

Antibodies in relation to oncology

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How are antibodies aiding CRC research?

Antibodies have had a long-standing history in the management of cancer care, with major applications in diagnostic immunohistochemistry and immunoassay of tumour-associated antigen markers. Moreover, the progress made with antibody therapeutics since the first therapeutic antibody debuted in the mid-eighties is more than encouraging. It seems antibodies have already proved their worth in the oncology arena; however, we have not yet achieved all we can with these valuable biological tools. As well as developing them for cancer treatments, there is niche for them in the design of faster and improved diagnostics – in tandem with new-generation genomic technologies, these diagnostics are closer now more than ever.

Colorectal cancer (CRC) is one example of where antibody applications are being used to validate genomic or proteomic data reporting on new biomarkers; there has been a wealth of publications published in recent years exemplifying this. Proteitech has found its antibodies featured in many interesting papers representing such work. Cherry-picking a few from the bunch, it is clear to see progress is being made in the CRC biomarker field.

The survival time of CRC patients strongly correlates with the stage of tumor at diagnosis: a patient with advanced CRC and metastasis to a lymph node for example, has a much poorer chance of survival (around 11 %) than one whose disease is localized at its origin (90 %) (Jemal, et al., 2009). Investigations into protein indicators of CRC metastasis are vital. A paper published in the Journal of Proteome Research in 2009 describes efforts to develop a method of prognostic detection of metastasis, by-passing the conventional tissue-based approach for identifying markers (Xue, et al.). This change in tactics is a step in the right direction towards a truly translational form of biomarker discovery; using blood serum as the basis for its investigations, this rationale is moving towards

the development of non-invasive and rapid diagnostic assays. The use of body fluids such as serum to identify novel markers however, is made difficult by the presence of abundant physiological proteins such as albumin and fibrinogen etc. – which inevitably mask less abundant proteins during proteomic analysis of potential biomarkers for cancer. Instead Xue and colleagues have analyzed the cancer “secretome” – all the secreted proteins from a given cancer type previously identified by genomic and cell biology studies.

Using measurements of mass spectral peak intensities or spectral counts, Xue, et al. were able to compare the secretome of cancer cells from the CRC origin and cells from its lymph metastasis from the same patient. These quantitation protocols had rarely been used in secretome analysis previously [refs]. Using these methods, Xue and colleagues were able to identify 145 new markers associated exclusively with CRC metastasis to the lymph; of these, six could be validated as having differential protein expression patterns between the two cell types, including trefoil factor 3 (TFF3) and anterior gradient homologue 2 (ARG2), as validated by two of Proteitech's antibodies. Initial ELISA experiments done by Xue suggested that TFF3, along with another protein of the six identified: growth/determination factor 15 (GDF15), potentially has some prognostic value in the prediction of CRC metastasis. A diagnostic tool for the prediction of CRC metastasis will be invaluable to the treatment of this disease. However, what is also needed is a non-invasive screening method that can detect CRC at a very early stage, before the threat of metastasis even has chance to arise.

One way a recent Clinica Chimica Acta paper approached finding candidate biomarkers for early CRC detection was to take advantage of the human body's own defences – the immune system. Autoantibodies targeting tumor-associated antigens (TAAs) are produced by the body in an initial attempt to eradicate cancerous cells. They are fast becoming alternative candidates in

the hunt for easily detectable biomarkers as these autoantibodies may be generated in measurable amounts, well before the levels of TAAs become detectable (ref). Chen and colleagues had previously reported that the Rabphilin-3A-like (RPH3AL) protein was overexpressed in CRC (ref). In their recent 2011 Clinica Chimica Acta paper, Chen, et al. furthered their investigations into RPH3AL's role in CRC by examining the presence of anti-RPH3AL antibodies in sera. Western blots carried out using recombinant RPH3AL as ‘bait’ (which was quality controlled using Proteitech's RPH3AL antibody) showed that detectable levels of RPH3AL autoantibodies prevailed in CRC patients' sera. They found that the frequencies of RPH3AL autoantibodies in early or advanced stage CRC patients were 64.7% and 78.0% respectively and that these values are significantly higher than the frequency of RPH3AL autoantibodies in healthy controls (15.9%). Interestingly RPH3AL autoantibodies were found in 34 out of 49 CRC patients who tested negative for carcinoembryonic antigen (CEA) – the first blood marker discovered currently in use for the detection of CRC. Chen and colleagues, in their conclusions, consider that screening for RPH3AL autoantibodies could be potentially used for CRC diagnosis in the future. So it seems, whether made by a biotechnology company or by the body, antibodies will form the foundations of developing and promising diagnostic tests for cancer; it appears to be definitely so in the case of CRC.

References

1. Xue H, Lu B, Zhang J, Wu M, Huang Q, Wu Q, Sheng H, Wu D, Hu J and Lai M. Center MM, Jemal A and Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 2009; 18(6): 1688–1694.
2. Ransohoff DF. How much does colonoscopy reduce colon cancer mortality? *Ann Intern Med* 2009; 150: 50–52.
3. NCI cancer factsheet <http://seer.cancer.gov/statfacts/html/colorect.html#incidence-mortality>. and the rate of its incidence is increasing due to advancing westernization.

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