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Mini-array of multiple tumor-associated antigens to enhance autoantibody detection for immunodiagnosis of hepatocellular carcinoma

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Abstract

Liver cancer, especially hepatocellular carcinoma (HCC), is particularly prevalent in Africa and Asia. HCC affects the Hispanic population of the United States at a rate double that of the white population. The majority of people with HCC will die within 1 year of its detection. This high case-fatality rate can in part be attributed to lack of diagnostic methods that allow early detection. How to establish a methodology to identify the high-risk individuals for HCC remains to be investigated. The multi-factorial and multi-step nature in the molecular pathogenesis of human cancers must be taken into account in both the design and interpretation of studies to identify markers which will be useful for early detection of cancer. Our recent studies demonstrated that a mini-array of multiple tumor-associated antigens (TAAs) might enhance autoantibody detection for diagnosis of HCC, especially for the alpha fetoprotein (AFP)-negative cases. It also suggested that different types of cancer might require different panels of TAAs to achieve the sensitivity and specificity required to make immunodiagnosis a feasible adjunct to tumor diagnosis.

Keywords: Tumor-associated antigen; Autoantibody; Immunodiagnosis; Hepatocellular carcinoma

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1. Introduction

Studies in autoimmune diseases have provided abundant evidence suggesting that the autoantibodies are antigen-driven responses and that autoantibodies can be viewed as reporters from the immune system revealing the identity of antigens which might be playing roles in the pathophysiology of the disease process [1]. The highly specific autoantibody response in systemic autoimmune disease generally predicts the biologic phenotype of the disease, making autoantibodies clinically valuable and diagnostically useful. Whether a similar mechanism is operating in the humoral immune response in cancer remains to be established, but appears to be a possibility. Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide, particularly prevalent in Africa and Asia. The majority of people with HCC will die within 1 year of its detection. This high case-fatality rate can in part be attributed to lack of diagnostic methods that allow early detection. How to establish a methodology to identify the high-risk individuals for HCC remains to be investigated. Although serum alpha fetoprotein (AFP) is the most effective marker available to detect HCC, the sensitivity and specificity is not optimal, especially in patients with small tumor or in well- to moderately-differentiated HCC cases. Therefore, there is a need for the development of more sensitive and specific methods that supplement AFP in the early detection of this cancer. The purpose of this review was not mainly directed at addressing the methodology of identification of TAAs in HCC. The review will focus on the recent advances in our studies primarily associated with the idea and possibility that a mini-array of multiple TAAs can be used for immunodiagnosis of HCC.

2. Tumor-associated antigens (TAAs)

Many studies demonstrated that cancer sera contain antibodies which react with a unique group of autologous cellular antigens called tumor-associated antigens (TAAs) [1–3]. One of the most extensively studied TAAs is p53, the tumor suppressor protein. Autoantibodies to p53 in cancer were first reported in 1982 [4] and since then there have been numerous reports confirming and extending this finding [reviewed in [5]]. The types of cellular proteins which induce autoantibody responses are quite varied and include oncogene products such as HER-2/neu [6], cellular proteins which shield mRNAs from natural physiological degradation such as p62 [7] and CRD-BP [8], onconeural antigens in the paraneoplastic disorder syndromes [9], differentiation-antigens such as tyrosinase and the cancer/testis antigens [10]. Factors leading to the production of such autoantibodies are not completely understood but the available data show that many of the target antigens are cellular proteins whose aberrant regulation or overexpression could lead to tumorigenesis, such as p53 [4,5], HER-2/neu [6] and CENP-F [11], or are proteins whose dysregulation could have tumorigenic potential including mRNA binding proteins such as p62 [7] and cell-cycle control proteins such as cyclin B1 [12]. A highly informative study showed that lung tumors contained several types of p53 gene mutations including missense, stop codon and frameshift mutations, but it was the missense mutations with overexpression of protein which altered function and increased stability that correlated with antibody production [13]. In the case of p62 which is a fetal protein absent in adult tissues, immunogenicity appears to be related to abnormal expression of p62 in tumor cells [14] and with the onconeural antigens in paraneoplastic neurological disorders, antibody responses are thought to be related to ectopic expression of neuron-restricted cellular proteins in tumor cells [9]. The immune system in certain cancer patients appears to have the capability of sensing these abnormalities and it was proposed that autoantibodies might be regarded as reporters identifying aberrant cellular mechanisms in tumorigenesis [1]. In recent years there have been a steadily increasing number of studies describing and characterizing autoantibodies in cancer. Research on antibody immunity to cancer-associated proteins has received great attention. As the detection of antibody immunity to tumor antigens becomes more routinary, investigators have evolved to begin to address specific clinical questions such as the role of antibody immunity as a marker for patients exposed to cancer, as a tool to monitor therapy, or as an indicator of disease prognosis.

3. Identification of TAAs

The approach which we have used in the identification of putative TAAs has involved initially examining the sera from cancer patients using extracts of tissue culture cells as source of antigens in Western blotting and by indirect immunofluorescence on whole cells. With these two techniques, we identify sera which have high-titer fluorescent staining or strong signals to cell extracts on Western blotting and subsequently use the antibodies in these sera to isolate cDNA clones from cDNA expression libraries. In this manner, several novel TAAs including HCC1 [15], SG2NA [16], CENP-F [17], p62 [7] and p90 [18] have been identified. Several novel as well as previously defined tumor antigens have been recently identified with autoantibodies from patients with different types of cancer [3] using a methodology called SEREX (serological analysis of