Editorial

Human Papillomavirus (HPV) and HPV-Associated Tumour Vaccines

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Human papillomaviruses were found to be closely associated with cervical cancer (CC) and some other, less common anogenital carcinomas, with genital warts (condyloma accuminata), cutaneous warts, epidermodysplasia verruciformis, laryngeal papillomas and, less frequently, also with oropharyngeal and particularly tonsillar carcinomas. Of more than 100 HPV types characterized until now, at least 11 have been classified as high-risk types and detected by molecular and immunological methods in human tumour tissue. The most important problems are connected with CC. Whereas in US the CC is the 11th most common cancer among women with an estimated 10,370 new cases and 3,710 deaths in 2005, worldwide and among women in developing countries where effective screening programmes are often lacking, CC is the second most common cancer and leading cause of cancer-related death (Steinbrook, 2006). For comparison, in the Czech Republic CC is the fifth most common cancer with 1,000–1,200 new cases per year.

Immunological intervention against high-risk HPV types can be envisaged at two levels, prophylactic and therapeutic (Bubeník, 2002a). Two prophylactic HPV vaccines are currently being tested in large-scale phase III clinical trials. Both are expected to provide protection against the two most common HPV types observed in CC, types 16 and 18.

GlaxoSmithKline developed a bivalent vaccine, CERVARIX, composed of virus-like particles (VLP) derived from HPV 16 and 18, and adjuvant ASO4 (Harper et al., 2004). The study included 1,113 women from 32 centres in USA, Canada and Brasil, aged 15-25 years. Vaccination with this vaccine was capable to protect completely against persistent infection with HPV 16 and 18, and almost completely (93.5 %) against pathological findings in cervical cytology. Merck & Co. developed a quadrivalent vaccine, GARDASIL, composed of VLP derived from HPV types 16, 18, 6, and 11 with a conventional alum adjuvant (Villa et al., 2005). The multicentric study performed with this vaccine in Brasil, USA and Europe involved 1,158 women, aged 16-23 years. The efficacy of this vaccine against development of pathological findings associated with the respective HPV types was 100 % and the ability of the vaccine to protect against persistent infection with the respective HPV types was 86-100 %. Since the tetravalent vaccine is also directed against the HPV types 6 and 11 associated with genital warts (condyloma accuminata), it also protects against their development.

It is generally accepted that HPV types 16 and 18 are responsible for approximately 70 % of CC and the HPV types 6 and 11 cause approximately 90 % of genital warts.

Both types of vaccines were shown to be safe, since the VLP consist of empty shells with viral structural proteins. The extremely high efficacy of prophylactic vaccines represents one of the highlights of vaccination in general and a perspective for eradication of CC and other HPV-associated neoplasms in the near future.

Whereas the prophylactic vaccines utilize the L1 structural protein of viral particles synthesized during the late period of the virus cycle, the therapeutic vaccines, which are being constructed in order to cope with CC that have already developed or are in the process of development, utilize two non-structural proteins encoded by the HPV genome, the late oncoproteins E6 and E7, products of the *E6/E7* oncogenes of the HPV virion. The E6/E7 oncoproteins are expressed in every CC, they are involved in the malignant conversion of the CC precursor cells, their presence is required for the maintenance of the malignant phenotype of CC, and, therefore, they are the target of choice for the construction of the therapeutic vaccines. The distinction between the prophylactic and therapeutic vaccines, however, is not too sharp and one type can be used to help the other. The prophylactic vaccines designed for prevention of HPV infections and eliciting immunity against type-specific late structural HPV protein L1 can also suppress virus replication in the individuals who were already infected, in this way preventing transformation of further target cells and decreasing tumour burden

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Abbreviations: HPV – human papillomavirus, CC – cervical carcinoma, VLP – virus-like particles

(Bubeník, 2002b), which is important for the success of therapeutic vaccination.

During the last decade, animal models have substantially contributed to the development of therapeutic vaccines against the high-risk HPV type 16-associated tumours. The E6/E7 oncoproteins, either in adjuvants or in the form of fusion proteins or VLP, could successfully be used for vaccination. Virus-based vectors and wild-type/mutated HPV 16 E6/E7 DNAs, either native or after linking to lysosome-associated membrane protein 1 (LAMP 1) that helps target the E6/E7 proteins to the endosomal/lysosomal cell compartment, were efficient. The HPV 16-positive tumour cells could be genetically modified with DNA encoding immunostimulatory cytokines or co-stimulatory molecules and then used for vaccination. The genetically modified tumour cells were found to be substantially more effective than the parental tumour cell vaccines. To improve HPV 16 antigen presentation in tumour-bearing individuals, dendritic cell-based vaccines loaded with HPV 16 E6/E7 antigen-containing tumour lysates, the relevant peptides, or E7 DNA have also been successfully employed (Bubeník, 2002a, b; Bubeník et al., 2003; Reiniš et al., 2006).

Unfortunately, when these encouraging approaches used in the animal models were translated into clinical trials, the results were less optimistic (Boursnell et al., 1996, Tamm-Hermelink et al., 1999; Kaufmann et al., 2002; Smyth et al., 2004). Many problems are still to be faced before therapeutic vaccines against HPV-associated tumours can be designed and approved for clinical purposes. In contrast, the prophylactic GlaxoSmithKline bivalent vaccine CERVARIX and the Merck quadrivalent vaccine GARDASIL, which are expected to be comercially available in some countries for vaccination against high-risk HPV types at the end of this year, represent a perspective for eradication of at least some HPV-associated human neoplasms in the near future.

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