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Review

Autoantibodies to tumor-associated antigens as biomarkers in cancer immunodiagnosis

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ABSTRACT

Cancer sera contain antibodies that react with a unique group of autologous cellular antigens called tumor-associated antigens (TAAs), and therefore these autoantibodies can be considered as reporters from the immune system, to identify authentic TAAs involved in the malignant transformation. Once a TAA is identified, different approaches would be used to comprehensively characterize and validate the identified TAA/anti-TAA systems that are potential biomarkers in cancer immunodiagnosis. In this manner, several novel TAAs such as p62 and p90 have been identified in our previous studies. p62, a member of IGF-II mRNA binding proteins (IMPs), is an oncofetal protein absent in adult tissues, the presence of anti-p62 autoantibodies relates to abnormal expression of p62 in tumor cells. p90 was recently characterized as an inhibitor of the tumor suppressor PP2A (protein phosphatase 2A), and an autoantibody to p90 appears in high frequency in prostate cancer. The present review will focus on the recent advances in studies mainly associated with these two novel TAAs as biomarkers in cancer immunodiagnosis.

Contents

1. Introduction

Many studies demonstrated that the immune system can recognize the antigenic changes in cancer cells, and further develop autoantibodies against these cellular antigens that have been generally called tumor-associated antigens (TAAs). Therefore, these cancer-associated autoantibodies might be considered as "reporters" from the immune system, to identify the antigenic changes in cellular proteins involved in the transformation process [1–3]. There has been a growing interest in using serum autoantibodies against TAAs as biomarkers in cancer immunodiagnosis. The major reason is that these antibodies are generally absent, or present in very low titers, in normal individuals and in non-cancer conditions [3]. Their persistence and stability in the serum of cancer patients is an advantage over other potential markers, including the TAAs themselves, some of which are released by tumors but rapidly degrade or are cleared after circulating in the serum for a limited time [4]. Furthermore, the widespread availability of methods and reagents to detect serum autoantibodies facilitates their characterization in cancer patients and assay development.

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The definition of what constitutes a TAA is a major issue in the field of cancer immunodiagnosis. It is erroneous to include all cellular antigens identified by autoantibodies in cancer sera as TAAs since some autoantibodies may exist in conditions that pre-date malignancy. This was particularly evident in several studies of subjects with liver cancer where serial serum samples were available several years before malignancy when these subjects had conditions such as chronic hepatitis and liver cirrhosis [5–11]. Autoantibodies to cellular components were readily detected by Western blotting during the pre-malignant conditions of chronic hepatitis and liver cirrhosis but the interesting observation was that coincident with or closely preceding the clinical detection of liver cancer, novel autoantibodies were detected in Western blotting and by immunofluorescence assay. In cases where the novel antigen–antibody systems were characterized, many antigens turned out to be cellular components that have been described to be aberrantly expressed in cancer. Failing to recognize the likelihood of pre-malignancy circulating antibodies would result in the inclusion of many antigens erroneously as TAAs, especially if serum drawn at one time point from a cancer subject was used to characterize the antigens since this might include both cancer-related and unrelated antigens. Our work to identify authentic TAAs has been influenced by several observations. Some of the cellular proteins identified by cancer autoantibodies were initially of unknown function but eventually were shown to be involved in tumorigenesis pathways. The identification and characterization of two novel TAAs p62 and p90 are examples of this kind of studies. This review will focus on the recent advances in studies mainly associated with p62 and p90 as biomarkers in cancer immunodiagnosis.

2. p62, a member of IGF-II mRNA binding protein family

As shown in Fig. 1, while analyzing a group of sera from hepatocellular carcinoma (HCC) patients originating from China, it was observed in Western blotting that a number of these sera were reactive with a protein which blotted in the region of 62 kDa [11]. This 62 kDa protein appeared to be expressed in high abundance in a T24 (bladder carcinoma) cell line and in a HepG2 (liver cancer) cell line, whereas the expression was low in a MOLT-4 (T-lymphocyte) cell line. Serum from a patient with high antibody titer to the 62 kDa protein was used to immunoscreen a T24 cDNA expression library and ultimately, a full-length clone was isolated. When the nucleotide sequence for p62 was first identified, it was shown to be a novel unreported gene. Of great interest was the findings that the deduced amino acid sequence of p62 was highly homologous to a family of mRNA binding proteins such as human Koc (k-homolog protein overexpressed in cancer) [12] and chicken ZBP1 (β-actin mRNA zipcode-binding protein) [13]. This family of proteins has distinct structural characteristics, with a consensus RNA binding region called the RNA recognition motif in the N-terminal region and four hnRNP K homology (KH) domains in the C-terminal half of the proteins. A feature which appears to be possessed in common by all members of this family is that they are mRNA binding proteins (see Table 1).

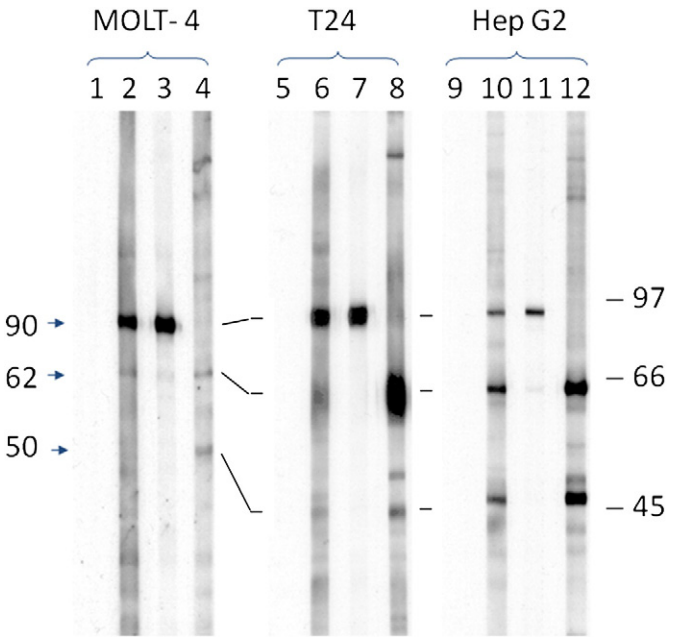

Fig. 1. Reactivity of three HCC sera in Western blotting against whole cell extracts from MOLT-4, T24, and HepG2 cell lines. Lanes 1, 5, and 9 were normal human sera. One HCC serum (lanes 2, 6, and 10) showed strong reactivity with a 90-kDa protein in MOLT-4 cells and reacted weakly with a 62-kDa protein in MOLT-4 cells and T24 cell extracts. A strong reaction with the 62-kDa protein was detected with HepG2 cell extracts, together with a strong reaction with a 50-kDa protein. The second serum (lanes 3, 7, and 11) and the third one (lanes 4, 8, and 12) demonstrate other types of reactions. These representative data demonstrate that HCC sera are heterogeneous in their antibody repertoires and that different cell lines apparently have different expressions of 90-, 62-, and 50-kDa proteins.

While our paper was in press, Nielsen et al. reported on a family of three proteins that bind to the 5′-untranslated region of leader 3 IGF-II mRNA, which is developmentally regulated and expressed in the fetus but undetectable in adult tissues [14]. These IGF-II mRNA binding proteins (IMPs), which they called IMP 1, 2 and 3 all contained the same RNP consensus sequence and KH motifs. IGF-II mRNA binding by p62 and Koc (IMP2 splice variant and IMP3, respectively) is especially interesting with regard to the possible relationship to cancer. IGF-II has been shown to be overexpressed in many cancers and one of the earliest demonstrations was its overexpression in human hepatocellular carcinoma [15,16]. An inherited disorder called the Beckwith–Wiedemann Syndrome is associated with IGF-II overexpression, and the syndrome consists of organomegalies and tumors in different organs [17,18]. There have also been transgenic models of IGF-II overexpression and these have resulted in carcinogenesis in the transgenic animals [19–21]. In hepatitis B virus transgenic mice, chronic hepatocellular injury led to HCC in some animals, and in examining for abnormalities in structure and expression of a large number of oncogenes and tumor suppressor genes, including ras, myc, fos, abl, src, Rb, and p53, only IGF-II overexpression was found [22]. Most proteins from the IMP family have been shown to have some possible relationship to malignancy. p62/IMP2 was characterized as a TAA, and antibody to p62/IMP2 was present in 21% of patients with HCC but not in the precursor conditions chronic hepatitis and liver cirrhosis [11]. Our subsequent study has demonstrated that the expression of p62 is developmentally regulated, and expressed in fetal, but not in adult liver [23]. Koc/IMP3 had been shown to be

Table 1
p62 and IMP family of proteins.

Acronym (reference)	Reported properties
Human p62 [11]	Identical to human IMP-2. A splice variant missing 43 amino acids between KH2 and KH3 domains. An autoantigen in HCC.
Human Koc [12]	hnRNP K homology protein overexpressed in cancer. Identical to human IMP-3.
Chicken ZBP1 [13]	Chicken β-actin mRNA zipcode-binding protein. Identical to chicken VICKZ1.
Human IMP-1 [14]	IGF-II mRNA binding protein. Binds to 5′ UTR of the leader 3 fetal IGF-II mRNA. Human homolog of mouse CRD-BP.
Human IMP-2 [14]	Binds to 5′ UTR of leader 3 fetal IGF-II mRNA. Splice variant of p62.
Human IMP-3 [14]	Binds to 5′ UTR of leader 3 fetal IGF-II mRNA. Identical to human Koc.
Mouse CRD-BP [24,25]	Murine c-myc coding region instability determinant binding protein. Shields c-myc mRNA from endonucleolytic cleavage. Homolog of human IMP-1.

Underlined letters represent the acronyms used by various authors to describe the proteins in column one.