains why is difficult to treat successfully some different malignant clones with Chemo (the more antitumor toxicity the more peripheral tissues toxicity and the more probability of the emergence of resistant clones).

As this, there´s no Cancer – specific process: the dividing tumoral metastatic cells, its intra and extravasation and posterior seeding in the connective tissue of different organs, makes us remember, normal tissue clonality expansion behavior (e.g. bone marrow and peripheral blood cells migrations).

The nearly cure of "the all" will come in the next 20 years, when also apart from the novel drug developments and a Cancer cell "still more dissected", our minds will definitively have "new concepts" of what really is considered as "patient cure" in this elusive disease.