SPONTANEOUSLY INDUCED CELLULAR IMMUNITY TO HPV-16/18 AND THE THERAPEUTIC VACCINATION OF PATIENTS WITH HPV-16/18 (PRE-)MALIGNANT LESIONS

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Cervical carcinomas arises as result of an uncontrolled persistent infection with a high-risk type of human papillomavirus, in particular types 16 (HPV-16) and 18 (HPV-18) that account for approximately two-third of these cancers. The HPV E6 and E7 proteins play a pivotal role in carcinogenesis and are expressed in both pre-malignant and advanced cervical lesions. Because HPV proteins are foreign to the body, one would expect the immune system to mount a response against these antigens when expressed in the cervical epithelium. Indeed, circulating HPV-16 E6, E7 and E2-specific Th1- and Th2-type CD4+ T-cells, able to migrate into the skin upon antigenic challenge, were frequently detected in healthy individuals (1–5), showing that successful defense against HPV-16 infection is commonly associated with the installment of a systemic effector T-cell response against these viral antigens. In contrast, the development of high-risk HPV-positive cervical cancer is associated with a HPV-specific T-cell response that fails at least at three different levels. In about half of the patients, PBMC lack the capacity to mount a detectable proliferative response against HPV-16 E6, E7 and E2, whereas the other half displayed antigen-specific proliferative responses exhibiting a non-inflammatory cytokine profile (6). Analysis of the local immune response revealed that in many cases HPV-specific effector T-cells failed to home to the tumors or to infiltrate the cancer cell nests (7, 8). Furthermore, we recently demonstrated that HPV E6- and E7-specific CD4+ regulatory T-cells can be isolated from lymph node biopsies of cervical cancer patients and, moreover, that such T-cells can infiltrate tumors, suggesting that anti-tumor immunity in cervical cancer patients is suppressed at both the induction and effector level (9). Notably, the viral antigens concerned are the prime components of all therapeutic vaccines against cervical cancer that are currently under development (10, 11). Although such vaccines are designed to enhance CD4+ and CD8+ T-cell effector immunity against the E6 and E7 oncoproteins of HPV-16 and/or -18, the presence of pre-existing E6 and E7-specific CD4+ regulatory T-cells in lymph nodes and tumors from cervical cancer patients brings forward the possibility that vaccination might also – or instead – result in activation and expansion of this regulatory T-cell subset. Indeed we observed that in addition to the expansion of HPV-16-specific CD4+ effector T-cells (12–13) also a population of HPV-16-specific CD4+Foxp3 regulatory T-cells expanded after vaccination (13). Our data indicate that strategies to eliminate or disarm regulatory T-cells prior to vaccination, which are now widely considered in the context of modalities that aim at inducing effective immune responses against tumor-associated auto-antigens, should also be considered for immunotherapic strategies against cancers with viral etiology.

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