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Tumor progression and invasion

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Cancer is the disease of the gene. The very first event that damages nuclear DNA is initiated by an initiator (substance, radiation), which may cause different effects, such as mutations, DNA breaks, etc, which may or may not cause cancer. Additional hits, which do lead to the development of cancer, are caused by tumor promoters. At present, detailed knowledge of all the events leading to a malignant disease, are not yet understood. Molecular description of tumor progression envisages that each type of cancer will progress in stages: the step-wise genetic changes accompanying this progression, are unique to each type of cancer. To study these events, various in vitro and in vivo approaches were developed. The first part of the workshop will be dedicated to the methodology used to identify DNA damage, while the second part will be dedicated to the experimental models used to identify biological markers, associated with tumor and/or endothelial cell invasion.

Metastasis of primary tumors is comprised of biologically distinct steps and is rather inefficient process. Local tumor cell invasion is a common denominator in many of these steps and was first described by Liotta[1] as a three-step process, where, first specific attachment (I) is followed by the induction and/or release or hydrolytic – proteolytic – enzymes, which degrade (II) extracellular matrix components, thereby facilitating tumor cell locomotion (III) and penetratioan into the host tissues. Several experimental models are used to study the molecular mechanisms of invasion. Most in vitro invasion assays are using natural tissues, such as amnion membrane, eye lens and fragments of various tissues, such as chicken heart, mouse liver, lung, etc. Organotypic co-culture models were mostly used for studying brain tumor invasion. The most simple are invasion assays using modified Boyden chambers[2,3] and Matrigel or other isolated proteins of extracellular matrix. However, the results may not be reproducible even when using the same system, due to several methodological problems, comprising variability in composition, concentration and preparation of Matrigel (or other proteins), quality of filters, treatment of cells (pH, trypsinization, organic solvents), chemoatractants, time of the assays and methods used for the quantitation of the invasion. The data in the literature confirmed that various proteinase inhibitors were effective in partial inhibition of invasion, indicating that one or several proteinases are involved in this process. The results on inhibition of invasion of breast tumour cells, using synthetic and natural (peptide) cysteine proteinase inhibitors are not yet conclusive, due to variability of methodological approaches, described in the literature.

References

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