like glass or plastic, is relevant for its behavior in its natural environment.

Destruction

When malignant mouse fibroblasts (C3H/MO_4 cells) invade an embryonic chick heart fragment, cultured in a three-dimensional system, they completely destroy the heart tissue. In contrast, if heart cells grow as a monolayer on glass, and are then confronted with the MO_4 cells, no destruction is observed. This example raises the question if the interaction of malignant cells and normal cells in monolayer culture is relevant for research on invasion properties.

Phagocytosis

TE micrographs have shown that invading HeLa cells internalize debris from heart tissue into large vacuoles. These observations suggest that phagocytosis of material from heart tissue accounts for its replacement by invading malignant cells, in three-dimensional cultures. We tried to directly observe this process by feeding debris from heart tissue to HeLa cells in monolayer culture. The debris was attached to the surface of the HeLa cells through filopodia, but internalization of particles into large vacuoles was not observed. Although it is not excluded that lack of internalization is due to the nature of the debris (prepared mechanically), this example also questions the value of two-dimensional cultures.

These comparative studies using two- and three-dimensional systems raise some doubts that the behavior of cells in monolayer cultures is relevant for their activity *in vivo*. Our policy for the future will be to use two-dimensional cultures for the study of cellular functions involved in invasion only under the condition that (a) the function is preserved in monolayer culture and (b) that it occurs in the same way as in three-dimensional sytems.

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Human Epidermal and Mammary Carcinoma Cells: Actin Distribution

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Spreading in the surrounding tissue is one of the most prominent features of cancer cells. Although the mechanisms which lead to invasion are little understood, it seems likely that cell movement is one of the phenomena involved in tumor invasion [1, 2, 3]. Evidence has accumulated indicating that several aspects of locomotion of nonmuscle cells are related to the presence of contractile proteins, in particular actin, in human carcinoma cells. Normal skin, basal cell carcinomas, squamous (skin, oral cavity, larynx) cell carcinoma as well as nonlactating mammary glands and infiltrating ductal carcinomas were compared by means of electron microscopy and indirect immunofluorescence using anti-actin antibodies. Anti-actin auto-antibodies were obtained from patients with chronic aggressive hepatitis [4].

Cancer cells stain more strongly for actin when compared with the normal cells. In particular, pronounced staining is observed in cells invading the surrounding tissue as is the case in invasive squamous cell carcinomas. The same holds true for mammary carcinoma, where the cells of the growing edge of the tumor, around small lymph and blood vessels, as well as the cells in isolated metastatic islets stain most intensely. The increase in immunofluorescent labelling for actin in cancer cells is correlated with an increase in microfilaments as revealed by electron microscopy [5–7]. The marginal cytoplasm contains a thick meshwork of microfilaments which extend into fingerlike cytoplasmic protrusions. These projections are in direct contact with the surrounding tissue. Concomittantly, the large tumor cells appear to be more detached from one another: the intercellular space is enlarged, hemidesmosomes and tonofilaments are less abundant in cancer tissue than in

normal tissue. The basal membrane is often missing. These observations confirm previous findings [5, 7].

We do not know whether the observed increase in staining for actin reflects an increased synthesis of actin in cancer cells or whether it is due to a change in configuration of the actin already present in the cells. In the case of actin, we could imagine a shift of the polymerization equilibrium in favor of filamentous actin. It is tempting to assume that the observed increase in actin staining and the abundance of microfilaments in peripheral and metastasizing cancer cells are related to the ability of these cells to move and thus reflect their invasive activity.

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Locomotion of Cancer Cells *in vivo*

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Very few experimental models, among them the rabbit ear chamber, allow the microcinematographic recording of the motile behavior of cancer cells within living tissues [1]. Considerable progress is now being achieved with the mesentery model, in which locomotion of cancer cells, initiated *in vivo*, goes on *in vitro*, where it can be filmed [2]. By comparing the behaviour of cancer cells, e.g., V2 rabbit carcinoma cells and L5222 rat leukemia cells, under *in vitro*- and *in vivo*-conditions, we can conclude that on principle, the mode of locomotion and the shape of the cells are identical. Thus, *in vitro*-data on cancer cell locomotion are not, *a priori*, misleading. They are, however, incomplete, as they cannot demonstrate the adaptation of locomoting cells to the texture of their environment.

It is easily conceivable that cells migrating *in vivo* use the pathways of least resistance. In the mesentery, these are the compartments that appear unstructured in phase contrast and in sections. We know that this space is neither empty nor just a container of fluid, but filled by a network of molecular order made up by the proteoglycans of the extracellular matrix. What is the nature of the encounter between locomoting cells and this material? We are now accustomed to assume that cell propulsion is generated by the dynamic interaction of contraction and adhesion. In all likelihood, adhesive sites are provided by the more stable parts of the matrix, fibers and cell surfaces. Can the contractile elements, emanating from these temporary attachment points, pull the cell through the matrix by mere compression and/or displacement of the latter? There appears to be no theoretical objection, but the problem is practically unexplored.

Whatever the nature of this mechanism, its functioning is facilitated by shape adaptations of the translocating cells. We are inclined to interpret these configurational changes as