S11. Mouse Skin as a Model for Cancer Chemoprevention by Nonsteroidal Anti-inflammatory Drugs

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Nonsteroidal anti-inflammatory drugs are powerful inhibitors of human and animal tumor development. Using thc initiation-promotion model of mousc skin carcinogenesis we showed this effect to be due to a suppression of prostaglandins which mediate tumor promotion (reviewed in ref.[1]), In fact, overproduction of prostaglandins is a consistent feature of neoplastic development.

Moreover, an aberrant constitutive overexpression of proinflammatory prostaglandin-M synthase-2 alias cyclooxygenase-2 (COX-2) has been found in a wide variety of preneoplastic and neoplastic tissues. A causal relationship between COX-2 expression and tumor development has been strongly supported by inhibitor experiments as well as by studies on COX-2 deficient animals.

To investigate the consequences of aberrant constitutive COX-2 expression for normal and pathological skin development, we have produced transgenic mice carrying the complete COX-2 gene under the control of the keratin-5 promoter which is selectively expressed in the basal cell compartment of stratified epithelia. Heterozygous transgenic animals were viable and fertile. Tissue and blood levels of prostgandins were about 3-5 times higher than in wildtype mice. A greasy and shaggy phenotype of the animals was due to an impairment of hair follicle development accompanied by sebaceous gland hyperplasia and hyperactivity [2],

The epidermis of transgenics exhibited a dysplastic morphology characterized by hyperplasia and hyperkeratosis, loss of cell polarity, the occurrence of proliferative cells in suprabasal cell layers, the formation of horn pearls, and endophytic papillary growth into the underlying dermis. In addition, an almost 3-fold higher blood vessel density in the skin was found in comparison to wild-type animals, indicating an angiogenic effect of the COX-2 transgene. This transgenic phenotype widely corresponds to preneoplastic changes observed in the course of experimental skin carcinogenesis and could be reversed completely by treating the animals with a specific COX-2 inhibitor.

In a two-stage carcinogenesis experiment with DMBA as the initiator, wild-type animals developed papillomas and carcinomas only when subsequently treated with the tumor promoter TPA for several weeks. In contrast, TPA treatment was not required for tumor growth when the experiment was carried out with transgenic mice. This result shows that the COX-2 transgene acts as an endogenous tumor promoter, i.e. that COX-2, when overexpressed, dramatically sensitizes a tissue for carcinogenesis. Moreover, the DMBA-treated transgenic mice developed tumors of the mammary alveolar epithelium (which also expresses keratin-5) at a high rate. A strong sensitization for mammary gland carcinogenesis was also found in animals carrying the COX-2 gene under the control of the MMTV promoter [3]. Specific inhibition of COX-2 is supposed, therefore, to provide a promising means of cancer chemoprevention. Whether this method will remain restricted to certain tumor types and to high-risk populations or may become generally applied, will depend, first of all, on the management to side-effects which are expected to occur upon long-term COX-2 inhibition, as is required for cancer chemoprevention.

References

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