Chapter 3
Apoptosis in Carcinogenesis and Chemotherapy of the Uterine Cervix

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Abstract The development of cervical cancer is tightly linked to Human papillomavirus (HPV) infection. The expression of HPV oncogenes, notably E6 and E7 disturbs the coordinate regulation of cell cycle and apoptosis. By interfering with these cell processes HPV oncoproteins cause cancer precursor lesions that may progress to invasive cancer. Treatment of invasive cancer is successful with surgery or chemoradiotherapy in early stage disease. If the cancer is metastatic or the cancer recurs after primary therapy, the patients are usually treated with cisplatin based chemotherapy, but the impact to survival is poor. Chemotherapy represses the transcription of E6/E7 and this DNA damaging stress can activate p53 tumor suppressor in cervical cancer cells, where its function is abrogated by E6 in non-stress conditions. p53 can trigger apoptosis as a result of chemotherapy or it can induce DNA repair and inhibit proliferation by arresting cell cycle progression. Due to its central role in the development of cancer, maintenance of transformed phenotype or response to therapy, E6/E7 oncogenes are unique targets for novel therapeutic strategies. RNA interference has evolved from the recent studies as the most promising targeted therapy approach. This review will summarize the present central knowledge of the role of HPV and apoptosis in the carcinogenesis and responses to current treatment modalities of cervical cancer and will view perspectives for therapies aiming to downregulate HPV oncogene expressions.

Keywords Apoptosis · Cervical cancer · Chemotherapy · Human papillomavirus · p53

Introduction

Cervical cancer is the second most common malignancy in women worldwide after breast cancer. Each year, approximately 480,000 new cases are diagnosed, and the death toll is nearly 300,000 lives (Bosch and de Sanjose, 2003). Cervical cancer is...
a major cause of cancer-related morbidity and mortality among women, especially in developing countries that lack efficient screening programs and adequate health care system. In the last three decades a substantial body of evidence has accumulated showing that genital human papillomavirus (HPV) infection plays a critical role in the pathogenesis of both squamous and adenocarcinoma of the cervix (zur Hausen, 2002). The development of the cancer is a multistep process that involves cervical mucosal cell transformation by oncogenic E6 and E7 proteins. E7 inactivates the cell cycle regulator pRb inhibiting cell cycle arrest while E6 inactivates the tumor suppressor protein p53, the main regulator of apoptosis (Dyson et al., 1989a; Hubbert et al., 1992; Huibregtse et al., 1993). HPV infection alone is unable to cause cancer. Only a small fraction of the patients will develop invasive disease (Steben and Duarte-Franco, 2007). The host immune defense plays a pivotal role in the clearance from the virus. This is compellingly shown in the recent studies using preventing vaccines developed against the L2 capsid protein. In these studies nearly a 100% prevention against cervical cancer precursor lesions was achieved (Stanley, 2007). In case of viral persistence and possible viral integration to the host DNA, genomic instability with chromosomal alterations occur leading to severe cell cycle perturbation, clonal outgrowth and ultimately invasive cancer. The research efforts during the last two decades have paved the way for the efforts to develop targeted therapy particularly against high risk HPV E6. Still today, surgery, radiation and chemotherapy remain the mainstays of the treatment. It appears that the genotoxic treatment in the foreseeable future will remain in the treatment in different combinations like chemoradiation or different chemotherapy drug combinations, but an interesting possibility will be to use them together with E6 silencing therapies.

Cervical Cancer Carcinogenesis and Apoptosis

Initial Events in HPV Carcinogenesis

Human papillomaviruses are small, double-stranded DNA viruses that infect mucosal or cutaneous surfaces, causing warts or epithelial tumors. About one third of the over 100 virus types identified thus far are specific for epithelia of the lower anogenital tract. These can be divided into two groups: the “low risk” HPVs such as types 6 and 11, which are rarely found in malignant tumors but induce benign genital warts, and the “high risk” HPVs such as 16, 18, 31 and 45, which are frequently found in cervical carcinoma and are regarded as etiologic agents for both cervical cancer and its precursors. The cancer develops from well-defined precursor lesions referred to as squamous intraepithelial lesions. The first step in an HPV infection appears to be the access of the HPV to basal or parabasal cells as a consequence of microtrauma (Giroglou et al., 2001). For an active infection to take place, the virus must have entry to the generative compartment of the epithelium, capable of mitotic division. This is thought to be the principal reason why the squamocolumnar junction of the uterine cervix is so often involved in HPV infections (Fig. 3.1). In this