

Bulletin Board

Enzyme study reveals potential biomarkers for colon cancer

Researchers from the University of Cincinnati (OH, USA) are the first to identify two genetic changes that may provide diagnostic and prognostic information about colon cancer. The study, published in *PLoS Genetics*, has revealed deletion hotspots in the α -methylacyl-CoA (*AMACR*) gene that correlate with varying aggressiveness of colon cancer. Xiang Zhang, first author of the study, explicates, “from the colon tissues, we’ve identified two types of genetic deletions that may allow us to predict whether people will have a good or bad cancer outcome”.

α -methylacyl-CoA is a peroxisomal and mitochondrial enzyme involved in the oxidation of fatty acids from red meat and dairy products. It is well known that high consumption of these foods increases the risk of developing colon cancer. Previous investigation into prostate cancer has indicated that expression of *AMACR* is increased in cancer cells, and *AMACR* overexpression is now established as a diagnostic marker in cancer of both the colon and prostate. However, the mechanisms behind the abnormal regulation of the *AMACR* gene in cancerous cells are not well understood, and the study by Zhang *et al.* aimed to shed light on this.

Examination of normal and progressively malignant colon tissues, using the laser-capture microdissection technique, detected two nonrandom events in the CpG island that may trigger the abnormal expression of *AMACR* in colon cancer. The research team found a double-deletion at CG3 and CG10, and a deletion at CG12–16. These have different, almost opposite, effects on the regulation of *AMACR* during colon carcinogenesis. The double-deletions at CG3 and CG10 are genetic events occurring in somatic cells of the colon and were found in healthy cells and benign tumors. The deletion at CG12–16 was found to be a constitutional

allele with a frequency of 43% in a general population, and prevalent in more aggressive colon cancers that strongly expressed *AMACR*.

The findings led Zhang *et al.* to hypothesize that growths in the colon with double-deletions of CG3 and CG10 might have a low likelihood of development into colon carcinoma, and those with a deletion at CG12–16 are more likely to become aggressive forms of cancer. Zhang explains, “if a person carries one of the deletions, it may predispose him or her to a more aggressive type of colon cancer.” These hotspots provide enormous potential for further research into colon carcinogenesis. “Our hope is that this new knowledge will help us develop better diagnostic tools for colon cancer,” comments Zhang.

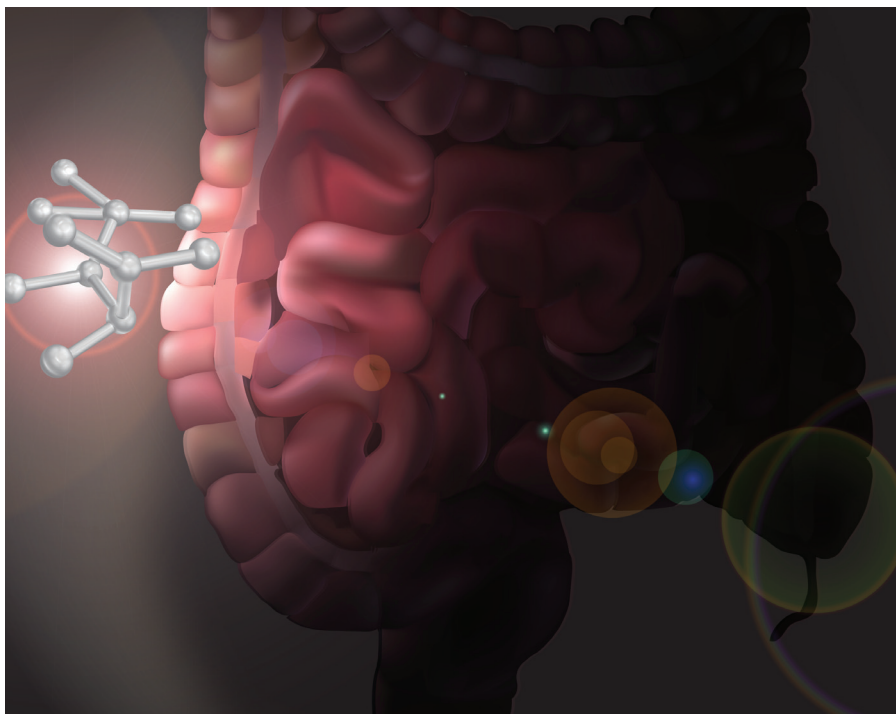
The researchers speculate that the newly discovered hotspots could provide information about the individual risk of developing colon cancer and help people make suitable

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lifestyle choices to combat this. Shuk-mei Ho, senior author of the study, states, “we need to start paying closer attention to how the environment we live in and the things we put in our bodies interact with our genetic makeup and to influence our cancer risk,” advocating a holistic approach to reducing the risk of developing cancer.

Source: Zhang X, Leav I, Revelo MP *et al.*: Deletion hotspots in *AMACR* promoter CpG island are *cis*-regulatory elements controlling the gene expression in the colon. *PLoS Genet.* 5(1), e1000334 (2009); www.sciencedaily.com/releases/2009/01/090116073157.htm



Study shows grape-seed extract kills leukemia cells

Grape seed extract has potential to be incorporated into the treatment of hematological cancers now that it has been found to induce apoptosis in leukemia cells. A laboratory-based study has revealed that grape-seed extract could be a useful tool in the fight against cancer. "What everyone seeks is an agent that has an effect on cancer cells but leaves normal cells alone, and this shows that grape-seed extract fits into this category," explains lead author of the study, Xianglin Shi.

Shi, from the University of Kentucky (KY, USA), led research into the effects of grape-seed extract on human leukemia cells. Cancer cells were exposed to various concentrations of grape-seed extract over 12 and 24 h, and to 50 µg/ml of the extract over varying time intervals. It was found that grape-seed extract induced leukemia cell apoptosis in a time- and dose-dependent manner. Grape-seed extract caused death in cancer cells but did not damage noncancer cells,

increasing its potential as a component of cancer treatment.

Gao *et al.*'s investigation into grape-seed extract has been preceded by a number of studies into natural compounds with anticancer properties. Research has revealed that proanthocyanidins, a group of antioxidants, may be responsible for the association between increased fruit and vegetable consumption and the prevention of cancer. These antioxidants have been found in apple peel, and were shown to trigger cell death in cancer cells, while leaving noncancer cells intact. Indeed, grape-seed extract has already been studied for its anticancer properties. However, Gao *et al.* are the first to demonstrate its effect on hematological malignancies. "This is a natural compound that appears to have relatively important properties," stated Shi.

The researchers took the study further by looking into the underlying mechanisms behind grape-seed extract's apoptotic properties. It was found that the extract induces

apoptosis in leukemia cells through a process that involves the sustained activation of c-Jun N-terminal protein kinase and Cip/p21 upregulation. Pharmacological and genetic methods then confirmed that grape-seed extract promotes cell death in this way.

The effect of grape-seed extract on leukemia cells has added to the field of knowledge, illustrating the potential value of natural compounds in the treatment of cancer. However, Shi made it clear that these findings were not enough to warrant advising people to start eating lots of grapes in the hope they will avoid getting cancer. He concludes, "it's too early to say for sure that grape-seed extract has this effect, even though the results are promising".

Source: Gao N, Budhraj A, Cheng S, Yao H, Zhang Z, Shi X: Induction of apoptosis in human leukemia cells by grape seed extract occurs via activation of c-Jun NH2-terminal kinase. *Clin. Cancer Res.* 15(1), 140–149 (2009); www.medicalnewstoday.com/articles/134311.php

Researchers identify genetic link to early-onset brain tumor

Research at the French National Institute of Health and Medical Research (Paris, France) has revealed a gene variant associated with the development of brain tumors at a young age. The recent study, led by Marc Sanson, has found that the Pro/Pro variant of the tumor suppressor gene *TP53* is significantly more prevalent in those with early-onset brain tumors compared with both healthy controls and those with brain tumors developed later in life.

The study was based on the comparison of blood samples from 254 patients with the most common form of brain cancer, glioblastoma, and from 238 people without cancer. El Hallani *et al.* found that the Pro/Pro genotype, a result of a functional single nucleotide polymorphism in codon 72, was overrepresented in patients under 45 years, with 20.6% of this group possessing it, compared with 6.4% of patients

with glioblastoma over 45 years and 5.9% in noncancer sufferers. This led the study group to the conclusion that the Pro/Pro variant of *TP53* is particularly critical for oncogenesis of glioblastoma in young patients.

Discovery of the link between this particular gene variant and early-onset brain tumor has prognostic value. However, "these brain tumors (glioblastomas) are infrequent in young people," explains Sanson. Nevertheless, Sanson suggests that "eventually we may be able to use this knowledge to help identify people who have a higher risk of developing brain tumors at an early age."

Source: El Hallani S, Ducray F, Idhahbi A *et al.*: *TP53* codon 72 polymorphism is associated with age at onset of glioblastoma. *Neurology* 72(4), 332–336 (2009). www.medicalnewstoday.com/articles/136736.php

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of oncology. If you have newsworthy information, please contact:

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Pharmaceutical company gets go-ahead for RNAi trial

Alnylam Pharmaceuticals, Inc (MA, USA), has been given permission by the US FDA to start patient enrolment for a Phase I trial testing an RNAi therapeutic for liver cancers. The trial is a multicenter, dose-escalation study aiming to assess the safety, pharmacodynamics and pharmacokinetics of the new drug ALN-VSP. ALN-VSP is designed to work against hepatic cancers and comprises two small interfering RNAs. The novel drug has been tested in mouse studies where it has been shown to reduce tumor size and increase survival. The targets of the RNAi therapeutic are two genes necessary

for carcinogenesis, kinesin spindle protein and VEGF. Alnylam, the company behind this research, is a biopharmaceutical company concentrated on the development of novel therapies based on RNAi. Akshay Vaishnav, Senior Vice President of Clinical Research explains, "ALN-VSP represents Alnylam's first investigational new drug for a systematically delivered RNAi therapeutic, which is a testament to the very strong progress we have made in achieving delivery of siRNAs".

Source: www.medicalnewstoday.com/articles/136641.php

Extended breast feeding may protect against breast cancer

A mouse model provides support for the association between extended lactation and reduced risk of breast cancer. Researchers from Thomas Jefferson University (PA, USA) have shown that the functional loss of a single gene is sufficient to confer constitutive milk production and protection against mammary tumor formation. This suggests that extended breast feeding could be investigated as a preventative treatment against breast cancer.

The study, published in the *American Journal of Pathology*, adds to research indicating a significantly reduced risk of developing breast cancer in women who breastfeed for more than 2 years. The mouse model investigated by Sotgia *et al.* facilitated investigation into the reason behind this association. The researchers found that mice deficient in Caveolin-3 (*Cav-3*), a muscle-specific calveolin-related gene highly expressed in muscle and mammary gland cells, had upregulated genes associated with lactation resulting in constitutive production

of milk. The mice lacking *Cav-3* also demonstrated dramatic protection against mammary tumor formation after orthotopic tumor cell implantation.

The association between extended lactation and protection from breast cancer development in mice suggests that this model could be applied to human cancer treatment. Michael Lisanti, lead author of the study, is hopeful for a new approach to breast cancer therapy. He proposes, "a lactation-based therapeutic strategy would provide a more natural and nontoxic approach to the development of novel anti-cancer therapies. In this regard, targeted reduction of Cav-3 levels in the mammary gland may represent a new therapeutic strategy for preventing the onset of human breast cancers."

Source: Sotgia F, Casimiro MC, Bonuccelli G *et al.*: Loss of caveolin-3 induces a lactogenic microenvironment that is protective against mammary tumor formation. *Am. J. Pathol.* 174(2), 613–629 (2009); www.sciencedaily.com/releases/2009/01/090122080721.htm

Priority Paper Alerts

Circulating mitochondrial DNA in the serum of patients with testicular germ cell cancer as a novel noninvasive diagnostic biomarker.

Ellinger J, Albers P, Müller SC, von Ruecker A, Bastian PJ: *BJU Int.* DOI: 10.1111/j.1464-410X.2008.08289.x. (2009) (Epub ahead of print).

Circulating mitochondrial DNA (mtDNA) was evaluated as a diagnostic tool for testicular cancer. This study compared serum mtDNA levels between 74 testicular cancer patients and 35 healthy individuals using quantitative real-time PCR. The integrity of the mtDNA was also compared between healthy subjects and cancer patients. Results showed that mtDNA levels were significantly higher in testicular cancer patients than in healthy individuals. The mtDNA integrity was not significantly different between groups. Receiver-operator curve analysis demonstrated that circulating mtDNA levels could be used to differentiate between patients and noncancer sufferers, and could also identify testicular cancer sufferers that did not display conventional cancer markers. This has implications for using circulating mtDNA as a biomarker for testicular cancer.

Bone turnover markers as predictive tools for skeletal complications in men with metastatic prostate cancer treated with zoledronic acid.

Lein M, Miller K, Wirth M *et al.*: *Prostate.* DOI: 10.1002/pros.20917 (2009) (Epub ahead of print).

Researchers investigated the usefulness of bone turnover markers in predicting skeletal-related events (SRE) in male prostate cancer patients with bone metastases, undergoing treatment with zoledronic acid. SRE and bone marker concentrations were assessed in 117 patients over 60 weeks. Higher baseline concentrations of bone turnover markers were found in those patients with SREs. All but two of the bone markers decreased in concentration as the treatment with zoledronic acid continued, but at all times during the study, bone marker concentrations were higher in the group with SREs than in the non-SRE group. Regression analysis demonstrated that the baseline concentration of one of the bone markers could be used as a predictor of SREs.