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PRIORITIES IN CANCER RESEARCH: RETROSPECTIVE AND PROSPECTIVE ASPECTS

The landmark events in the formation and development of the society inspire us to analyze the achievements and unravel the problems hampering the civilizational progress in the spheres of human activities aimed at the realization of the creative essence of humankind. Irrespective of the differences inherent in science and public policy as separate domains of human activities, the present-day challenges such as COVID pandemic require joint efforts of the power and the science in the interests of the people. Nevertheless, even in the extraordinary situation with COVID pandemic we should continue our efforts exploring the fundamentals of cancer growth. Moreover, the possible remote consequences of COVID pandemic should not be overlooked.

Cancer research has been and remains one of the complicated and most important as well socially significant research areas in medicine and biology. The advancement in fundamental knowledge aimed at the development of the novel technologies of risk assessment, screening, diagnosis, treatment and prevention could be realized only through the joint efforts and consolidation of the scientific community and public policy priorities aimed at the achievement of the human health as the top value. Nowadays, it is appropriate moment to take stock of the scientific achievements and to look ahead to the future trends in the development within the context of the past decade. Moreover, this triggered us to analyze retrospective and prospective priorities in exploring problems of cancer in our country.

Within recent years, Experimental Oncology and Onkologiya journals presented the columns prepared by the Editor-in-Chief wherein the key priorities of the developments in the fundamental and clinical oncology in postgenomic era have been analyzed.

The genomic technologies allowed us to unravel the novel fundamental molecular-genetic and epigenetic processes underlying the impairments in the signal cascade network that are important steps in the origin of the new features in the biology of cancer cell. The novel technologies designed for the diagnostic purposes and targeted therapies have been promising. The identification of the cancer stem cell has been in the limelight. The advancements in nanotechnologies seemed to bring us closer to solving the problems of cancer. The disclosed impairments in the system of antitumor immunity and suggesting a new principle for immune therapy (the discovery of cancer therapy by inhibition of negative immune regulation by James P. Allison and Tasuku Honjo honored by Nobel Prize in 2018) also claimed to approach the victory in combating cancer.

Over more than ten years, our editorial policy has delineated several priorities in the development of cancer research that seem to be advantageous in responding the current challenges:

- Whether the fantastic projects in the domain of nanomaterials could be helpful in “putting cancer into irons”?
- Whether the expectation of oncologists in achieving the balance between chemotherapy and biotherapy has been justified?
- Whether harmonization of molecular-genetic and epigenetic studies would be advantageous in understanding the nature of cancer and optimizing diagnosis and therapy?
- Whether our knowledge and our options in correcting tumor hypoxia and factors of metabolic and stromal microenvironment of tumor have been exhausted?
- What kind of character is cancer stem cell? What is its role in the origin of cancer and how to combat cancer backing on its features?
- Metastasis, what is it, the end-product or the form in which the biological process is engendered?
- Inflammation and cancer — the factor of cancer containment or the risk factor?

Over the past years on our editorials, we tried to focus on the priority directions that became advantageous for obtaining new data and formulating specific algorithms that as we hope will represent new steps towards solving problems of cancer.

In fact, the results of the modern research change drastically the “canonical” conceptualizations pertaining to the causes, mechanisms and peculiar features of the malignancies. The changes in molecular-genetic, epigenetic and metabolic patterns based on the numerous mutations in cancer cells contribute to the rapid formation of the individual phenotype of the components of tumor microenvironment. The impairment in the balance of growth and suppressor factors involved in the formation of the signaling network results in generation of cell diversity. Such heterogeneity provides for the survival, dissemination, colonization and metastasizing due to the underlying multiple variability.

In the search for oncosynergetic processes involved in the formation of tumor-host interactions, the team of RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology studies the key elements underlying the impaired pro- and anti-

oxidant system, the shifts in metabolome and signaling networks as well as molecular-genetic defects making up the entity of the malignant cell. The deepened understanding of the epigenetic mechanisms controlling the function of the genes continues to be relevant as the high-potential tool for controlling numerous multilevel processes in cancer cell.

The analysis of the role of epigenetic processes in modeling the landscape of gene expression not only changed drastically our perception of the basic mechanisms of carcinogenesis but also opened the unique options for understanding the interactions between the malignantly transformed cells and surrounding stromal components. Being potentially reversible, the epigenetic processes could be able to switch on/off the silent genes, in particular via CpG islets. The changes in DNA methylation patterns may represent both the indicators of the risks and the predictors of the course of the malignant process. Posttranslational modification via the system of the "histone codes" facilitates the modulation of the gene expression in setting of proliferation, differentiation, apoptosis as well as the guided pharmacological correction. The efforts of the team of our Institute were focused on the determining the potential of microRNA in the regulation of gene expression in the framework of the known triad of the factors of epigenetic modification. We put forward the concept on the role of microRNA in globalization of host-tumor relations that allows us to propose tissue- and tumor-associated panels of microRNA for risk assessment, screening and monitoring of cancer as well as for predicting individualized sensitivity of tumors to chemotherapeutics.

The rapid rise in nanotechnologies allowed the scientists to extend beyond the traditional approaches in solving problems of cancer. The advancements in nanomaterials open the novel layer in our understanding of the role of the essential trace elements in biological processes, in particular, the role of iron-containing proteins for maintaining cell functions as well as initiating malignant transformation and sustaining cancer progression. Metal-containing proteins are in the epicenter of the events that are relevant to the formation of drug resistance. In cooperation with the specialist in chemistry and material engineering, our team has developed the unique magnetically guided nanocomposition aimed at overcoming drug resistance. The further developments of the schedules and regimens of its application envisages the maximal selectivity of nanocomposition accumulation in tumor tissue offering new perspectives for overcoming drug resistance and curbing cancer aggressiveness.

The expression "aggressiveness of the malignant process" is frequently used both in scientific literature and in clinical practice. Nevertheless, the factors of this phenomenon have not been sufficiently analyzed from different perspectives. The "intellectual sequencing" of the molecular-genetic, cellular and subcellular components of all factors contributing to the aggressiveness of the tumor will allow better understanding of the mechanisms generating oncosynergetic processes in the heterogeneous systems and may be advantageous for discovery of the novel markers and targets. Heterogeneity is the pivotal component in tumor progression being the source for the formation of the cells of metastatic pool and generation of the resistance to various factors of anticancer modalities.

Until recently, the stromal component of the tumor seemed to be considered of secondary importance. Nevertheless, according to present day state of knowledge, a number of processes intrinsic to tumor such as intratumor signaling, enzymatic and transport mechanisms, metabolism, oxygenation, immunogenicity are coordinated by the extracellular matrix to a large extent. A crosstalk between cancer cells and the tumor stroma is highly responsible for the progression of tumors and their metastasis. The collagens maintaining well-ordered structure of the stromal component represent the major component of the extracellular matrix. Meanwhile one should be aware also of tumor-associated microbiome that is far from being only background or inflammatory infiltrate.

It is high time to revise such an approach and focus on the tumor-stroma assembly as multistructural matrix taking on the role of "director" or "conductor" governing multiple proliferative and metabolic processes in the setting of the failure of central neurohumoral control. Several researchers are inclined to consider the solid tumors as the complex abnormal organs composed of multiple cell types (both cancer cells and cells of microenvironment) and extracellular matrix, the latter being modified and remodeled.

The multilayered matrix of the stromal component of tumor and the unlimited heterogeneity of the cells of parencymatous complex in combination with the distorted extracellular matrix provides for the optimal incubation milieu generating differently directed processes including the possible reprogramming of the stem cell functions. According to the modern concept of the role of stem cells in malignant process originating from Virchow's ideas put forward more than 150 years ago, cancer stem cells represent the unlimited source of the proliferative pool in tumors. Due to the peculiar metabolic and proliferative features and the low content of the differentiation clusters, cancer stem cells are highly tolerant to the factors intended for their elimination; their identification is also fraught with difficulties. The high propensity for the activation of the molecular transporters provides for the mechanisms of the resistance towards exo- and endogenous toxic factors. The complex hierarchy and multiplicity of the regulatory networks is the serious obstacle preventing identification of the key players involved in the malignant transformation of the stem cells.

Until recently, the microorganisms as the components of the internal milieu of the body including have not been considered more than "background" in tumor process or inflammatory infiltrate. Meanwhile, the recently completed Human Microbiome Project (2008–2013) gave valuable insight into the variety

of microbiota of human body and its importance in the initiation of the numerous pathologies including malignant transformation. In fact, the microbial cells within the human body outnumber about tenfold the host somatic cells. Centuries ago, A. Leeuwenhoek stated that human body is a peculiar ecosystem inhabited by a myriad of microorganisms. The unique symbiosis of macro- and microorganisms is a result of the long evolution and microbiome on fact is associated as the separate organ of human body. The study of the human microbiome in oncology is a growing and rapidly evolving field. Nevertheless, the studies of microbiome in relation to the problems of carcinogenesis have been rather piecewise so far without attempts of multidisciplinary integration of the efforts for comprehensive understanding of the algorithms of malignancy. Nevertheless, tumor-associated microbiome seems to be the potential moderator of the whole complex of processes mediating tumor-stroma relations. The understanding of the hierarchy and logistics of these processes should provide us with the tools allowing for timely and adequate response preventing tumor expansion.

It is now evident that even opportunistic pathogenic species of normoflora comprising microbiota may be "duplicitous" serving as both inhibiting and promoting factors in carcinogenesis. From the very beginning of cancer initiation stages in the setting of disbalance of the regulatory systems, microbiota (considering its "evolutionary learning") is involved in the metabolic changes, activation of beta-catenin-dependent Wnt signaling pathways promoting expression of c-myc and cyclin D1 genes. This changed signaling leads to the production of proinflammatory cytokines interleukin-1β, -6, tumor necrosis factor-α, M2 polarization of macrophages and stimulation of cell proliferation. Recently, it has been proved that *Fusobacterium nucleatum* contributes to carcinogenesis by the induction of matrix metalloproteinases-9 and -13 secretion; the latter are actively involved in the cleavage of extracellular matrix facilitating invasion and metastasizing. This example demonstrates the potential of microbiome and inflammogenesis as the key trigger of the tissue damage that provides for autonomy and generalization of cancer.

It is quite possible to imagine the role of microbiome in formation of premetastatic niches and reprogramming the stem cell to cancer stem cell. When one consider the formation of the metastatic phenotype of cancer cell with inherent migration and adhesive properties as well the role of chemokines in attempted invasion of premetastatic niches, these processes could not be imagined without the unique resource of microbiome.

It seems that general stages of carcinogenesis and tumor progression are well known and understandable. Nevertheless, the lack of understanding the hierarchy of the separate mechanisms slows down the progress in target-directed efforts aimed at fighting cancer. It is one of the reasons why the current strategy aimed at eliminating separate inflammatory components, inhibiting several signaling cascades (nuclear factor kappa B, inducible nitric oxide synthase) and mediators of inflammation (cyclooxygenase-2) rather than eliminating the primary sources fails to achieve the desired objectives.

It is high time to consider the whole spectrum of the inflammation factors affecting the formation of microenvironment, neoangiogenesis and the distorted response to the hormones and pharmacologic agents. The multifaceted events in cancer growth should be seen in the context of the factors inherent to cancer cells as such and other components of this complicated phenomenon. Taking into account the ability of microbiota to use its unlimited resource in the numerous pathologies, it proves increasingly difficult not to consider the dominating role of microbiota in cancer origin and progression.

The further endeavors to delineate the origin of the initiation and induction of carcinogenesis open the window of opportunities for prevention of carcinogenesis and biotherapy of cancer. Provided the priorities in cancer research defined in the previous years, especially accounting for the data on the role of microbiota in cancer, we positioned ourselves as the advocates of the biotherapeutic strategy in the fight against cancer. We strongly believe that this is an approach for which a great future is reserved.

Nowadays, when the world is worried about finding the ways to curb COVID pandemic, a premium is placed on antiviral vaccination. Nevertheless, the findings on post-COVID syndrome that are accumulating might suggest the possible impact of this infection on other pathological processes in the body including cancer.

It should be recognized that the conceptual problems of cancer are still on the agenda, in spite of the achievements in deepening the fundamental knowledge, designing novel diagnostic technologies and therapeutic modalities. Therefore, not only personalization of cancer treatment but also identification of the pathogenetic components in the individual composition of microbiota should be prioritized. Such strategy should have been beneficial for improving the outcome of cancer treatment.

The scientific and technological progress based on the scientific achievements has been and remains the base for the success of the economically developed countries providing for designing the pilot platforms intended for solving the most difficult challenges facing the society.

Editor-in-Chief
Academician Vasyl Chekhun