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Over the past 50 years, there have been great many advances in chemotherapy and radiation treatment for hematological and lymphopoietic malignancies, and now some of them can be controlled quite successfully. The management of solid tumors, on the other hand, is still problematic, perhaps due partly to the misguided biology of mouse-tumor advocates.

Permit me to briefly reflect my personal experiences during the half century. After completing the residency programs in anatomic pathology and laboratory medicine at the Mallory Institute of Pathology and affiliated hospitals in Boston, MA in 1958, I sought an experience in experimental cancer research trainings under the late professor Jacob Furth at the Dana-Farber Cancer Institute, also known as the Children's Cancer Research Foundation in Boston. I worked closely with him for five years in his laboratories in Boston, through Roswell Park Cancer Institute in Buffalo and Columbia University Cancer Center in New York, learning a great deal of hormone-dependent and independent tumor problems and developed variously hormone dependent rat mammary tumors. During this period, under the guidance of Dr. Furth, I participated in the Breast Cancer Task Force of the National Cancer Institute, and had the good fortune to meet many renowned endocrinologists, including those who discovered and developed hormone-receptors on tumor cells. Then, in 1963, I was invited by the Roswell Park Cancer Institute to be an associate chief pathologist, and also establish and manage my personal research laboratory. In Buffalo, I worked for 34 years, as a fulltime clinical pathologist, and also participated in the Eastern Cooperative Oncology Group (ECOG) and the Cancer-Acute Leukemia Group B (CALGB). At the same time, I maintained an independent research laboratory with a few research staff carrying out separate experimental breast cancer metastasis research problems as well as developing and establishing many highly realistic rat mammary tumor cell lines vis-à-vis metastatic human breast cancer cells. These mammary tumor cell lines and my metastatic research programs seemed to have become more popular among European and Japanese scientists, and I often served as an invited guest professor at a number of cancer research centers in England, Germany, Japan, and other European countries.

In the meantime, it was well established that most common human cancers disseminate from the primary site to the regional lymph nodes first via the lymphatic channel, and then metastasize to other distant secondary organs by cascading via the blood stream after passing through the heart. Therefore, clinical oncologists were evaluating the common pattern of progression of human malignant solid tumors, and

staged the sequence by the numerical order of 0 to 4, and selected an appropriate treatment modality for each, and it became a common or standard clinical practice.

During this period, however, mouse tumor biologists seemed to ignore the lymphotropic dissemination of common human cancer cells, and emphasized how murine solid tumors metastasize directly to the lung via the blood stream in the form of tumor cell emboli. For yet unknown reasons, mouse tumors in general tend to disseminate via the blood stream, and rarely via the lymphatics, as common human carcinomas do. Also, another mouse tumor researcher called attention to the blood vessels, and that blocking the growth of tumor-associated blood vessels should control the growth of tumors, advocating the development of anti-angiogenesis drugs or reagents, and this hypothesis became rather popular. Contrary to this view, however, at the turn of last century, the Nobel laureate, Professor Otto Warburg had already shown that cancer cells tended to generate their necessary energy via anaerobic glycolytic pathway not requiring fresh blood supply as much as normal cells do. Also, more recently, by directly injecting radio-labeled fresh rat blood into the heart, and by measuring the amount of blood-flow in the mammary tumor-bearing rats developed in my laboratory, a radiation biologist (Jirtle, R.L.) has shown that the spontaneously lymph-node metastasizing rodent mammary tumors required much less blood supply, as little as 1/5~1/15 of blood supply of non-metastasizing matching rat mammary tumors, contradicting the importance of tumor angiogenesis factor for tumor growth as well as for metastasis. Therefore, the administration of anti-angiogenesis drugs or reagents is not likely to solve human cancer problems.

Lastly, for the past 40 years, tumor immunologists have emphasized the importance of tumor-associated T-lymphocytes in the control of tumor growth: It has been observed in certain cancer patients that the stimulation of host T-cells or direct injections of tumor associated T-lymphocytes to have caused shrinkage of some tumors. Recently, however, during the xenograft study of human carcinoma cells in athymic nude mice we have observed that some human carcinoma cells were readily accepted or tumorigenic, while some were non-tumorigenic or resistant to the xenograft in T-cell deficient nude mice but they can be made to grow by i.p. injections of anti-mouse NK antibodies to the host nude mice. Thus, human malignant tumor cells can also be classified by tumorigenic/NK-resistant or non-tumorigenis/NK-sensitive. Furthermore, with the xenograft study of highly realistic rat mammary tumor models vis-à-vis metastatic human breast cancer cells, it helped us to conclude that lymph node metastasizing human carcinoma cells may be better controlled or even eradicated by the suppression of T-cell primacy in tumor immunology. Thus, perhaps, the next decade may bring about some more effective measures for the control of common human cancer by reversing some of our traditional hypotheses on cancer.