S10. Tumor Promotion: A Target of Cancer Chemoprevention

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Tumor promotion is due mostly to a permanent de-regulation of cellular signal transduction resulting in a clonal expansion of initiated cells and an overproducgtion of genotoxic metabolites such as organic free radicals and reactive oxygen species.

The consequence is genetic instability (" mutator phenotype"), i.e. the probability of additional genetic defects to occur is drastically increased. By inhibiting the underlying molecular mechanisms cancer development can be brought to a halt at a still harmless stage. In this respect arachidonic acid metabolism has turned out to provide a most attractive target.

A characteristic feature of – probably all – human and animal carcinoma types and the corresponding pre-neoplasias consists in a constitutive overexpression of the inducible " wound and stress enzyme" cyclooxygenase 2 (COX2) leading to an imbalance of prostaglandin formation. Vice versa, cyclooxygenase inhibitors, i.e. non-steroidal anti-inflammatory drugs, have been repeatedly found to interrupt tumorigenesis both in man and experimental animals. Moreover, for COX2 "knock-out" animals the tumor incidence in colon and skin carcinogenesis was reported to be drastically reduced.

The opposite situation holds true for animals overexpressing COX2. Transgenic mice carrying the cox2-gene under the control of the constitutively active cytokeratin 5 promoter are hypersensitive to chemical carcinogenesis exhibiting a "tumor promoter phenotype", i.e. do not require tumor promotion in the classical approach of two-stage skin carcinogenesis [1]. Their epidermis shows a pre-neoplastic morphology . Moreover, in such animals COX2 overexpression is also observed in epithelia of other organs such as mammary gland [2], urinary bladder [3] and pancreas [4]. Like epidermis these tissues are pre-neoplastically transformed resembling distinct clinical stages in human pathology. In all cases the development of pre-neoplasias could be prevented by treatment with a COX2 inhibitor (celebrex).

These and corresponding data show de-regulated COX2 expression to provide a most abundant high-risk factor in carcinogenesis and, thus, an attractive target of secondary cancer prevention.

References

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