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**_Mastomys coucha_: A Natural Animal Model to Study Papillomavirus-induced Skin Carcinogenesis**

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Human papillomaviruses (HPVs) are closely associated with human malignancies. Several HPV types infecting the genital mucosa are considered as tumour viruses causing cervical cancer. Also non melanoma skin cancer (NMSC) is correlated with certain HPV types, especially in patients under systemic immunosuppression. NMSC is the most frequent type of cancer in fair skinned population and represents a very cost intensive health problem, despite low mortality. The main risk factor for NMSC is UV-irradiation and the numbers of patients are increasing constantly due to prolonged sun-exposure. Although epidemiological data has been collected favouring the concept of a role of HPV in NMSC, most aspects of the virus-host interaction leading to malignancy are still elusive.

To understand the role of HPV infection in the development of NMSC, an adequate animal model is indispensable. The *Mastomys coucha* colony at the DKFZ is an excellent model system to study papillomavirus-induced skin carcinogenesis in molecular and immunological terms. These animals are unique in the spontaneous development of cutaneous tumours. From these lesions, the *Mastomys natalensis* papillomavirus (MnPV) was isolated and shown to be the aetiological agent. The animals not only develop lesions on the hairy skin, but also on transitional zones between stratified epithelium and mucosa as found at the anogenital tract. These lesions have a different morphology and a novel papillomavirus, called *Mastomys coucha* Papillomavirus 2 (McPV2) could be isolated therefrom during this project. To date, virally induced anogenital lesions have never been described in any animal model.

This finding allowed to compare the distribution of the different viruses, which are phylogenetically not related. Both viral DNAs were found in various organs and in most cases a mutual exclusion was observed. Very little is known about the interaction of two viruses within one host and the target cells infected, which can now be studied in detail in this model. Interestingly, MnPV DNA could be detected by *in situ* hybridisation in neuronal cells of the brain and many organs were positive by Southern blot and PCR analysis. However, transcription and production of viral progeny was restricted to the skin and tumours. These findings suggest that the dictum of a strict epitheliotropism must be revised.

Beside the characterisation of the model for further research, another aim of this project was to analyse the mode of action of an immunostimulatory compound (Imiquimod) in the treatment of NMSC. In our animals, local Imiquimod application lead to a reduced growth rate in spontaneous skin tumours and even to regression in a substantial number of animals with chemically induced lesions. From these experiments it can be concluded that Imiquimod stimulates the immune system to eliminate genetically altered cells, but this response is not sufficient to overcome the viral infection.

Based on these findings, further research is ongoing to analyse the transcription pattern of both viruses, their transcriptional regulation and the immune response towards infection with the aim to establish prophylactic and therapeutic vaccines.