Review

Cell cycle alterations in endometrial carcinoma

Alessandro Bovicelli[1,2] Giuseppina D'Andrilli[2] and Antonio Giordano[2,3]

ABSTRACT

Endometrial carcinoma is the most common gynecological malignancy in Western countries and it is important to determine the genetic variants associated with disease since the genetic basis is poorly understood. Several molecular biological characteristics have been studied for their potential value in patient management.

Deregulation of the control mechanisms of the cell cycle can initiate carcinogenesis, and play a role in progression to cancer. This review describes the current state of knowledge about the alterations of cell-cycle regulations in the context of p53 pathway, RB pathway, and p27 pathway in endometrial carcinoma.

Keywords: ***cell cycle, endometrium, endometrial neoplasms, tumor suppressor genes***

Introduction

Endometrial cancer is the most common type of uterine cancer. Although the exact cause of endometrial cancer is unknown, increased levels of estrogen appear to play a role. Estrogen helps stimulate the buildup of the lining of the uterus. Studies have shown that high levels of estrogen in animals results in excessive endometrial growth and cancer. Estrogen and its metabolites have been associated with an increased risk of developing endometrial cancer due to their ability to cause DNA damaging events[1], therefore cell cycle control is integral for the recognition, repair and/or elimination of DNA damage to prevent the initiation of cancer. Most cases of endometrial cancer occur between the ages of 60 and 70 years, but a few cases may occur before age 40 (Cancer Fact & Figures 2008). The regulatory pathways controlling cell cycle phases include several oncogenes and tumor suppressor genes which display a range of abnormalities with potential usefulness as markers of evolution or treatment response in cancer. It is conceivable that most endometrial cancers occur as a result of acquired alterations in oncogenes and tumor suppressor genes that regulate signal transduction pathways involved in cell proliferation and differentiation, as well as in cell cycle control. There have been many reports indicating that the deregulation of p21WAF1 is related to carcinogenesis and the development of various tumors. p21WAF1 (p21) and p27KIP1 (p27) are both universal inhibitors of cyclin-dependent kinases and can therefore influence cell cycle or tumor progression.

The tumor suppressor gene p53 is a gene associated with many cancers that was identified by searching for loss of heterozygosity. RB is the first tumor suppressor gene cloned; it is the defective gene in retinoblastoma. Alterations in the retinoblastoma gene family (RB and RB2/p130) are common in human neoplasia.

p53 pathway

Alterations of the p53 gene have been widely suggested to be relevant to the development of endometrial carcinoma. However, contradictory results have been reported when immunohistochemical determination of p53 expression has been correlated with stage and histological features of the tumors. In a series of 240 endometrial carcinoma, p53 immunostaining did not differ between cases with different FIGO stages or histologic characteristics of the tumors. No relationship exists between the immunohistochemical determination of p53 expression and the biological aggressiveness of endometrial carcinomas.[2]

Buchynska et al. investigated the correlation links between expression level of protein p53, p21(WAF1/CIP1), p16(INK4) and proliferative potential in human endometrial adenocarcinoma (EC). The data showed that endometrial malignant tumors possess high proliferative activity, overexpression of p53 and high expression of p21(WAF1/CIP1). In low differentiated endometrial adenocarcinomas the highest level of Ki-67, p53 and p21(WAF1/CIP1) expression and lowest content of p16(INK4) protein were observed. The authors suggest that abnormalities of proliferation regulation in endometrial tumors may be connected with accumulation of mutant p53 protein, its disability to transactivate such target genes as p21, with changes in expression of p16 protein. The authors concluded that the indicated markers may be used along with traditional morphological and clinical characteristics for diagnosis of endometrial neoplasia.[3]

A recent study explored the expression of cell cycle proteins in normal, premalignant and malignant endometrial lesions representing the morphologically well defined stepwise model of human endometrial carcinogenesis. Paraffin-embedded specimens from inactive endometrium (n = 16), endometrial hyperplasia (n = 23) and endometrioid endometrial carcinoma (n = 39) were stained immunohistochemically for cyclin A, cyclin B1, cyclin D1, cyclin E, cdk2, p16, p21, p27, p53 and Ki67(MIB-1). Differences in expression between the tissues, and correlation with classical prognostic factors for the carcinomas were analysed. Expression of cyclin A and Ki67 gradually increased from normal tissue through hyperplasia to carcinoma, indicating that proliferation increases over the carcinogenetic spectrum. cdk2, p16 and p21 gradually increased from normal tissue through hyperplasia to carcinoma, indicating their potential importance in both early and late carcinogenesis. Cyclin D1, cyclin E and p53 especially increased and p27

[1]Department of Gynecologic, Obstetric and Pediatric Sciences, Sant'Orsola Hospital, University of Bologna, Italy

[2]Sbarro Institute for Cancer Research and Molecular Medicine, Dept. of Biology, College of Science and Technology, Temple University, Philadelphia,USA

[3]Department of Human Pathology and Oncology, University of Siena, Italy

Corresponding author:
Alessandro Bovicelli, M.D., Ph.D.
Department of Gynecologic, Obstetric, and Pediatric Sciences, Sant'Orsola Hospital, University of Bologna, Via Massarenti 13, 40138 Bologna, Italy
Telephone: 051-399520; Fax: 051-304751
E-mail: alessandrobovicelli@yahoo.it