MOLECULAR MARKERS OF APOPTOSIS AS PROGNOSTIC INDICATORS IN CANCER

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The practice of oncology would become more fulfilling if physicians could predict which of their patients will develop cancer and, if disease does occur, to determine who might remain disease-free after appropriate treatment. Although that era has not yet arrived, the currently available clinical tests provide information for physicians to make patients outcome predictions by combining different predictive factors. A predictive factor predicts an outcome (risk of disease, existence of disease, or prognosis) by virtue of its relationship with the disease process that causes the outcome. If the variable predicts the outcome with sufficient accuracy (where “sufficient” varies with the question being addressed) in a specific model, it is called a predictive factor. There are three types of predictive factors: risk, diagnostic and prognostic. They differ in their outcomes and predictive power. For risk and diagnostic factors the main outcome of interest is incidence of disease; for prognostic factors the main outcome of interest is death. A factor is rarely a strong predictor in isolation from other prognostic factors. Because of disregulation of apoptosis in cancer, studies that define the potential apoptotic markers to serve as prognostic or predictive factors in cancer are of critical importance. Defects in the processes controlling apoptosis can extend cell life span through neoplastic cell expansion independently of cell division. In addition, they contribute to carcinogenesis by creating a permissive environment for genetic instability and accumulation of gene mutations, promoting resistance to immune-based destruction, and allowing disobedience of cell cycle checkpoints that would normally induce apoptosis. These defects can also facilitate growth factor/hormone-independent cell survival, support anchorage-independent cell survival during metastasis, reduce dependence on oxygen and nutrients, and confer resistance to cytotoxic anticancer drugs and radiation. Elucidation of the genes that constitute the core machinery of apoptosis pathway has provided new insights into tumor biology, revealing novel strategies for detecting and combating cancer. Apoptotic and proliferative indices and/or expression of critical apoptotic markers like p53 or Bcl-2 family members have been extensively evaluated as prognostic markers for women with newly diagnosed breast cancer. The p53 protein is thought to act as a tumor suppressor either by inducing G1 arrest or by inducing apoptosis. Aberrant p53 expression is found in 20-50% of breast cancers, depending on the method of detection. Most studies suggest that the presence of mutant p53 is correlated with other poor prognostic factors such as high S-phase fraction and mitotic index, high tumor grade, tumor necrosis, aneuploidy, p65 expression, and lack of steroid receptors. Its value, however, as an independent prognostic
factor for recurrence or survival is still uncertain. The prognostic value of Bcl-2 and Bax protein expression in cancer has also been extensively studied. In breast cancer, Bcl-2 expression is associated with the presence of estrogen receptor, wild-type p53, lower grade histology, low proliferative index, and Bax expression. It is inversely correlated with EGFR, HER-2, and p21 expression. However, studies linking Bcl-2 expression with lymph node status have given mixed results. Again, work to date does not adequately address whether Bcl-2 and/or Bax expression is an independent prognostic factor for relapse or death. Since the apoptotic cells can be counted with good reproducibility in H&E-stained tumor sections, the apoptotic index, i.e., the number of apoptotic cells per mm², may also be used as an additional prognostic indicator in invasive breast cancer. Mutations of tumor suppressor gene p53 have been found in a variety of cancers, including urologic neoplasms. The overwhelming bulk of evidence suggests that the frequency of p53 abnormalities does increase with disease progression and is highest in tissues from patients with hormone refractory prostate cancer. Focal p53 expression in the primary tumor by immunohistochemistry is predictive of cancer recurrence after radical prostatectomy. Overexpression of Bcl-2 protein by immunohistochemistry has been commonly detected in advanced hormone refractory prostate cancer. Ki-67 is an antigen of cellular proliferation. Unlike the results with p53 and Bcl-2, Ki-67 protein expression was not an independent prognostic marker for cancer recurrence after radical prostatectomy. However, recent results strongly suggest that the Ki-67 labeling index and the apoptotic index have very similar clinical significance reflecting the existence of biologically aggressive phenotypes and poor disease-free survival rate in hepatocellular carcinomas. It was also shown that apoptosis and proliferative activity are positively correlated in colorectal cancer. Some studies suggest that apoptotic regulation in colorectal cancer may function independently of Bcl-2 and p53, while other studies indicate the existence of both a p53 dependent as well as an independent apoptotic pathway in colorectal cancer. The importance of p53 mutations in the pathogenesis of human lung carcinoma is well established, but it is still controversial whether the presence of p53 mutations or overexpression of p53 protein adversely affects an individual patient's chances of survival. Recent data suggest that the type of p53 mutation is important in prediction of outcome in early stage non-small cell lung carcinoma patients, whereas immunohistochemical staining for abnormal p53 gene products is not predictive. The apoptotic markers may also be useful in chemoprevention studies. We revealed the positive correlation between apoptosis and proliferation in benz[a]pyrene-induced mouse lung tumorigenesis as well as modulation of apoptotic and proliferation markers by dietary calcium D-glucarate. In conclusion, more research is needed to assess new biomarkers of apoptosis as prognostic indicators in cancer and most importantly, to standardize the methodology for sampling and assaying biomarkers in heterogenous and multifocal cancers.