

Foreword

Perspectives of contemporary papillomavirus research

Although warts and papillomas have been noted since prehistoric times, their infectious nature has only been recognized at the turn of the past century [1,2]. The molecular analyses, the establishment of papillomavirus plurality, genome structure and organization, gene activity and their role in human cancers were intensively studied in the 1970s and 1980s. A major impetus for these studies originated from hypotheses postulating a role of members of this group in human cervical cancer [3–5] and from finding novel human papillomavirus (HPV) types in skin cancers of a rare hereditary condition, epidermodysplasia verruciformis [6]. The discovery of novel HPV types in cervical and other anogenital cancers [7,8] and their precursors [9,10] resulted in an enormous boost of activities and a rapid increase in HPV publications.

By the end of the 1980s, a substantial degree of knowledge had accumulated [11]:

- The DNA of specific HPV types (mainly of HPV-16) was consistently found in cervical cancer biopsies throughout the world;
- Transcripts of specific viral genes, E6 and E7, were expressed in virtually all of these cancers;
- The same genes were able to immortalized human anogenital epithelial cells (but also other cell types) upon transfection and to malignantly transform rodent cells;
- These genes were essential for the maintenance of the malignant phenotype of cervical cancer cells. Inhibition of their expression resulted either in senescence of the cancer cells or triggered apoptosis.

Thus, the available experimental data indicated already at that time that viral gene expression of latently infected cervical cancer cells is a necessary precondition for growth properties and malignant phenotype of these cells.

In the beginning of the 1990s, epidemiological studies impressively supported this concept and identified high risk HPV infections as the prime risk factor for cervical cancer [12,13]. Today it is firmly established that the so-called high risk HPV infections, particularly HPV-16, cause cervical cancer [11,14].

The identification of these potentially cancer-provoking virus infections paved the way for preventive vaccines against primary high risk HPV infections, intended to act as a vaccine

against specific cancers. The development of this vaccine was based on expression of HPV structural proteins in recombinant vector systems. These proteins, as initially shown for murine polyoma virus, form virus-like particles (VLP) [15]. The same technique used for animal papillomaviruses resulted in successful vaccinations against esophageal papillomatosis in cattle [16], against oral papillomatosis of dogs [17], and against experimental infection with cottontail rabbit papillomavirus [18]. Similar vaccines were developed against HPV types 16 and 18 and subsequently also against viruses causing genital warts, HPVs 6 and 11 [19–21]. Large scale clinical trials proved the preventive potential of these vaccines [22–24]. This provides the basis for the hope for a significant reduction of the rate of cervical cancer, provided a substantial percentage of the world's population will be vaccinated prior to their sexual debut.

This monograph summarizes competently the present state of HPV vaccines and screening in the prevention of cervical cancer. It provides an excellent background of epidemiological achievements, technical developments and recent advances in vaccine development and expectations of vaccine acceptability. Even future research needs following the licensure of VLP vaccines are being discussed. But outside of the vaccine field and the urgent need for the production of effective and inexpensive new generation vaccines and of all follow-up consequences of vaccination, how does a hopefully successful vaccine application affect fate and future directions of papillomavirus research? Are new priorities arising? What are the perspectives for future work in the HPV field? Is there a risk for decreased funding of HPV-related research projects after successful introduction of HPV vaccines? I feel the latter risk is real but unjustified.

Plenty of questions remain open, and some of them should have substantial impact on translational aspects concerning papillomavirus-linked carcinomas and premalignant lesions. There exists the need to better understand details of viral oncogene functions and of cellular signaling cascades interfering with high risk HPV functions. This should permit approaches to targeted therapy of premalignant and malignant tumors caused by these viruses. The role of high risk HPV in non-genital tumors (particularly of the oropharynx and respiratory tract) needs to be better defined. What are

host-mediated and hereditary factors contributing to persistent infections and the eventual development of malignant tumors?

Clearly, there exist needs to establish a role of cutaneous HPV infections in premalignant and malignant tumors of the skin. Is the prevention of apoptosis, as ascribed to functions of some of these infections, sufficient to explain a contribution of such infections to cell transformation? Is there a combined effect of these infections with physical (UV-light) or chemical carcinogens? Is there a specific role of low risk anogenital HPV (specifically HPVs 6 and 11) in verrucous carcinomas of the anogenital and respiratory tract? Do as yet undefined papillomavirus types exist playing a role in other human cancers?

These are just some of the questions widely open for future research. The present availability of vaccines against HPVs 16, 18, 6 and 11 is obviously one milestone in the prevention of these infections. Immunological interference with persisting infections and early premalignant lesions could be achieved within a foreseeable future. Papillomavirus research turned out to be one of the best examples of translational research in oncology from the bench of basic studies to clinical application with the perspective of preventing one of the major human cancers in women. In view of the complexity of this virus family, it could represent a tragic mistake if our funding agencies would not recognize the importance of support for continued studies in this field.

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