

The Lectin *Helix pomatia* Agglutinin as a Marker of Metastases – Clinical and Experimental Studies

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Abstract. *The prognosis for the majority of patients suffering from a solid neoplasm remains bleak, due to the fact that most cancers have already formed metastases at distant sites. Any progress in cancer therapy will, therefore, depend on the understanding of the metastatic cascade and therapies derived from this understanding. The development of clinically relevant models of metastases, using lectin-defined human cancer cell lines and severe combined immunodeficient (SCID) mice, is described. In conjunction with modern imaging techniques, these models will help to elucidate the molecular mechanisms governing the metastatic spread of tumours.*

Despite recent advances in the understanding of the molecular basis of cancer, the outlook for patients suffering from the most common solid neoplasias such as breast, lung, colon and prostate cancer remains bleak. No statistically significant increase in the rate of patients cured has been achieved in the last 25 years (1, 2). This astonishing and depressing lack of progress can be attributed to our inability to cure tumours that have spread from their primary anatomical site to distant sites. These metastases can only be detected clinically once they have reached a certain size (about 1-2 cm for the current techniques used in medical imaging) but many cell- and molecular biological techniques now exist to detect metastases at the cellular/molecular level. When these techniques are employed it becomes evident that, unfortunately, many tumours have already metastasised at

the time of diagnosis of the primary tumour (3, 4). Therefore, any attempts at cure will remain futile unless effective therapies for the treatment of metastases have been developed, which in turn will depend on the knowledge of the molecular mechanisms which govern the processes underlying metastasis formation.

The process of metastasis formation is often described as a 'cascade', indicating that every step has to be completed successfully in an ordered sequence in order to result in a clinically detectable metastasis. In this process, cell-to-cell and cell-to-matrix interactions play a major role: migration of the tumour cell through endothelia, degradation of extracellular matrices and survival in the bloodstream (blood is a special form of extracellular matrix) are just a few examples (5, 6). The regulatory processes of the cells with other cells and extracellular matrix are mediated by the outer part of the cell membrane and changes in the membrane composition are frequently associated with malignant cells. The outer part of the cell membrane consists of carbohydrate residues, the glycocalyx. Valuable information about the structure of carbohydrate residues of this glycocalyx have been obtained by the use of lectins. Lectins are carbohydrate binding proteins of non-immune origin which bind non-covalently to saccharide structures. One lectin derived from the Roman snail, *Helix pomatia* agglutinin (HPA), has yielded the most promising results in metastasis research. When applied to sections from primary breast, colon and gastric cancer, HPA bound to tumours from patients with the worst prognosis (7, 8). These results indicated that HPA bound to a carbohydrate residue which is associated with metastases. Experimental proof of this association has been achieved by transplanting human breast and colon cancer cell lines onto immunodeficient (SCID) mice. With a few exceptions, only those human breast and colon cancer cell lines metastasised which were HPA-positive, while HPA-negative cell lines did not metastasise (9). As the cell lines were of human origin, all

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types of monoclonal antibodies directed against human antigens can be applied in this system.

PET and γ camera imaging studies were carried out in these model systems as well. Normal and multidrug-resistant (MDR) human tumour cell xenografts were used to monitor the uptake of sestamibi, which has been suggested as a marker for MDR in some clinical studies, although other studies have denied its usefulness in assessment of MDR of tumours. Our results indicate that sestamibi uptake is not suitable as a general MDR marker (10).

The human cancer cell-SCID mouse xenograft model is, therefore, well suited to investigate the role of particular tumour cell antigens within the metastatic cascade. As this model is also suitable for imaging studies, monitoring of novel anti-metastatic therapies can be performed as well giving valuable additional information.

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