THE WOUND RESPONSE AS A KEY ELEMENT FOR AN UNDERSTANDING OF
MULTISTAGE CARCINOGENESIS IN SKIN

Friedrich Marks¹, Gerhard Fürstenberger¹, Michael Gschwendt¹, Michael Rogers¹, Bärbel Schurich¹, Bernd Kaina² and Georg Bauer³

¹German Cancer Research Center, Institute of Biochemistry, Heidelberg. ²Kernforschungszentrum (Nuclear Research Center), Karlsruhe. ³Institute of Medical Microbiology and Hygiene, University of Freiburg Federal Republic of Germany

INTRODUCTION

The general appearance of skin carcinoma is that of a steadily growing wound. Thus, Haddow's famous affirmation "the wound may be regarded as a tumor which heals itself"¹ may be also read the other way around, i.e. that a tumor may be regarded as a wound which does not heal. A huge amount of literature dealing with the assumed relationship between wound repair and carcinogenesis has indeed been accumulated (see ref. 1, 6). Only very recently, however, the methods of cell biology, biochemistry and molecular biology have reached a level where they enable the investigator to proof this relationship in clear-cut experimental approaches aiming at an understanding of the molecular mechanisms involved in both wound repair and carcinogenesis. One of the most exciting results of these novel approaches is the discovery that the majority of proto-oncogenes code for components of cellular pathways which are required for the transduction of growth-stimulating signals, especially of those provided by the peptide growth factors². While the physiological role of such growth factors is still not entirely understood, there is accumulating evidence indicating that at least some of them (such as EGF, TGFα, TGFβ, PDGF) may be involved in tissue repair and regeneration rather than in the control of everyday tissue growth³.

For the investigation of both wound repair and carcinogenesis, mouse skin represents one of the most advanced model systems. The reason for this is not only that skin is easy to manipulate and to observe, but also that the skin model offers the invaluable possibility of subdividing the process of tumor development into several defined stages. Under proper experimental conditions these stages can be induced by distinct manipulations or agents.

Presently at least 4 stages of skin carcinogenesis can be distinguished, i.e. initiation, conversion, promotion and malignant progression (Fig. 1). Although these stages are first of all operationally defined by special experimental set ups, recent research has opened several avenues leading to a better understanding of the underlying biological and molecular mechanisms. It is hoped that these investigations will result in the evaluation of new preventive and therapeutic measures.
Fig. 1. The stages of experimental carcinogenesis in mouse skin. Following initiation, papilloma development is induced by continuous growth stimulation resulting in clonal expansion of tumor cells (promotion). Papilloma growth can be promoted only if conversion has occurred within a certain period of time either prior to or after initiation. Using NMRI mice, initiation is carried out by "subthreshold" carcinogen (DMBA) treatment, conversion by limited applications (1-4x) of the phorbol ester TPA or by single wounding and promotion by continuous treatment with the phorbol ester RPA (once a week over a period of 16-20 weeks) or by repeated wounding. Under these conditions progression to malignancy occurs spontaneously in 10% of the papillomas within 8-10 months. The rate of progression is increased by carcinogen treatment of papilloma-bearing skin. From Marks and Fürstenberger.

Skin was the first and, until recently, the only tissue where a tumor-inducing effect of mechanical wounding could be unequivocally demonstrated. Recently, this phenomenon has been shown to be due to convertogenic and tumor-promoting effects of wounding.

THE STAGES OF EXPERIMENTAL SKIN CARCINOGENESIS (for a review see refs. 8-10)

Whether or not a distinct stage of skin carcinogenesis can be observed depends entirely on the experimental conditions employed, i.e. animal species and strain, tissue or cell type, agents used, regimen of treatment, time-point of observation etc.. Thus the experimental approach of multistage carcinogenesis appears to be highly artificial. This does not devaluate, however, its heuristic value as far as an understanding of carcinogenesis in general is concerned. To deal with misunderstandings which have been coming up again and again in the literature, it has to be emphasized that the multistage approach represents a model situation created to investigate mechanisms of tumor development in a reductionistic way rather than mimicking "spontaneous" carcinogenesis, i.e. the human situation.

Generally a multistage carcinogenesis experiment starts with initiation. This is achieved by (local or systemic) treatment of the animal with a carcinogenic agent, such as a polycyclic aromatic hydrocarbon, UV-light etc.. If a very low ("subthreshold") dose of a carcinogen is used, the animals will not develop tumors. It is thought that under such conditions latent (or "dormant") tumor cells are generated in the epidermis, but that latency period of tumor development starting from such cells surpasses the lifespan of the animal. The existence of latent tumor cells can be experimentally demonstrated by subsequent tumor induction occurring in the stages called conversion and promotion. The latent tumor cells generated during initiation survive over the whole lifespan of the animal. This indicates that they are either not subject to normal terminal differentiation or that initiation has occurred in a self-regenerating stem cell population of epidermis. Dormancy and persistence of initiated cells means that they have no proliferative advantage over the normal neighbour cells. When, in addition, their program of