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Editorial Open Access

Stromal Biomarkers as Putative Targets in Cancer Chemotherapy

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Editorial

Surgery and radiation therapy were dominant treatment in cancer until middle 1970s, except hematological malignancies where, since the first use of aminopterin to treat childhood leukemia almost 60 years ago, chemotherapy for leukemias has come a long way. For solid tumors only terminally patients were considered at that time for some courses of chemotherapy. Obviously, the results were highly questionable putting in a gloom this otherwise heroic medical approach. However, chemotherapy gain ground and succeed to develop new concepts in cancer therapy based on their cell and tissue toxic effects. The drugs available at that time were further tested for their specificity for tumor types and grouped together in so called standard regimens, cyclical sequences scheduled for a definite number of applications at some time intervals and proficient of achieving even long time remission in certain cancer localizations. The randomized clinical trials that today sustain modern oncology were relatively rare and prompted stiff opposition from physicians reluctant to assign patients randomly to competing treatments.

Nevertheless, over time, the clinical trials have demonstrated their significant impact on cancer treatment progression and redefined the clinician's day by day practice.

Early concepts on cancer treatment focused on tumor burden and tumor cells.

The development of repetitive cycle protocols considered to administer multiple hits on multiple biochemical targets of tumor cell, mainly cellular metabolism and DNA synthesis. The hope and proud of each practitioner was to achieve a complete response, otherwise not equivalent with cure of the disease. On the other hand anticancer drugs have not been designed for a particular function or molecular target, but they have been found in assays based on inhibition of cell proliferation and clonogenicity.

Although cytotoxic drugs found to be efficacious in the treatment of cancer fit in a rather limited list of chemical compounds, it is important to acknowledge that innovation in empirically discovering operational combinations have fundamentally changed the practice of medicine. For example, testicular cancer is for some time a curable disease not because of the approval of new drugs but rather because of optimization of a regimen of already existing therapeutics.

The incremental benefit of adjuvant or neo-adjuvant chemotherapy, albeit becoming important treatment option for most prevalent cancers, reaches a plateau over time without a visible approach for further development.

New weapons were added to the cancer therapeutic armory: molecularly targeted agents.

Novel treatments rationally design is based on exploiting the specific molecules implicated in signaling pathways of tumor growth. Translational drug research focused on alteration of a specific bio-pathologic function comprises, first, target identification, second, demonstration that candidate drugs inhibit this target, and third, documentation that cancer growth is affected as a consequence of target inhibition.

By acting more selectively against cancer cells than healthy cells, these molecular targeted agents offer the potential for improved efficacy and less toxicity, as compared with conventional chemotherapy. Conversely, this sharp orientation on the expression of a molecular tumor marker makes them exclusively effective in tumor types dependent on the pathways to be inhibited.

It is worth to mention that few of such molecular treatments succeed to shape dramatic advanced results with the use of bcr-abl and c-kit-targeting agents on chronic granulocytic leukemia and gastrointestinal stromal tumors, epidermal growth factor receptor (EGFR) inhibitors in a small subset of non-small-cell lung cancer, and monoclonal antibodies targeting HER2 protein in approximately 30% of patients with breast cancer, but also ovarian, gastric, and aggressive forms of uterine cancer, such as uterine serous endometrial carcinoma [1].

The list of targeted cancer therapies already approved and developed to interfere with a variety of cellular processes is rather long: signal transduction inhibitors, regulation of gene expression, apoptosis inductors, anti-angiogenesis agents, monoclonal antibodies that deliver toxic molecules to cancer cells specifically, and cancer vaccines. However, all these pharmaceutical classes, that are by now commercially offered, provide only, even if significantly, small gains in symptom control and survival, whereas some have consistently failed in the clinical testing stage [2].

The research that is being done to promote these agents, only accommodating to tumor types dependent on the inhibition of a particular pathway, was as well influenced by new scientific paradigms that persuade the questions asked and the methods used in clinical research. It is no more adequately persisting to rely on randomized controlled trials and meta-analyses when looking for necessary interpretation and patient guidance.

The practitioner is faced to therapy responses and disease evolution that are much more heterogeneous than expected and combining evidences and effect size delivered by meta-analyses does not help him to much. Surrogate outcome do not reflect at all times clinical consequences and may not have been sufficiently validated [3].

Usually by designing the treatment plan based on tumor-derived predictive and prognostic factors and patient status, the clinician seek to personalize the protocol although he basically do not have yet the tools to conduct the therapy with such a superior category of

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precision. Alternatively, large trials promote drug testing in patient population that also largely differs genetically from individuals who will be exposed to a certain pharmaceutical product. Adding to this the fact that majority of solid tumors are the result of numerous genetic and epigenetic alterations it turn clear that inhibiting a single cellular pathway may not result in significant therapeutic activity. On the other hand it would be not certain that mixture of agents that target a sequence of different pathways will amplify the therapeutic effect, except treatment-related toxicities.

As a final point, is not to forget that even the most successful cancer treatment is evenly limited by the development of acquired drug resistance.

Moreover, to make things worse a subset of patient experiences early progression during systemic anticancer therapy [4].

Not considering the steps forward in cancer management, the real reason we don't have curative therapies yet is primarily because of a lack of complete understanding of disease biology. We should realize that cancer is a complex structure and therefore to reduce the treatment to malignant cell compartment only will be nonproductive or even resulting in proliferation enhancement. With great probability cancer stromal component has no less than the same importance as tumor parenchyma. Tumor cells develop surrounded by a joint structure referred as stroma - fibroblasts, vasculature, immune cells and interstitial extracellular matrix (ECM). Stroma creates functionally the microenvironment which is responsible for tissue homeostasis. As such provides tumor-suppressive signals as long as the tissue architecture is effectively controlled. This is an otherwise essential function present in development. Considering that indolent or occult tumors occur much more commonly than is usually recognized we can admit that initiation of tumors is genetically unavoidable, but their progression to malignancy should be controllable by mechanisms not understood so far. Nevertheless, once homeostatic function is lacking balance the altered microenvironment can itself become a potent tumor promoter [5].

It was already demonstrated in a series of elegant studies that embryonic microenvironmental signals, ECM and tissue architecture, could lead to tumor cell reversion [6,7].

Recently was showed that the mouse mammary gland can reprogram human embryonal carcinoma cells into cells that have phenotypes of differentiated mammary epithelial cell phenotypes [8].

If microenvironment can provide crucial signaling to maintain tissue architecture, inhibit cell growth and suppress or revert the malignant phenotype the opposite must also be true: incorrect signals from the microenvironment should lead to destabilization of tissue homeostasis and initiation and promotion of normal cells to malignancy.

Immune cells in the microenvironment build up a stromal functional network, the tissue control unit, which consists of monocyte-derived cells, vascular pericytes, T lymphocytes, precursors and mature dendritic cells, immunoglobulins [9].

Tumors are heterogeneous population and growth and invasion involve largely the combined kinetic interactions of these cells with the extracellular matrix (ECM) and stromal cells that confines tumor microenvironment. The overall phenotype of a developing neoplasm is not determined only by the evolutionary competition among malignant clones but, to a large extent, by the tumor stromal tissue. Tumor cells and stromal cells undergo a stepwise co-evolution and phenotype transition successfully generating particular molecular markers eventually with diagnostic and therapeutic aptitudes. Inflammatory and immune stromal cell component play important cooperating roles by generating a microenvironment that could be supportive for growth and metastasis and/or development of anti-tumor response. This double way behavior is consistent with the concept that the immune system plays an important role in counteracting foreign antigens and also in regulating tissue homeostasis. As an important constituent of tissue control unit it is possible that its performance is connected more to the enhancement of tumor organ formation than rejection, suitable with what might be the basic function of immune cell compartment in development, generation of organ memory, tissue regeneration and homeostasis.

The outcome of this rationale would be that the immune system along with and in concert with fibroblasts, endothelial cells, and interstitial ECM correspond to an incredible rich source of biomarkers and therapeutic targets. In this context, not to be overlooked the stromal cell complex implication in epithelial-mesenchymal transition (EMT), or mesenchymal-epithelial transition (MET), as well as pre-metastatic niche induction.

Worth to mention the consequence of anticancer treatment on tumor-stroma interactions, including so called environment-mediated drug resistance [10].

This *de novo* resistance implies stromal protection from inductors of apoptosis like chemotherapy, radiotherapy or molecular targeted agents. Although the precise resistance mechanism remains obscure for the present, the recent demonstration that stromal gene expression signatures were stronger predictors of clinical responses stimulates the translational research of microenvironment molecular markers [11].

Among others attributes of the tumor stroma, one that might generate a major concern in tumor biology is the network support offered to cancer stem-like cells. It is highly possible that tumor microenvironment may influence the plasticity and trans-conversion of tumor stem and non-stem cells [12].

Stem-like tumor cells contribute also to resistance to treatment and some mechanism have been proposed including activated Wnt/β-catenin and Notch signaling pathways which might be considered for novel targeted therapies [13].

At present among molecular targeted agents predominates kinase inhibitors for suppressing tumor growth pathways- like Bcr-abl, c-Kit, B-raf – on the one hand, and stromal signaling - as vascular-endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR) and colony-stimulating factor-1 receptor, on the other hand.

In the end by acquiring more knowledge concerning the supportive network afforded by tumor stroma to cancer development, scientists will be able to design new treatment instruments and to establish the microenvironment contribution to clinical outcome.

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