DICTIONARY OF THE NORMAL CELLS

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In the last decade, huge efforts have been made in research to change something in the field of diagnosis, prognosis, and therapeutic strategy in a broad spectrum of human diseases. This is maybe more evident in the continuous battle against cancer, in which obviously, current therapeutic methods are far to be enough, particularly in advanced-stage disease. Excepting for some anatomic locations, the incidence of human cancer continues to increase in most of the organs. Fortunately, the overall survival slowly increases, based on the new acquisitions in the field of early detection and therapy. As some malignant tumors, like breast and prostate cancer seem to have some important therapeutic tools, in others, like malignant melanoma and squamous cell carcinoma of the head and neck, results are disappointing and disease-free survival is short. Based on these data, an analysis of the current concepts in defining therapeutic targets becomes compulsory. We frequently look for the answer(s) checking only for malignant cells, and just in the last years on the precursors and microenvironment. What about normal cells in these pathological conditions?

A new section has been introduced with this issue by the Editors of Research and Clinical Medicine: Dictionary of Normal Cells. We really believe that documents associated with this section will be extremely helpful not only for a better understanding of the biology of tissue and organs in normal and pathological conditions, but also to identify new fields in basic and clinical research. Moreover, the knowledge on the structure, functions, and behavior of normal cells is a prerequisite of identification of new targets for therapy, particularly in neoplastic disease. Targeted therapy is already defined and applied in many human diseases, and this approach is strictly based on the identification of specific molecules in the cell membrane, cytoplasm, and/or nucleus of normal cells and their pathologic counterparts. In addition, a lot of efforts are made nowadays to implement personalized therapy, which will move therapeutic procedures from the cohort of patients, as the current standard, to an individual based on the molecular profile of the disease and peculiarities of the patient.

What could find the reader in this section? In each issue the reader will find out one to three short reviews about a given cell. Each cell will be characterized in terms of basic structure, functions, molecular profile, and clinical significance. This will be not a classical presentations of the long series of human normal cells. Reviews will include new acquisitions in the field, controversies, and unknown data. I really believe that such a modality of writing will be helpful to remember some data we learned many years ago, and now stored and hidden somewhere in our brain. At the same time, these data will open and promote new ideas for basic and clinic-pathological research.

In the last decade, production of humanized monoclonal antibodies became usual, and their application in different human diseases is a subject of many clinical trials, or even they already belong to current therapeutic protocols. It is important and maybe enough to mention bevacizumab, a powerful antiangiogenic drug, and trastuzumab, largely used in therapeutic strategy of advanced-stage breast cancer. All the improvements of current treatments were the consequence of extensive studies on normal cells, which were characterized by gene analysis, expression of specific protein, and finally, synthesis of specific inhibitors. In such a way it was possible to discriminate between blood and lymphatic endothelial cells, and the most specific marker of lymphatics, podoplanin, has been used not only as a diagnostic and predictive marker, but also to produce a specific antibody against lymphatic endothelial cells that in experimental model inhibits metastasis. Looking to the list of potential targets identified only in the last years in normal cells, we can expect a broad spectrum of biologic drugs with significantly increased efficiency in human diseases with high rate of mortality.

The story of personalized therapy begun more than two decades ago, when it has been shown the beneficial role of hormone therapy in breast cancer. Few years later, Food and Drug Administration approves trastuzumab for patients with advanced-staged breast

cancer, and then to all patients which overexpress the human receptor for epidermal growth factor 2, known as HER2. The treatment with inhibitors of hormone receptors and HER2 do not exclude conventional procedures, like chemotherapy or/and radiotherapy. Based on the response to combined therapy, patients were stratified as responsive or non-responsive, but globally, a significant overall survival was noticed after long-term follow-up. The potential response to hormone and trastuzumab therapy is well predicted by immunohistochemistry alone. On the other hand, gene analysis has shown that many human tumors show different molecular profile, associated with different behavior and response to therapy. This observation was the precursor for personalized therapy, starting from the molecular classification of human malignant tumors, like in breast cancer, colorectal carcinoma, or renal cell carcinoma. One example is related to the molecular profile of primary versus lymph node metastasis in breast cancer. If the primary breast cancer is hormone receptors positive and HER2 negative, it does not mean that the lymph node metastasis is identical. We found that more that 12% of the cases fall in this category, and therefore, adjuvant therapy should be adapted to the individual case (Raica et al, 2014). Unfortunately, such a procedure is not yet included in clinical oncology therapeutic protocols.

Another reason to look more carefully to the so-called personalized therapy is the story of bevacizumab. In 1980s, Ferrara et al identified, characterized and purified vascular endothelial growth factor (VEGF) that has been demonstrated to be the most potent angiogenic growth factor (Ferrara and Henzel, 1989; Ferrara, 2011). An antibody against VEGF was synthesized, and its humanized version was later on the base for bevacizumab, approved by Food and Drug Administration in 2004 as Avastin for patients with metastatic colorectal carcinoma. In experimental models in vivo, the team of Ferrara demonstrated a strong suppression of tumor vasculature and inhibition of tumor growth using anti-VEGF (Kim et al, 1993). Unfortunately again, in clinical trials with patients with metastatic colorectal cancer only the clinical criteria were used to select patients. Additional molecular criteria, like VEGF expression or VEGF receptor status in both primary tumor and/or metastasis were not included, and as expected, the overall survival increases only with some months in comparison with the control group (Hurwitz et al, 2014). Again, a cohort approach study and not personalized. However, it should be pointed out that bevacizumab was the first humanized antibody approved by FDA for use in patients with cancer (colorectal, kidney, breast, lung, brain /glioblastoma/). The original enthusiasm has been limited by the follow-up of patients, and it has been shown that spectacular results obtained in the lab do not overlap clinical findings and expectations. An example is related to the approval of bevacizumab in advanced-stage breast cancer and its quick withdrawn in 2011, based on inconclusive results. Somehow expected, as advanced-stage breast cancer rarely expresses VEGF at protein level (Cimpean et al, 2008).

Based on these data, we decided to introduce the section Dictionary of Normal Cells, as a permanent chapter of the journal. We will bring together old and new data, known and unknown fact, controversies and hypothesis, and basic science versus clinical application. We really hope that the reader will like and find it useful, and as far as we know, it is the only journal in the world with this section.

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