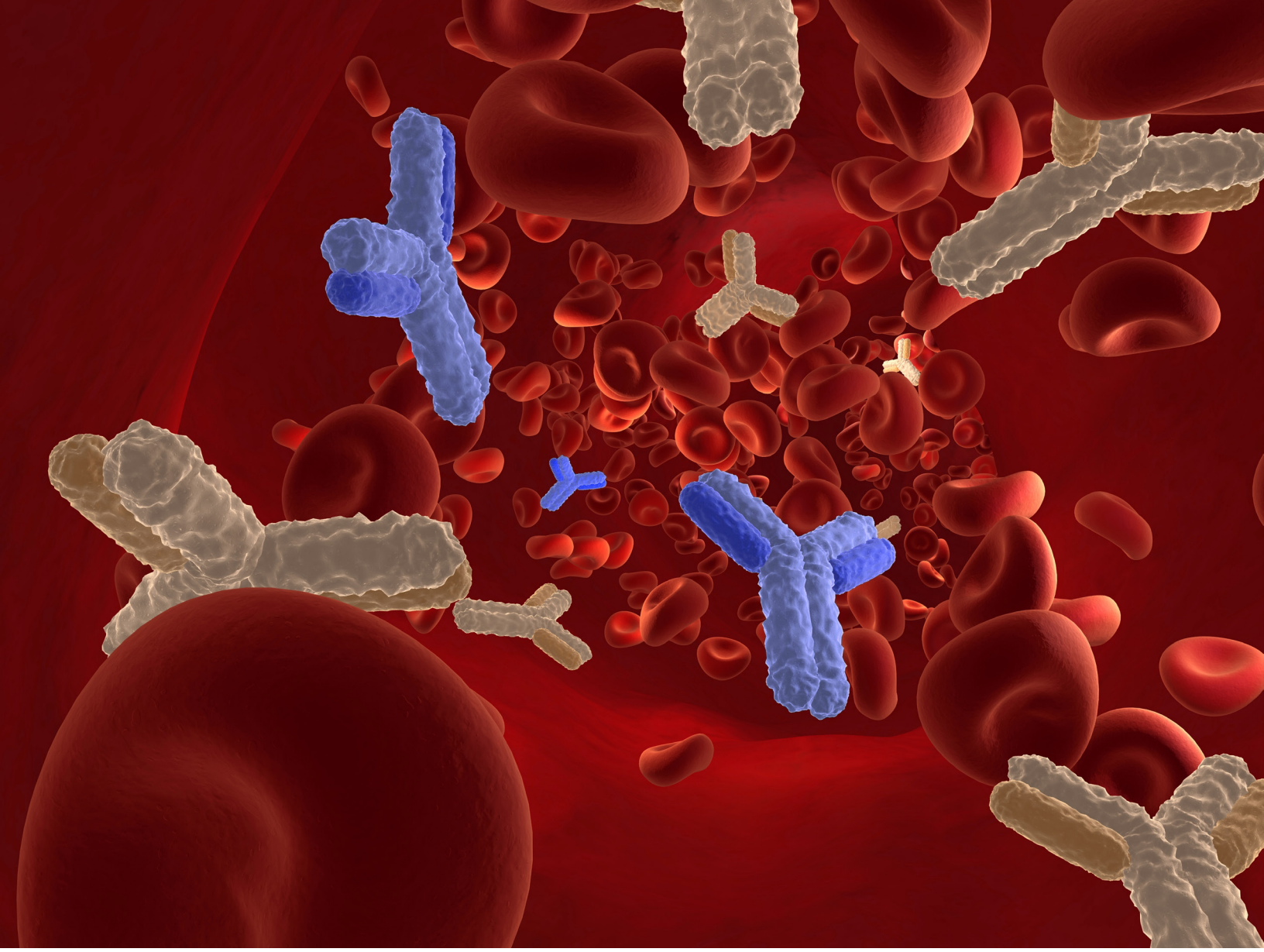

REVIEW

Autoantibodies as Biomarkers in Cancer and Neurological Diseases

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Autoantibodies as Biomarkers in Cancer and Neurological Diseases

Introduction

As scientists we all know what antibodies do regarding protection from foreign organisms that try to invade our system. However, I am not sure we all realize that autoantibodies can provide a very powerful tool regarding prognosis, diagnosis or whether a particular disease treatment may be useful or harmful.

Over the last several years steady advances have been made regarding the development of biomarkers to help diagnose or treat cancer. For the most part much of the published work has focused on genetic markers or the presence of certain circulating proteins (ie. PSA, p53 Braca1, etc.). However one approach to biomarker discovery that is not commonly thought of is to use serum or plasma autoantibodies themselves as biomarkers of disease. Autoantibodies are certainly well studied regarding auto-immune diseases (such as lupus, Crohn's, arthritis, etc.), and recently some very exciting studies have been published that describe the use of autoantibodies in diagnosis of cancer and neurological diseases. Increasingly it is looking like autoantibodies may be reflecting the immune system's natural response to disease as part of the body's attempt to clear debris generated by the disease from the blood (3, 4).

Autoantibodies as biomarkers for cancer

Discovery of blood-based biomarkers in cancer are very important since many of the current techniques, such as X-rays and CT scans, can discover the presence of a tissue mass, but more invasive procedures (biopsy followed by pathology study) are then needed to confirm if the mass is cancerous. Auto antibodies to tumor associated antigens are starting to gain traction as biomarkers for cancer, since they can provide a very sensitive assay and are inherently more stable in serum than most other proteins or tumor-derived DNA (8)

In a 2016 paper Tao et al. (7) described a group of 4 autoantibody biomarkers (COPS2, CTSF, NT5E, and TERF1) that, when combined, provide high diagnostic power, with 95% sensitivity and 92% specificity to differentiate gastric cancer patients from healthy individuals. An interesting aspect of this paper was a cohort of 87 serum samples that were assayed using CDI's human proteome array (HuProt), which contains 75% of the human proteome. Use of the array allowed the investigators to quickly narrow down the number of potential biomarkers. It will now be possible to print focused arrays containing a relevant subset of the total proteome array. This method is particularly useful because it provides a substantial saving regarding cost, since CDI Laboratories can print up to 14 sub-arrays on one slide, with each sub-array containing 1–150 proteins. With the use of gaskets that separate the sub-arrays, this method allows for the processing of 14 patient serum samples on one chip, rendering the discovery of auto-antibody biomarkers very cost-effective.

Biomarkers for Immune Checkpoint Inhibitor Therapies

More recently, the very promising antibody based cancer treatments that target immune checkpoint pathways have been progressing at a fast rate because they are proving to provide many patients a longer life or even remission. However one problem associated with this very promising therapy in a large fraction of the patients is toxicity. It seems that when the brakes are taken off the body's immune system, some patients, who may have an underlying undetected auto-immune problem, have very negative reactions, with symptoms similar to serious auto-immune diseases. One recently considered use of high content proteome arrays, like CDI's HuProt array, is to enable the discovery of auto antibody biomarkers that could help predict which patients may react negatively and, conversely, which patients may respond best to this type of treatment. Several pilot studies carried out with CDI's HuProt arrays have indeed suggested that the above may be possible, and more extensive work along these lines needs to be done.

Autoantibodies as Biomarkers for Neurological Diseases

In the past several years there have also been some very interesting papers from the lab of Robert Nagele at Rowan University regarding diagnosis of Parkinson's and Alzheimer's diseases. Both of these diseases are notoriously hard to diagnose and in most cases, diagnosis only occurs at very late stages and in some cases true diagnosis only occurs by examining tissue after death. In a 2015 (1) paper Nagele describes a panel of blood-based auto-antibody biomarkers for Parkinson's. This study looked at 398 patients, including 103 early stage disease patients. The derived auto-antibody biomarker panel was shown to be able to distinguish early stage PD with 90% confidence. In addition, this panel was shown to have 97.5% accuracy differentiating between early and progressive disease patients, as well as being able to distinguish between other neurological diseases (Alzheimer's, MS) and non-neurological diseases (breast cancer). In another study (2) Nagele's group searched for autoantibody biomarkers for Alzheimer's disease. This study looked at 236 patients, 50 of which were determined to have the disease as determined by low CSF Ab42 levels, a feature consistent with the presence of ongoing AD-related pathology as well as a high likelihood of rapid transition to AD. In this study Nagele discovered a set of auto-antibody biomarkers that exhibited 100% overall accuracy in distinguishing individuals with mild to moderate AD from matched controls. The array screening data also allowed researchers to distinguish between different stages of AD, with the panel of auto-antibody biomarkers showing a 98.5% overall accuracy in staging AD (5, 6).

Conclusion

Autoantibodies are no longer only pertinent to classical auto-immune diseases but now appear to be potential biomarkers for some of the most serious afflictions, such as cancers and the neurological diseases Alzheimer's and Parkinson's.

In addition, ongoing pilot studies suggest that autoantibodies may also be important biomarkers with which to pre-screen patients for the likelihood of adverse toxicities associated with the very promising checkpoint inhibitor treatments.

As more data is gathered and this method of biomarker discovery is more widely adapted, it is probable that many of the most serious diseases effecting humans may have an auto-antibody signature that is useful for diagnoses and/or directing treatment.

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