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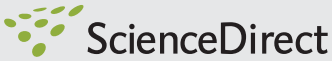

Monday 28 June 2010

Monday 28 June 2010 07:00–08:00

After Sunrise: Meet the Expert

315 p53 and cancer: a complex affair

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p53 is a pivotal tumour suppressor, mutated in about half of all human cancers. The p53 protein monitors and responds to a plethora of stress signals, thereby maintaining genome stability and preventing tumourigenesis. The p53 protein is a transcriptional regulator, which modulates the expression of hundreds of genes in a context-dependent manner. This can dictate changes in cell fate, including apoptosis and replicative senescence, and abort the propagation of transformed cells.

The role of p53 has been mainly studied in a cell-autonomous context, namely within tumour cells or cells at risk of becoming cancerous. However, p53 also exerts cell non-autonomous effects that help to inhibit tumour progression. One example is p53 activity within the stromal compartment of the tumour. For instance, p53-deficient fibroblasts can preferentially augment the growth of prostate cancer cell-derived tumours in a xenograft model. Of note, p53-deficient fibroblasts produce elevated levels of secreted proteins such as SDF-1/CXCL12 and several matrix metalloproteases, which may facilitate tumour growth and spread. Indeed, inhibition of SDF-1 expression in p53-null fibroblasts severely compromises their tumour growth-enhancing activity. Interestingly, epithelial tumour cells can repress p53 activation in both mouse and human fibroblasts. This ability is acquired when epithelial cells undergo neoplastic transformation. Of note, this p53-repressive effect of tumour cells is exerted more readily on cancer-associated fibroblasts (CAFs) than on normal fibroblasts.

Besides abrogating the tumour suppressor function of wild type p53, cancer-associated p53 mutations can endow the mutant protein with novel, pro-oncogenic gain of function activities. Thus, emergence of p53 mutations in tumour cells can alter their biological properties, including their response to anti-cancer treatments. An interesting example is provided by the cross-talk between p53 and vitamin D3. Earlier studies have demonstrated that vitamin D3 can synergize with p53 to augment the growth inhibition and killing of cancer cells by anti-cancer agents. However, the situation becomes profoundly different if the cancer cells harbor common p53 mutations. In that case, exposure to vitamin D3 actually often attenuates, rather than increases, the killing of the cancer cells by chemotherapy drugs. This chemoprotective effect is mediated through an interaction between mutant p53 proteins and the vitamin D3 receptor (VDR). In fact, mutant p53 increases the nuclear accumulation of VDR and potentiates its transcriptional activity, but this is done in a gene-selective manner, such that proapoptotic genes tend to become underexpressed whereas pro-survival genes tend to become overexpressed. These observations suggest that p53 status should be considered when contemplating the use of vitamin D3 analogs for combinational cancer therapy.

316 Functional and molecular MR for breast cancer characterization

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Background: Molecular MR assessment of breast cancer can address dynamic changes in the metabolome and thereby the downstream products of the preceding gene expression and protein activity [1–5]. Important factors in shaping the metabolic composition of a breast tumour would be the basic geno/phenotype and effects of treatment. The molecular findings will also depend on changes in the microenvironment that can be monitored by functional MR imaging methods [6–7]. The overall objective of this work is to obtain individualized treatment of breast cancer patients based on molecular and functional features of the tumours.

Material and Methods: High resolution magic angle spinning (HR MAS) MR spectroscopy (MRS) gives a comprehensive window into tissue biochemistry. MR signals from a number of metabolites such as amino acids, glucose, lactate and choline compounds can be quantified or classified using multivariate data analyses. The non-destructive nature of HR MAS allows intact specimens to be subsequently analyzed by histopathology and other molecular techniques.

Dynamic contrast enhanced (DCE) MRI can image tumour vasculature and address perfusion, microvessel permeability and extracellular volume fraction. The spatial heterogeneity caused by different cell types, hypoxia and necrosis, as well as the density of the vascular bed, can be correlated to metabolic activities. Diffusion weighted (DW) MRI assesses the mobility of water molecules and high cellular density in tumours causes restricted motion. In vivo MR metabolic profiling can map metabolic changes throughout the tumour. By combining all these in vivo methods in a single experiment, detailed and comprehensive information is obtained from each tumour.

Results: The metabolic composition in breast cancer tissue is distinctively different from non-involved breast tissue. The results obtain show a near-complete separation based on multivariate data analysis. The metabolic profile of different breast cancer samples correlates to sample tumour cell fraction, estrogen receptor status and lymph node involvement. The combination of metabolic and genetic profiling has also showed more refined subgroups of breast cancer. Preliminary investigations suggest that MR determined metabolic phenotype may correlate with long term breast cancer survivor. However, further validation, including more samples and blind testing, is necessary to validate these results.

The HR MAS technique is now also being explored as a tool for assessing treatment effects, in combination with in vivo MR methods. Changes after chemotherapy were found with DCE-MRI in breast cancer patients, in addition to a correlation between DCE-MRI before treatment with overall survival. The apparent diffusion coefficient derived from DW-MRI in breast cancer patients increased after chemotherapy, also confirmed in a study of breast cancer xenografts. In addition, treated breast tumour models had lower levels of choline compounds when compared to controls, as measured with in vivo MRS. Overall, the set of complementary in vivo MR methods are coincident and well suited for treatment monitoring.

Conclusions: Metabolic phenotyping of breast cancer using HR MAS MRS has demonstrated distinct patterns correlating to clinical and histopathological findings. An important finding is that molecular and functional MR methods predict treatment response and possibly overall patient outcome.

Reference(s)

[1] Sitter B et al. Quantification of metabolites in breast cancer patients with different clinical prognosis using HR MAS MR spectroscopy. NMR Biomed 2010 Jan 25 [Epub ahead of print].
[2] Giskeødegård GF et al. Multivariate modeling and prediction of breast cancer prognostic factors using MR metabolomics. J Proteome Res 2010 5; 9(2): 972–9.
[3] Sitter B et al. High resolution magic angle spinning (HR MAS) MR spectroscopy in metabolic characterization of human cancer (review). Prog Nucl Magn Reson Spectrosc 2009; 54: 239–254.
[4] Bathen TF et al. MR-determined metabolic phenotype of breast cancer predicts lymphatic spread, grading and hormone status. Breast Cancer Res Treat 2007; 104(2): 181–9.
[5] Sitter B et al. High-resolution magic angle spinning MRS of breast cancer tissue. NMR Biomed 2002; 15: 327–337.
[6] Jensen LR et al. Assessment of early docetaxel response in an experimental model of human breast cancer using DCE-MRI, ex vivo HR MAS, and in vivo (1)H MRS. NMR Biomed 2009; 23(1): 56–65.
[7] Johansen R et al. Predicting survival and early clinical response to primary chemotherapy for patients with locally advanced breast cancer using DCE-MRI. J Magn Reson Imaging 2009; 1300–7.

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