The following aspects are mainly concentrated on in this Division:
- Identification and characterization of new papillomavirus types
- Functional analyses of cutaneous papillomavirus infections and their interaction with cellular factors
- Association of new and known viruses with the development of malignant tumors

In collaboration with: Dr. Nancy Kiviat, University of Washington, Seattle, USA; Dr. Rita Mulherkar, Mumbai, India; Dr. Charles Buck, Seattle USA; Prof. Dr. M. Löhr, Universitätsklinik Mannheim; PD Dr. H. Scherübl, Freie Universität Berlin; numerous university hospitals in Germany and abroad.

Identification and characterization of new papillomavirus types

E.-M. de Villiers

During the course of this report period we have identified 10 putative new papillomavirus types, mainly originating from cutaneous and oesophageal lesions. We have cloned the complete genomes of 2 of our previously identified putative new types and are in the process of sequencing these. In our capacity as Reference Center for Papillomaviruses, we have verified 8 cloned papillomavirus genomes as new/additional HPV types and distributed cloned HPV DNA to many laboratories worldwide.

We have initiated an epidemiological study in collaboration with Dr. Nancy Kiviat to determine the prevalence of papillomavirus infections in squamous and basal cell carcinomas of the skin, as well as the influence of UV radiation as measured by UV-induced p53 mutations. Both degenerate and consensus primers are applied in the amplification of DNA by the polymerase chain reaction, after which all products are cloned and sequenced. Preliminary data have already been obtained. We have, in addition, continued our analyses of biopsies from various organs for the presence of papillomavirus infections. Emphasis was mainly on oral carcinomas developing after betel nut chewing, on biopsies from the oesophagus in patients with a history of head and neck cancer and on early premalignant lesions of the nipple in patients with breast cancer.

Functional analyses of cutaneous papillomavirus infections

E.-M. de Villiers

Non-melanoma skin cancer is the most prevalent cancer amongst the Caucasian population worldwide. Ultraviolet light has been established as one of the factors involved in the etiology of this disease. Studies to examine the mechanistic aspects of the interaction between cutaneous papillomavirus infection and ultraviolet radiation have been continued. We could demonstrate that UV activated the promoter activities of certain types of papillomaviruses, whereas other types were inhibited. We furthermore demonstrated that the pro-inflammatory cytokines induced by UV-irradiation, influence the promoter activities of these HPV types and that the JNK pathway is involved. The presence of wild type p53 or mutant p53 plays an important role in this pathway (7, 12). Interaction of other cellular factors with the promoters of HPV 20 and HPV 27 are presently being analysed.

Association of new and known viruses with the development of malignant tumors

E.-M. de Villiers

We have screened 222 tumors of different origins for the presence of known tumorviruses. We used PCR to identify known and possibly new herpes viruses in these biopsies.
Although we were unable to identify any new herpesviruses, we demonstrated herpesvirus DNA in about 20% of the tumors, mainly in the aerodigestive tract. The relatively high prevalence of HHV-6 was surprising, as well as the simultaneous presence of multiple infections (up to 3 types) within one tumor. These tumors were also analysed for the presence of adeno-associated viruses (AAV) using consensus primers. The number of positive biopsies was very low, but we identified one new AAV type.

We subsequently also screened these tumors for the recently identified Circoviruses. The tumors of the digestive tract very frequently harbored these TT viruses in comparison to the other tumor types, although we cannot, at this stage, exclude the possibility that these viruses were present in the circulating blood. We identified more than 100 new types during the course of this investigation [5]. These studies were performed in collaboration with many hospitals, local and abroad. The complete genomes of 2 of these viruses have been isolated and sequenced. These studies are presently being extended to specific types of tumors in which TTV DNA was highly prevalent.

Studies investigating the extent to which papillomavirus infections lead to the induction of free-radicals have been initiated and are being extended to investigating the resulting influence on the cellular control functions.

**Oligonucleotide synthesis and sequencing (F0100)**

H. Delius

This unit synthesized oligonucleotides (ca. 6000 oligonucleotides annually) and performed sequencing of cloned DNA (ca. 9000 sequencing runs annually) as a service to other divisions of the DKFZ. In addition, sequencing methods were improved and developed.

The sequencing of papillomavirus genomes was extended to include the complete sequences of 3 bovine papillomavirus types.

Publications (* = external co-author)


