Current view

Antibodies against the carcinoembryonic antigen in the sera of colon cancer patients. Their biological significance

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INTRODUCTION

Until recently it was not known whether CEA can evoke an antibody response in the tumor bearing host. In 1967, Gold,[1] mentioned the existence of circulating antibodies against CEA in patients with digestive system cancers and in pregnant women. This was challenged by a number of researchers who claimed that these anti-CEA antibodies are actually anti-blood group antibodies or antibodies of low specificity.[1-4] However, recently, the presence of anti-CEA antibodies has been described in a large number of colon cancer patients. These antibodies were found to be of high specificity and to have a high titer in the sera of cancer patients, although their prognostic significance remained unknown.[3,4]

THE CARCINOEMBRYONIC ANTIGEN (CEA)

Carcinoembryonic antigen (CEA) is a glycoprotein initially isolated by Gold and Freedman in 1965.[5] Its molecular weight is 180,000 dalton. It has a high carbohydrate content (~40,75%), while it contains multiple immunoglobulin domains.[6] CEA is a cell adhesion molecule and a member of a large, closely related family of molecules sharing many common epitopes.[7,8] CEA is capable of binding to an 80 Kb Kupffer cell receptor by the peptide sequence PELPK and stimulates cytokine production. Cytokines induce sinusoidal endothelial cells to express intercellular adhesion molecules and increase the adhesion of the tumor cells.[9] Recent studies in rodents have shown that CEA may be directly involved in the malignant transformation process by blocking the terminal differentiation in rodent myoblasts in vitro. Additionally, tumor released CEA is believed to be one of the factors involved in cancer metastases.[10] In order to avoid the effects of the excessive CEA concentration observed in patients with certain malignancies, a number of studies have designed aiming the minimization of the CEA concentration in the blood circulation. Trials up to now have concentrated on the chemical synthesis of antibodies or parts of antibodies (mABs or Fabs) which would be able to recognize and destroy the CEA molecules in the circulation and therefore prevent the spreading of the tumor cells.[10-12]

CEA is overexpressed in a wide variety of human malignancies, including colon cancer.[13,14] Elevated CEA levels have also been reported in a small percentage of patients with non-malignant diseases of the colon, liver, pancreas and lungs.[2,15] Although a large number of patients with cancer of the large bowel have elevated serum CEA levels, serum CEA level may be normal in many colon cancer patients, especially at early disease stages of the disease.[18]

ANTIBODIES AGAINST THE CARCINOEMBRYONIC ANTIGEN

Although CEA is a valid tumor marker for the follow up of colon cancer patients, its use in diagnosis is limited due to its frequent elevation in a number of non-neoplastic disorders.[14,16] Additionally there is a significant number of colon cancer patients with no detectable blood CEA levels.[3,16,18]

Albanopoulos et al[19] recently reported, after they examined 58 colon cancer patients, that a large number had detectable amounts of circulating IgG and or IgM

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anti-CEA antibodies in their sera. The presence of IgG anti-CEA antibodies did not statistically correlate with better survival. Still, they reported that patients with antiCEA IgG antibodies in their sera had a better survival rate after the first 8 months of the follow up compared to those patients who were anti-CEA negative. Hence, there is always the possibility of achieving a statistically significant difference if a larger number of patients were examined and followed for a longer period of time. They also reported that patients with IgM anti-CEA antibodies in their sera, had a statistically significant better two-year survival, compared with the rest of the patients. Furthermore, in the multivariate statistical analysis, it was determined that IgM anti-CEA antibodies, together with stage were the only independent prognostic factors. This indicates that these antibodies may represent a useful marker of the immune response of the patient. Patients with a normal, functional immune system produce anti-CEA antibodies and have prolonged survival.

Patients with normal CEA levels may have increased anti-CEA IgG and/or IgM antibody concentrations in their sera. The presence of anti-CEA antibodies in these patients may be due to the lack of release of CEA from the tumor, into the circulation, while the immune cells are exposed to non-circulating antigens by direct contacting with the tumor.

According to the literature, almost two thirds of the patients with colon cancer have elevated CEA levels in their sera. This, though, has been the case in previous studies with colon cancer patients of Greek and some other nationalities, and may be due to genetic variations in the CEA-producing gene.[4,15,20,21] For this reason anti-CEA antibodies may be an even more useful tumor marker in populations with different phenotypes.

Anti-CEA antibodies can also be found in a small number of healthy individuals. This prohibits their use as a conventional tumor marker. Their presence in healthy individuals could be due to a prior antigenic exposure of the three positive controls, to CEA releasing malignancies, immunosurveilance.

CONCLUSIONS

Circulating anti-CEA antibodies, especially of the M isotype, in colon cancer patients, correlates with a better survival. Furthermore, the IgM antiCEA antibodies apart from being associated with better prognosis in patients with colon cancer, can also be used as an independent prognostic factor. These findings indicate the biological significance of these antibodies in colon cancer patients.

Further studies are required for the determination of the biological mechanism that leads to the generation of the anti-CEA antibodies in some healthy individuals, and their correlation with other markers of the immune status of cancer patients.

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