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Discovery of widespread tumor growth gene holds promise for effective anti-cancer treatment

Italian scientists will announce today (Monday September 24) that they have found a new and promising target for anti-tumour therapy in cancer. Professor Saverio Alberti, from the CESI, University of Chieti Foundation, Chieti, will tell the European Cancer Conference (ECCO 14) that he and his team have found a widespread mechanism for the stimulation of tumour growth in man, and that this is leading to the development of novel diagnostic and therapeutic procedures.

Professor Alberti and his team have discovered the function of the Trop-2 gene, a product of the TACTD2 gene, which is expressed in placenta, an 'invasive' normal tissue. "The function of Trop-2 was a mystery until now," says Professor Alberti, "but knowing its expression in the trophoblast (cells forming the outer layer of the blastocyst – the stage between the fertilised egg and the embryo) during pregnancy, we thought that it might well be involved in another invasive function – tumour growth."

The scientists analysed the genes in human tumours and found that Trop-2 was expressed in the vast majority of human cancers, for example, breast, colon, stomach, lung, prostate, ovary, endometrium, uterine cervix and pancreas. Over-expression of the Trop-2 gene was also found when immunohistochemical (IHC) analysis of 1,755 tumours was undertaken. IHC analysis looks at the interaction of antibodies and antigens in tissues, and has the advantage of showing exactly where in a tissue a given protein is located. "This has allowed us to develop anti-Trop-2 monoclonal antibodies for immunotherapy (modulation of the immune system to reject and destroy tumours) of Trop-2 expressing tumours," explains Professor Alberti.

Trop-2 over-expression was found in between 65% and 90% of the tumour types analysed, with an average of 74% across the board. "These figures are high," explains Professor Alberti. "In comparison, telomerase over-expression, possibly the most fundamental mechanism for cell immortalisation, is observed in 80% of all tumours. Telomerase is an enzyme that adds specific DNA repeats to the ends of chromosomes, so not strictly comparable. When we come to look at genes, her2/neu is a key determinant of breast cancer aggressiveness and is over-expressed in 25% of the cancers, and amplified in only a subgroup of them; and p53, possibly the most fundamental of tumour suppressors, is mutated and/or over-expressed in 50% of tumours. Mutations of the epidermal growth factor receptor gene (EGFR) are relatively infrequent in most cancers, reach 30% of the non small-cell lung cancers and are present at frequencies of around 75% in only a small subgroup of the latter. Most other markers known to date show lower figures and/or can be detected at high frequency in only a subgroup of tumours, for example PSA in prostate cancer. So Trop-2 really stands out."

"It is also a unique marker of cancer metastases in different tumour types – including colon, stomach, breast, and ovary in man – and across a number of species," he says. In man, most metastases in lymph nodes or down-stream organs, for example liver in colon cancer, express higher levels of Trop-2 compared with the primary tumours. Trop-2 induces these metastases through mechanisms that the scientists are beginning to unravel. The most intriguing of these findings, they say, is the presence of two sequence elements in the Trop-2 cytoplasmic tail, the signalling engine of Trop-2, which act as,

respectively, an enhancer and a silencer of metastatic propensity. This may be the key to the identification of signalling molecules that promote or inhibit the formation of metastases.

“If we can identify such molecules we will be approaching a situation where we could influence their activity and hence either encourage or prevent it,” says Professor Alberti. “This could be an important step towards stopping cancer in its tracks.”

In addition, the scientists want to extend their knowledge of the cell changes induced by receptor activation, or signal transduction pathways, triggered by Trop-2. “This will be crucial for the better understanding of the way in which tumour growth is regulated by the gene, and will also provide additional targets for anti-cancer drugs,” says Professor Alberti. “We are very excited about the prospects for therapy which we can see arising from this discovery.”

Source: ECCO-the European CanCer Conference