Symposium no. 4: Biology of Tumour Invasion and Metastasis

4.043

The initiation of attachment of metastatic cells.
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Metastasis is initiated when a circulating malignant cell attaches to an endothelial cell. A major obstacle is the electrostatic repulsion between the glycocalyces of the two cells.The glycocalyces of both cells are essentially similar and negatively charged due to the sulphated glycosaminoglycans.If the charge on one surface is reduced then attachment is more likely to occur. Malignant cells produce large quantities of the polyamines spermidine and spermine and we have demonstrated that these polyamines neutralise the charge on glycosaminoglycans and also cross link them.Both these properties would increase the chance of a cell attaching, and since they are reversible it is possible to decrease the chance of the cell attaching and becoming a viable metastasis.

4.044

DISTRIBUTION OF FIBRONECTIN IN BREAST CANCER:PROGNOSTIC SIGNIFICANCE
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Fibronectin(FN)was investigated in 54 cases of breast cancer using immunohistochemistry.Rabbit antibody to human FN was applied on formalin fixed paraffin-embeded tissue sections using the PAP staining technique. Distribution of FN was classified into three patterns:1 .pericellular staining,forming a FN-positive line around tumor islands,2 .diffusely network of FN-positive fibers penetrating the tumor elements,3. mixed staining(combination of the two).Pericellular staining pattern was observed in patients without metastase to axillary lymph nodes.Most cases with metastases to lymph nodes displayed network of FN-positive fibers in stroma of primary tumor of breast cancer.These data suggest that stromal FN staining patterns might be an indicator of tumor invasiveness.

4.045

MALIGNANCY INDUCED BY FUSION OF NORMAL CELLS
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Referring to our hypothesis concerning the fusion induced malignancy (Is cancer a macrophage-mediated autoagressive disease ? Lancet i, 1987, 952) we present the outcome of fusion between normal embryonic mouse cells with normal mouse macrophages and discuss the resulting transformed hybrid cell lines with high take on syngeneic mice. The process resulted in formation of fibrosarcomas with invasive properties.
Cells of monocyte-macrophage lineage are unique in their genetically determined tendency to fuse andin vivo they might be very dangerous from this point of view. In consent to our hypothesis is the fact that properties of macrophages are strikingly similar in many respects to those of malignant tumour cells.(Biology of melanoma is an example that is in keeping with all aspects of this hypothesis.)

4.046

Relationship between DNA ploidy, cytological grade of malignancy and in vitro invasiveness for human sarcomas
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DNA ploidy and histological grading predict tumor aggressiveness and patient survival for several neoplasms. Recent studies show a correlation between in vivo malignancy and invasive growth on a basement membrane gel (Matrigel) for cell lines. Here we have compared DNA content, cytological grade of malignancy (Coindre), and extent of invasive growth on matrigel (primary cultures) for 13 human sarcomas of different histotype. Another 5 cases are currently under evaluation. Using the Spearman's formula for rank correlation we have found good direct correlation between invasiveness and cytological grading ($r=0.63$, $p<0.05$) and invasiveness with DNA index ($r=0.55$ $p<0.05$). Ploidy and histological grading correlated less well ($r=0.39$), however when low histological gradings (1+2) were combined we found that 83.3% of the low grade tumors were diploid and 71.4% of the high grade tumors were triploid or tetraploid. 100% of the high grade tumors were highly invasive while only 17.7% of low grade tumors were highly invasive. All non invasive tumors and only 25% of the highly invasive tumors were diploid. Our preliminary studies suggest that the analysis of invasiveness in vitro and of DNA index of human sarcomas may provide objective markers of biological aggressiveness of the disease. *Financed by AIRC and CNR.*

4.047

CELLULAR AND MOLECULAR MECHANISMS OF RENAL CARCINOGENESIS INDUCED BY AVIAN ERYTHROBLASTOSIS VIRUS
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Besides erythroleukemias and sarcomas, avian erythroblastosis virus strain ES4 (AEV-ES4) induces renal adenocarcinomas (RCas) in chickens. To search for the cells of origin and the mechanism of the development of RCas, we investigated the RCas produced by td359AEV, a mutant of AEV-ES4 which lacks a leukemogenic effect, but which is sarcomagenic. Spindle cell sarcomas in various organs and RCas developed in a high number of chickens inoculated with td359AEV. RCas were tubulocystopapillary structures of basophilic cells and originated only from principal cells (PCs) of the renal collecting duct system. The origin of tumors from PCs was indicated by connections of tumor epithelium to segments of the collecting duct system, including connecting tubules and cortical and medullary collecting ducts. Tumor cells showed typical mucopolysaccharide-containing vacuoles which are characteristic of chicken PCs. Viral particles were observed throughout the kidney. Moreover, the highest numbers of particles as well as budding-images of them were seen (besides tumor cells) in podocytes and distal tubule cells which did not undergo neoplastic change. The susceptibility of PCs to undergo neoplastic transformation could not be related to a particular activation state of the erbB gene, in view of the fact that c-erbB expression was detected by *in situ* hybridization in the epithelium lining the Bowmann's capsule and the entire renal tubule system. From data of Northern blot and *in situ* hybridization techniques, it was suggested that the neoplastic transformation of PCs was elicited by overexpression of the v-erbB oncogene, a feature of tumor cells. According to Southern blot analysis, td359AEV proviruses were randomly inserted in tumor DNAs and the RCas were polyclonal in nature.

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4.048

INTERACTION OF MALIGNANT MELANOMA TUMOR SPHEROIDS WITH ENDOTHELIAL CELL MONOLAYERS: MODULATION BY RGDS
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As a result of adhesive interactions cancer cells may aggregate to form tumor cell emboli which are much more effective initiators of metastasis than are single cells. We have established an in vitro-threedimensional model of extravasation to study the interaction of multicellular tumor spheroids (MCTS) of the melanoma cell line ST-ML-12 with human umbilical vein endothelial cells (HUVEC). To imitate the vascular wall the latter were grown on extracellular matrix (ECM) produced by dextran-stimulated bovine cornea endothelial cells. We have recently demonstrated that the attachment of the MCTS (after 1.5h) is associated with a damage of HUVEC by melanoma-derived radicals. In this contribution we report on the effects of the anti cell-adhesive synthetic peptide RGDS on our model system. RGDS (1mg/ml) neither effected the aggregation of the tumor cells during spheroid formation nor the attachment of the MCTS to HUVEC. In three out of five experiments a significant later onset (after 3h) of the HUVEC injury was observed. The most prominent effect however, was noticed after the penetration of the endothelium. RGDS suppressed the migration of the tumor cells from the tumor cell cluster in a dose- and time-dependent fashion. Within the first 24 h an almost complete inhibition of the migration on the ECM was observed. The sequence RGES was used as a control and proved to be ineffective. Although RGDS is widely used as an anti-metastatic agent the precise mode of action in vivo is not well defined. Our model enables us to study the biology of dynamic cell-cell and cell-extracellular matrix interactions and indicates that RGDS might predominantly act after the penetration of the endothelium.