

## “TUMOR AND HOST” BY R.E. KAVETSKY (1962): IMPLICATIONS FOR THE PAST, PRESENT AND FUTURE

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This paper aims to present a short history of the concept of the development of tumor-host interaction. The numerous facets of this concept started to be discussed in detail quite a long time ago, but especially over the last decades and even more so over recent years. This topic has received new impetus due to a re-assessment by scientists of the biological nature of tumor growth as well as the appearance of methodological technologies that have allowed the clarification of many older findings and the discovery of new mechanisms. Especial attention has been devoted to these issues by pathophysiologists from Germany, Russia and Ukraine who have studied general pathology and, in particular, oncology. The fruitful development of Thiersch's idea has been implemented in the works of A. Bogomolets and, especially, by his follower R. Kavetsky who made a significant contribution to the formation of the tumor-host concept.

The 50<sup>th</sup> anniversary of R. Kavetsky's monograph "Tumor and Host" (Kiev, Gosmedizdat, 1962) which was perhaps the first main summary of data on this subject is being celebrated in 2012. It is worth noting that the special session "Tumor and Host Interrelationships" held within the framework of the VIII<sup>th</sup> International Cancer Congress which was held in Moscow was organized as a result of Kavetsky's initiative. The plenary lecture given by Kavetsky, together with presentations by other scientists and active discussions, provided a special impulse for new investigations in this field. As part of the celebration of these two relevant scientific events, an attempt will be made here to familiarize the readers with a short history of the tumor-host problem while also presenting some recent publications that have focused on the background established more than hundred years by prominent pathophysiologists of our time.

### HISTORICAL PERSPECTIVES

At present it is hard to imagine that at the end of the 19<sup>th</sup> and the beginning of the 20<sup>th</sup> centuries the ideas on the autonomy of tumor growth were shared by a number of leading pathologists, among whom Virchow predominated. However, as far back as in 1861, the Russian pathologist Pelikan pointed out that Virchow's concept was erroneous and declared that a tumor is host-dependent and cannot be autonomous

in its growth (cited from Ruchkovsky, 1953 [1]). In the quest for the truth, it is of interest to recollect that one of the known misleading theories, namely that all tumors, including carcinomas — i.e. tumors of epithelial origin — are derived from connective tissue, in fact belongs to Virchow [2]. Virchow's claim has been opposed and disproved by Cornil, Thiersch and von Waldeyer. It was shown that in the case of epithelial tumors, cells originate from the existing epithelium. The studies of von Waldeyer showed that in their very various locations, cancers are, in their origin, connected with epithelial structures (cited from Coats and Sutherland [3]). But in the above-mentioned studies, an explanation of the mechanisms of tumor cell invasion, in particular for cells of epithelial origin into adjacent tissues, was absent.

Cohnheim, and in part, Ribbert, suggested that the invasion of epithelial tumor cells is only possible when an alteration of the connective tissue primarily occurs. On the basis of this assumption, the concept that the neoplastic growth is determined by tumor stroma was formulated. Coats and Sutherland [3] have presented the data concerning Thiersch's point of view on the cause of cancer, taking into account the differences between benign and malignant tumors. In the case of benign tumors, normal tissues are able to prevent tumor penetration into surrounding tissues, but in the case of malignant tumors, adjacent normal tissues become unable to form a barrier against tumor expansion. In 1902, Borst summed up the discussion and put forward a hypothesis concerning the relationship between tumor and stroma [2].

It is possible to imagine that Virchow's postulate partially originated from his own observations concerning the stromal, i.e. the connective tissue component, of neoplasia. In 1863, Virchow was the first to identify leukocytes in the center as well as in the periphery of tumor foci, ascertaining that the inflammation is one of the predisposing factors of tumor development [4]. It should be emphasized that Cohnheim, who has been recognized as a pioneer of the theory of inflammation, wrote: "There is no inflammation without the involvement of blood vessels" [4]. Cohnheim explained the presence of leukocytes in tumor tissue (characteristic of any inflammatory focus) to occur through the migration of polymorphonuclear leukocytes from blood vessels supplying the tumor. In total, all of the mentioned works have

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completely overthrown Virchow's notion which was dominating at that time [5].

An assumption concerning the destructive impact of a tumor on its host, leading to anemia and general weakness and sometimes even to serious constitutional consequences was made by Coats and Sutherland [3]. The authors used terms such as dyscrasia and diathesis to designate the state of a body predisposed to the initiation and formation of a malignant tumor. Nevertheless, direct evidence for such a predisposition was not available at that time. As early as 1865, Thiersch for the first time declared the idea of the role of connective tissue in cancer pathogenesis, taking into account the ability of the connective tissue to oppose the invasion of epithelium (cited from Kavetsky [6]). Developing this idea further, Bogomolets proposed the concept of the physiological system of connective tissue. According to his concept, connective tissue is of utmost importance in the development of many pathological processes including malignant growth. Bogomolets noted: "Cancer can hardly arise in a body displaying sufficient resistance of the reticulo-endothelial system". In this respect, he introduced the term of "cancer diathesis, i.e. the predisposition of an organism to cancer development" which was in line with the preceding assumptions of Coats and Sutherland. Working actively on this problem, Bogomolets arrived at a negation of tumor autonomy, in the sense of tumor cells being independent of the host, whereby he recognized that metabolic disturbances and the reaction of the body are of utmost importance for the origin and development of pathological processes [7]. It should be emphasized here that he addressed the problems of the etiology and pathogenesis of malignant growth from the point of view that the organism should be considered as being one unity and can itself be recognized as forming one unit with its external environment. At the same time, he supported the idea that metabolic disturbances and the reaction of the organism are very important in the genesis and development of pathological processes.

In Bogomolets's text-book "Pathological Physiology" (1923), the chapter on tumors contained sub-chapters devoted to local and more general effects of tumors on their host and the reaction of the host to tumor development [8]. It is important to note that Bogomolets, when considering connective tissue as a physiological system, suggested that the internal milieu of the organism, with its cellular and non-cellular components possesses not only plastic but also trophic and protective functions (cited from Nejman [9]). At the same time, Bogomolets considered cancer as not being able to develop in a host in which the connective tissue exhibits normal resistance properties [10]. The same idea was almost simultaneously declared by a number of French scientists (cited from Bogomolets [10]). At that time, much attention had been given to the study of connective tissue. The active connective tissue, or in the words of Maximov, the "mesenchymal reserve" (comprising histiocytes,

reticulocytes, endothelial cells and hematopoietic elements and their derivatives, namely leukocytes and monocytes, and Hortega cells in the brain) was considered to be the most powerful system in the organism under either physiological or pathological conditions [11]. As early as 1909, Ulezko-Stroganova formulated a thesis dealing with the significance of connective tissue and its customary role in the initiation and development of malignant tumors, explaining the possible causes of spontaneous recoveries from cancer [12]. At present, the cellular and non-cellular components referred to above do in fact mirror the current concept of the tumor microenvironment, or more specifically, the molecular-cellular microenvironment of tumor cells [13–21].

Bogomolets' ideas on the active mesenchyma being a factor involved in restraining tumor growth were fruitfully further developed by his follower Kavetsky, the founder of the Ukrainian School of Oncology. In 1937, Kavetsky proposed that: "Two interconnected processes comprise the basis of carcinogenesis: (a) the local process of carcinogenesis that later develops into the real malignant tumor, growing by infiltration, and (b) general changes in the body predisposing the possibility of the primary node being transformed into the genuine tumor, with its further dissemination by means of metastasis" [6]. This statement comprises the unity of processes of malignant transformation of normal cells as well as the development of the general disposition of the organism to tumor growth initiation, "which in conjunction promote the development of malignant neoplasia in the organism".

Similar issues were raised by Greenstein in 1941 when he contended that "tumor-host interaction is the key to the problem of cancer" (cited from Begg [22]). In Begg's publications from the 1950s, many questions concerning tumor-host interaction were discussed. While some of them could not be confirmed later, the principal statements still hold true at present [22]. According to Begg, the concept of "tumor-host interaction" referred to alterations triggered by the tumor in metastasis-free remote tissues of the host. In fact, in normal tissues of tumor-bearing hosts, some alterations were evident, depending on the stage of disease. Initially, such findings concerned several enzymatic systems of the liver and spleen. An important observation was that, as a rule, tumors contain more nitrogen than that accumulated in the tumor-bearing organism, due to a redistribution of nitrogen in favor of the tumor and at the expense of the host tissues, in particular muscle tissue. Mishchenko was apparently the first to carry out careful investigations of nitrogen metabolism in animals with experimental tumors as well as in cancer patients at different stages of the disease [7]. Tumors utilize both exogenous and endogenous substances in order to meet their own synthetic requirements. Later, Mider et al. in 1948 concluded that the tumor-bearing host is in the peculiar state of negative nitrogen balance and thus designated the tumor as a "trap of nitrogen"

with nitrogen only being lost to the urine (cited from Kavetsky [7]).

The pronounced ability of tumors to utilize glucose for amino acid synthesis was also discovered. Based on the observations of Carrie and Ham (1949), suggesting that tumor growth is accompanied by a decreased blood glucose concentration, Begg [22] proposed that malignant tumors must be capable of extracting glucose from the blood. This idea was further developed by Shapot [23, 24] who characterized the tumor as being a “trap of glucose”. The biochemical changes in the tumor-bearing organism were also observed to be accompanied by disturbances in the endocrine system, in particular the activation of the pituitary-adrenal axis.

In the 1950s and 60s, Kavetsky and his collaborators distinctly outlined the concept of “tumor-host interaction”. Having summarized vast amounts of experimental and clinical data, Kavetsky [7] stated that at first, tumor growth as such is a host reaction to a variety of physical, chemical and biological factors of the environment. In this respect, it is possible to accept the definition of the tumor as a “dystrophic proliferative reaction of the body to various harmful intrinsic and external factors that fundamentally disturb the composition and structure of the tissues and cells and alter their metabolism” as formulated by Petrov [25]. Secondly, an autonomy or independence of tumor growth is out of the question due to the mutual relationships between the neoplasm and the host from an early stage of tumor formation. At the VIII<sup>th</sup> International Cancer Congress, Kavetsky summarized the principal issues of “tumor-host relationships”, which were accepted by almost all oncologists [26, 27]. The importance of the above-mentioned problem was confirmed by the number of monographs published in the following years in which data on the mechanisms and different aspects of the tumor-host interaction were documented [28–30]. Two scientific conferences, entitled “Tumor and Host” and “Tumor and Host Relationship” were held in 1974 and 1980, respectively, by the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology (IEPOR) of the National Academy of Sciences of Ukraine [31, 32].

Two decades later, the rising interest in tumor-host relationships on a more up-to-date methodological level was marked by Kerbel’s article published in 1995 in the special issue of *Cancer and Metastasis Reviews* [33]. This review highlighted the role of the organ and tissue microenvironment in the behavior of solid tumors. The scope of the subjects covered was very broad and included the biology of intratumoral stromal fibroblasts, desmoplastic reactions observed in invasive carcinomas, and the ability of stromal cells to secrete different matrix metalloproteinases which may contribute to metastatic processes. The author pointed out that it is important to take tumor-host interactions into account in almost every aspect of tumor biology, especially metastasis.

The molecular aspects of tumor-host interaction are now the focus of intense research. Liotta and Kohn [14] considered the malignant tumor to be a “product” of pathological misbalance in the tissue-cell assembly. Here, the malignancy may be characterized as a state formed in the setting of specific tumor-host relationships at the molecular and cellular microenvironment levels when the “host” participates in the induction, selection and expansion of neoplastic cells, and in turn receives potent impacts generated by the developing tumor. From the human viewpoint, the behavior of tumor cells seems to be driven by “their intention not to become outcast”. For this reason, they synthesize and secrete a variety of stimulating growth factors and cytokines, which recruit stromal and other elements into the tumor in order to provide the living environment appropriate for tumor cells.

In turn, the locally activated “host” microenvironment (cellular and non-cellular components) modifies the proliferative and invasive behavior of tumor cells resulting generally in an increased aggressiveness of the primary tumor and malignant tumor progression. Zigrino et al. [34] indicated the significant role of the interaction of tumor cells with stromal elements during tumor progression, focusing on the ability of tumor cells to modify the stroma, to change the adjacent connective tissue and to modulate the cellular metabolism of the “host”. In this way, stroma will be formed which is “most comfortable” for the realization of the tumor cell’s aggressive potential. The main vital principle of “tumor cell life” may thus be characterized as an intention to achieve optimization and preservation of the metabolism even at the expense of the “host” resources.

The immunological, metabolic, and hormonal mechanisms mediated by the nervous system are considered as being the “classical” mechanisms of tumor-host interaction [35]. It is worth mentioning that all of them are very closely connected and that their molecular “crosstalk” forms the pathological state referred to as tumor disease. Here, the metabolic alterations will be briefly discussed to demonstrate their impact on immune reactions of the host that are of high importance in maintaining tumor-host interactions. As far as a tumor-host relationship involving the nervous system is concerned, it should be noted that such studies have been considered as being obsolete for a number of different reasons. Nevertheless, these questions have again been recently brought into focus [36].

Pyter et al. [37] verified the hypothesis concerning the ability of the tumor to induce a depression-like state and to “switch on” the production of both peripheral and central anti-inflammatory cytokines. Authors have observed increased signs of depressive and anxious behavior in rats with induced mammary cancer in comparison to that seen in control animals. Tumors have been found to produce significantly more IL-1 $\beta$  than normal mammary tissue. The levels of the inflammatory mediators IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ,

which provoke behavior similar to depression, as well as the anti-inflammatory mediator IL-10 are seen to be increased in the hippocampus of rats with mammary carcinoma as compared to control animals. In tumor-bearing rats, the level of circulating corticosterone inhibiting cytokine signals decreased while the expression of genes coding the glucocorticoid receptors in the hippocampus increased. The data obtained clearly show that tumors are potent inducers of shifts in emotional behavior. The suppression of glucocorticoid-related reactions to stress may exaggerate the negative effects of tumor-produced cytokines in the context of the psycho-emotional state of tumor-bearing animals. Based on the data concerning tumor cell production of anti-inflammatory cytokines capable of inducing depressive behavior (anhedonia, anorexia, lethargy), a direct impact of the “peripheral” tumor on the hypothalamo-hypophysis-adrenal axis has been inferred.

Different physiological-biochemical reactions that promote the vitality of tumoral as well as normal cells form the basis of the metabolic mechanisms of tumor-host interaction. This aspect of the tumor’s relationship with the host is based on the microenvironment of tumor cells which, as it is clear from numerous investigations, is the dominant factor in the “tumor-host” dialogue.

### RECENT ACTIVITY

The current problems of tumor-host interactions were the subject of the international conference entitled “Tumor and Host: Novel Aspects of the Old Problem”, that was held on September 21<sup>st</sup>–24<sup>th</sup>, 2010 in Kiev, Ukraine. The meeting was hosted by the R.E. Kavetsky IEPOR and was dedicated to the 50<sup>th</sup> Anniversary of the IEPOR. Plenary lectures, presentations and the general discussion emphasized the impact of different aspects of tumor and host interactions and their influence on tumor aggressiveness and cancer progression, focusing in particular on immunological aspects of tumor growth, the microenvironment of tumor cells, signaling pathways mediating the formation of the biological profile of tumors, and new trends in cancer prevention, diagnostics and therapy. The issues covered at this conference were published together with a meeting report [38, 39]. A further noteworthy scientific conference entitled “Tumor-Host Interaction and Angiogenesis: Mechanisms and Therapeutic Implication” was also held this year in Switzerland [40].

It is very important to underline that at present, the interactions between tumor and host mainly concern the interactions between tumor cells and stromal cells as well as immune cells and bone marrow-derived cells that were recruited into the tumor node. It somewhat narrows the classic concept of the tumor-host relationship which includes the different organs and systems of the body and considers both systemic reactions of the organism in addition to responses of stromal elements to the tumor.

McAllister and Weinberg [41], while summarizing the recent advances in tumor-host relationships declared that many aspects of tumor biology can only be explained by a detailed understanding of both local and systemic interactions.

One of the manifestations of the systemic interrelationships between the tumor and host can be considered to be the well-known recruiting of normal cells into the tumor by signals from tumor cells that support the survival of the neoplasia. It allows a characterization of “the cancer as an ecosystem composed of tumor cells and of non tumor cells residing in the tumor microenvironment or recruited to this site” [42]. It was recently emphasized that “the original concept that cancer cells do not manifest the disease alone, but rather conscript and corrupt resident and recruited normal cell types to serve as contributing members to the outlaw society of cells” [43].

In this aspect, the statement of Goodwin et al. [44] that “there is growing evidence that it is necessary to go beyond the cell into the whole organism to fully understand the biology of cancer and its treatment” is very important and highly relevant. It has to be noted that a personalized therapy needs to be rooted in a consideration of the reality that any tumor growth and progress involves a close interconnection with the individual organism, and that the problem of an individual patient’s management may only be successfully achieved within the frame of the concept of “tumor-host interaction”.

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