Applied Tumor Immunology

Editors
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Methods of Recognizing Immune Phenomena Specific to Tumors

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Preface

Experimental as well as clinical findings have led to the knowledge that in case of carcinoma and in systemic malignant tumor diseases the organism's autologous immunological reactivity becomes decisive concerning the tumor cells' development and patients' fate. Basing on experiences of modern tumor immunology special methods for detecting tumor-specific immune phenomena and also concepts for an efficient immunotherapy of cancer have been developed. Although, the results of these efforts are not as yet satisfactory in clinical medicine, one should not fail to prove the applicability of efficient data from basic research work to clinical interests in the sense of "applied" tumor immunology.

It was the intention of the "1st International Symposion on Applied Tumor Immunology" held in Berlin on November 17th and 18th, 1972, reviewing the present status of this field, discussing advances in basic tumor immunology and promoting research work by mutual exchange of experience.

The symposion dealed with *problems of developing special methods for the detection of tumor-specific immune phenomena* including the interpretation of findings in clinical medicine.

The present volume records lectures and those papers that contributors submitted for publication.

We would like to present our gratitude to all speakers and participants for their contributions and for their open and fair discussions. The widespread interest of basic scientists as well as of clinical and laboratory specialists and practitioners will perhaps stimulate organizing a second symposion on this field of applied tumor immunology.

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We would finally like to thank the secretary of the symposion, Mrs L. Weinberger and her helpers and the interpreter group of Mrs. D. Helmrich.

Though, the contributions of the symposion in 1972 come out but now, most of the papers were brought to the recent state of knowledge.

Berlin and Göttingen, October 1975

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Contents

1 Methods for Detection of Tumor-Specific Sensitized Lymphocytes

1.1 Tumor-Specific and Cell-Mediated Immune Reactions Expressed in Pathomorphological Findings

E. Grundmann

Three separate processes can be distinguished during oncogenesis (1):

1. The initiation, i. e. the transformation of normal somatic cells into cancer cells,
2. the extension of the tumor promoted by excessive growth,
3. the escape of tumor tissue from endogenous regulations leading finally to the death of the patient.

Immunologic reactions are involved in each of them, but their respective value is unequal.

The primary process is a matter of molecular biology. Chemical carcinogens, for example, will transform DNA-bases by way of metabolic products. Diazoalkane could be mentioned as an instance: produced by hydroxylation and heterolysis of dialkylenitrosamines (2), it can methylize the guanine of the DNA double helix. The reaction of "terminal cancerogenes" (i. e. dialkane in this case) with a transfer-RNA by means of a transfer-RNA-methylase may be more important than a direct methylation of guanine (3). Oncogenic RNA-viruses are able to transform DNA by an intermediate of invert transscriptase, a RNA-dependent DNA-polymerase.

This primary process has to be mentioned first because of its considerable importance in tumor immunology. We know today that cancer cells, be they induced by chemical agents or by viruses, will be recognized as "strangers" by the tumor host, and will be treated accordingly. This may be the consequence of an antigen defect or of newly arising antigens. Neo-antigens have been found particularly in experimentally induced viral cancers.

They can be of viral nature determined by specificity of viral nucleic acids. If an organism possesses beforehand antibodies for the specific virus, the primary process can be suppressed. Experimental evidence can be obtained by viral infection, or even by injection of irradiated cells from viral tumors: the animals are specifically virus-resistent. The meaning of such immunities against certain tumor viruses and its impact on human oncogenesis, are rather vague for the time being. Principally, the primary process of cancerization appears controlled by immunologic mechanisms.

Practical evidence of a malignant tumor cannot be obtained before it has entered the second stage, the growth phase. Immunological reactions are more easily grasped in this phase, and that is why almost every approach to tumor immunology starts here. When murine or rodent tumors are grafted on isogeneic animals, excessive growth will start immediately. In allogeneic or heterogeneic animals growth will stop after a few days, and tumors disappear. Heterologous transplantation of JENSEN-sarcoma from rats to mice is an adequate example: tumors are growing until day 11 after grafting, then they turn necrotic and are rejected. Histologically, the process is accompanied by an infiltration of lymphocytes and plasma cells surrounding the transplant (Fig. 1). This inflammatory wall was known for quite some time (4) and was called "Immunitätsgewebe" by WALLBACH (5). It is found in most malignant tumors. In histodiagnostical practice we may go by the formula: Many lymphocytes indicate slow progress, fewer lymphocytes mean rapid growth of a tumor. Such a rule of thumb has, of course, to be taken with all necessary precautions.

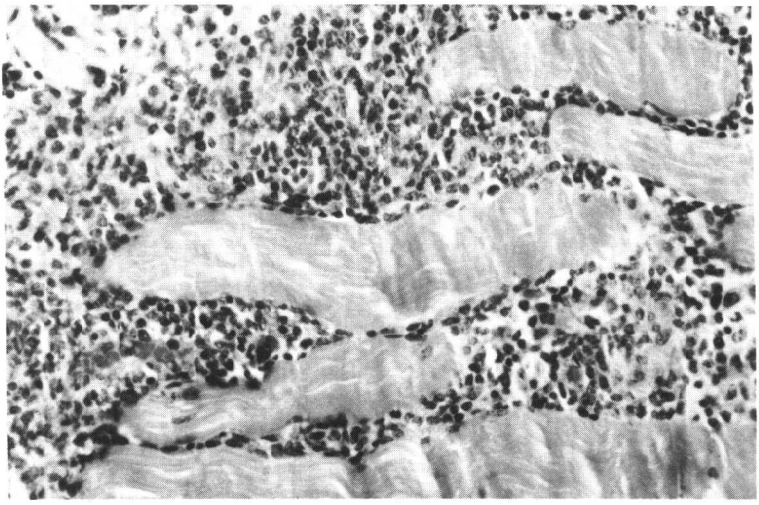

Fig. 1. Abundant lymphocytic infiltration after heterologous transplant of JENSEN-sarcoma to the mouse. Many lymphocytes, but only a few tumor cells preserved among muscle fibres. Typical graft rejection. HE x 320.

Three model cases can be described:

A basalioma must be defined as malignant skin tumor on account of its primary process. It is surrounded by a dense wall of lymphocytes with many histiocytes which are some times accumulated in small knots (Fig. 2). Histologically, this "Immunitätsgewebe" presents an analogy to graft rejection in an allogeneic transplant, for instance of a skin graft in mice (6).

In terms of morphology, female chorion carcinoma is an example for the opposite. This tumor owes an exceptional position in oncology to the fact that it is a human transplantation tumor, indeed. When it is left untreated, rapid local and massed metastatic growth will lead to death in most cases. Even the earlier chorial invasion into the placenta is completely free from lymphocytes, and the same phenomenon is often seen in

the full grown tumor and its metastases. - The most simple explanation would be that the mother had acquired immune-tolerance against embryonal cells. As the problem does not exactly belong to my topic, it will not be considered for the moment; but it may be of interest that chorial carcinomas can spontaneously regress when lymphocytes are abounding in their immediate vicinity.

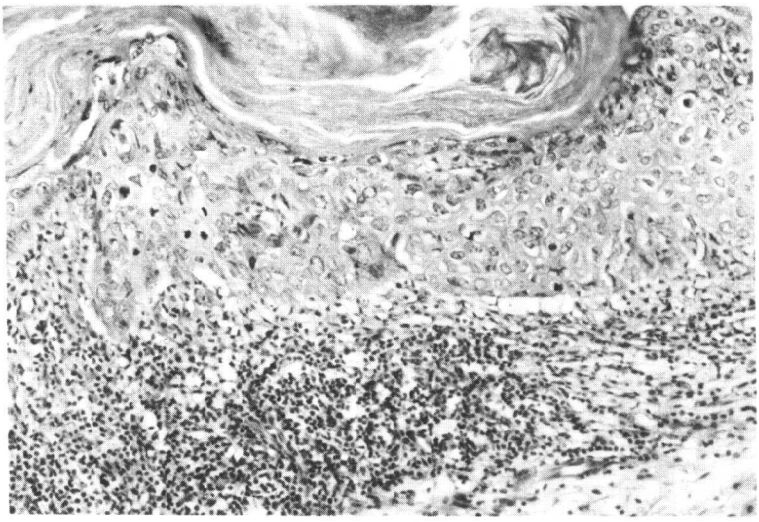

Fig. 2. Morbus BOWEN with intense lymphocytic reaction below intraepithelial carcinoma cells. HE x 130.

Lymphogranulomatosis provides a third example in pathological histology. Following LUKES and Coll. (7), Morbus HODGKIN today is staged in at least 4 histologic types: the lymphocytic predominant type, the mixed lymphocytic-histiocytic type, the lymphocytic depleted type, and nodular sclerosis (the latter might possibly be seen as a disease sui generis). We have to emphasize that in the first three types histologic features will undoubtedly