The search for cancer markers is on, but finding non-invasive tests that are predictive of disease is not easy. Now, Andrew Feinberg and colleagues, reporting in the 14 March issue of Science, have moved a step closer to answering this elusive problem, as they show that a simple blood test could predict the risk of developing colorectal cancer.

Both genetic and epigenetic changes can initiate tumorigenesis, so detecting these could predict the risk or presence of cancer. Imprinting is epigenetic in origin and causes gene silencing; consequently, loss of imprinting (LOI) results in re-expression of previously silenced alleles of genes that could contribute to tumour formation. LOI of insulin-like growth-factor 2 (IGF2) has been found in several tumour types, but is it predictive of cancer?

LOI of IGF2 is more common in the colonic mucosa of patients with colorectal cancer than in those without, and the authors investigated whether LOI was also more common in the peripheral blood lymphocytes (PBLs) of people with a family history or personal history of colorectal cancer. They found that LOI was 5.15 times more likely in those with a family history of colorectal cancer than without, and 4.72 times more likely if they had previously been diagnosed with adenomatous polyps or colorectal cancer. This indicates that LOI is strongly linked with colorectal cancer, and that it can be detected in the blood.

Further analysis showed that patients with a history of colorectal cancer were more likely to have LOI than those with a history of adenosmas (21.7 times those with neither, compared with 3.46 times). This is consistent with the adenoma-carcinoma progression hypothesis of colorectal cancer, and indicates that LOI of IGF2 could be associated with initiation or progression.

So, what is the association between LOI in the colon and in PBLs? If LOI was present in PBLs, it was also present in the colon, but there were cases in which LOI was only present in the colon. In these, however, there was no statistically significant association with cancer, so the use of detecting LOI in the blood is not undermined.

The ease of performing blood tests of risk assessment is improved if the test is based on DNA, rather than RNA. Fortunately, a differentially methylated region within IGF2 is predictive of LOI. Its hypomethylation is associated with LOI in normal tissue and blood, as well as in colorectal cancer patients. An LOI blood test might be a useful screening test in the general population, as it is predictive of colorectal cancer, and is more prevalent than other colorectal-cancer-predisposing mutations. However, large prospective trials must be performed before it could be introduced.

Emma Greenwood

References and links


WEB SITE Andrew Feinberg’s lab: http://www.hopkinsmedicine.org/geneticmedicine/Faculty/FacultyProfile.cfm?ProfileID=3
HIGHLIGHTS

IN THE NEWS

**Detection technology**

Mammography is an important screening method that detects breast cancer at an early stage. However, conventional X-rays can only identify lumps that are 10-12 mm across, because the similar densities of normal and cancer cells mean that only a large collection of tumour cells can be detected. Now, a new technology could allow lesions to be found when they are less than half that size.

Scientists at University College London, UK, led by Robert Speller, discovered that X-rays scatter in a unique way on contact with tumour cells, but not normal cells. The team developed a device to measure this effect — diffraction enhanced breast imaging (DEBI) — and initial results on normal tissue and tumour biopsies have been promising. Robert Speller told New Scientist magazine that “we should be able to pick up something from 4 mm in diameter”.

The device works by scanning the breast in the normal way, but it includes a second detector that measures the scatter. “The team now needs to work out how to build the extra detector and analyse electronics into existing mammography systems” (Health-news.co.uk, 20 February 2003).

Although this is a potential breakthrough that could improve breast cancer detection, further research is needed. “Andy Hanby, a breast pathologist from Leeds University, said the method needed to be put through clinical trials before its ability to detect smaller tumours is confirmed” (Health-news.co.uk), and Clara Mackay, at the UK charity Breast Cancer Care said that “these kinds of advances in early detection raise issues about appropriate management of such early lesions” (BBC News).

Emma Greenwood

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**TUMOUR SUPPRESSORS**

Ever-decreasing effects

Knockout and conditional mouse models allow investigators to compare phenotypic differences when gene expression is either ‘on’ or ‘off’, but mutations that occur in real life could generate expression levels that fall between these two extremes. In the March issue of Nature Genetics, Greg Hannon, Scott Lowe and colleagues used RNA interference (RNAi) to generate a series of p53 hypomorphs, and show that the level of p53 markedly affects the level of disease.

The authors generated three retroviral vectors that each contained a distinct short hairpin RNA to target the Trp53 gene. When transfected into cultured cells, these constructs — p53-A, -B and -C — had differential effects on p53 protein expression, which corresponded to differences in the ability of mouse embryonic fibroblasts (MEFs) to form colonies in a colony-formation assay. Following expression of p53-A, which had the least effect on protein levels, only a few colonies were able to grow, whereas p53-C significantly decreased protein expression and many more colonies grew.

So, do these RNAi constructs also affect the tumorigenic capacity of cells? Haematopoietic stem cells were infected with viruses produced from these constructs and were transplanted into Eµ-Myc mice, which develop B-cell lymphomas at 4-6 months. All mice developed palpable lymph nodes within 3-5 weeks, indicative of lymph-node hyperplasia, but only those with p53-B and p53-C developed B-cell lymphomas and showed a decrease in survival, compared with control Eµ-Myc mice.

Further analysis showed that p53-B recipients developed smaller and less-malignant tumours than p53-C recipients. The tumours of p53-B recipients still had a high rate of apoptosis, a low mitotic index and did not significantly infiltrate into the lung and liver, whereas the p53-C recipients had low levels of apoptosis, a high mitotic index and a large amount of infiltration. Interestingly, the tumours produced in both of these recipients were not genomically unstable, unlike those that are found in Trp53–/– mice. These results confirm how important the apoptotic function of p53 is for tumour suppression.

In Eµ–Myc mice that are heterozygous for Trp53, all tumours that develop show loss of heterozygosity at the Trp53 locus. M. t. light expression of the RNAi constructs relieve this selection pressure? Of the two tumours that developed in p53-B recipients and four of the four tumours that developed in p53-C recipients had not lost the second wild-type Trp53 allele, indicating that loss of heterozygosity is not required for tumour development in the presence of the RNAi constructs. So, as well as producing null phenotypes, RNAi can generate intermediate phenotypes that can help dissect protein function. This protocol also has interesting therapeutic implications, as it shows that stable RNAi can suppress the deleterious function of genes in stem cells ex vivo, and that these retain their function in vivo.

Emma Greenwood

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References and links


**WEB SITES**


Scott Lowe’s lab: http://www.cshl.org/public/SCIENCE/lowe.html
Seed or soil?

There is an ongoing debate as to whether the metastatic potential of a cancer cell is already present in the primary tumour, or whether it is acquired by cancer cells after they have broken free. A gene-expression profile analysis performed by Quin-Hai Ye et al., coupled with a supervised machine learning algorithm, has generated a molecular signature that indicates the former, and can be used to detect primary hepatocellular carcinomas (HCCs) with metastatic potential. This approach could therefore be used to identify patients with HCCs that are most likely to metastasize.

Ye et al. compared gene-expression profiles of 50 primary and metastatic HCC samples from 30 patients whose tumours had or had not metastasized. Unexpectedly, the gene-expression profiles of primary and matched metastatic HCCs were not very different. Primary tumours that had not metastasized, however, had a gene-expression profile that was quite different from that of primary HCCs that had undergone metastasis. This means that metastatic tumours have a similar gene-expression signature to their parent tumour, whereas metastasis-free HCCs are distinct from metastatic primary HCCs. The metastatic gene signature was independent of tumour size, tumour encapsulation or patient age. So, metastatic potential seems to be predetermined in primary HCCs.

To define a gene set that could accurately be used to predict which patients’ HCCs were most likely to metastasize, the authors used a supervised machine learning classification algorithm known as a compound covariate predictor, which includes a cross-validation test to avoid overestimation of prediction accuracy. This strategy correctly predicted 90% of primary tumours that would become metastatic, and the prediction outcome was correlated with patient survival.

So, what genes are upregulated in metastatic HCC? The secreted cytokine osteopontin (OPN) was overexpressed by an average of threefold in metastatic tumours. This gene is also overexpressed in metastatic breast tumours, and malignant lung, colon and prostate cancers. HCC cell lines were also found to express high levels of this protein, and the authors showed that antibodies against OPN could block HCC metastasis to the lung in nude mice. Because increased OPN levels can be detected in the plasma of cancer patients, it might make a good diagnostic marker, as well as a therapeutic target.

The finding that the HCC metastatic programme is initiated in the primary tumour indicates that analysis strategies such as these can also be used to identify patients with pre-metastatic tumours. This predictor, however, awaits confirmation from larger independent data sets. Furthermore, all the HCC samples in this study were obtained from hepatitis-B-virus-positive Chinese patients, so this model must be tested in other populations, including those with hepatitis-C-virus-related HCC.

References and links

IN BRIEF

IMMUNOTHERAPY

Eradication of systemic B-cell tumours by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15.


T cells have been engineered to recognize specific tumour antigens, but co-stimulatory signals are needed to activate their cytolytic activity, localize them to tumours and prevent apoptosis. Brentjens et al. generated mouse autologous T cells that recognized a B-cell leukaemia antigen, and activated the cells, ex vivo, with modified antigen-presenting cells. They showed that these T cells migrated to the bone marrow of mice and eradicated established B-cell tumours. Using a similar approach, the authors transduced human autologous T cells and showed that they were able to destroy tumour cells in patients with chronic lymphocytic leukaemia.

EARLY DETECTION

Inactivation of hMLH1 and hMSH2 by promoter methylation in primary non-small cell lung tumours and matched sputum samples.


Wang et al. performed a genetic and epigenetic analysis of 77 resected primary non-small-cell lung tumours, and found that 70% had lost expression of the mismatch-repair genes hMLH1 or hMSH2. Promoter methylation of hMLH1 occurred in 56% of tumours, and seemed to be the main mechanism of gene deregulation. This methylation pattern was detected in sputum samples, making it a potential diagnostic marker for lung cancer.

TUMOUR SUPPRESSORS

Mutated APC and Asef are involved in the migration of colorectal tumour cells.


The adenomatous polyposis coli (APC) tumour suppressor has many functions, including signal transduction and cytoskeletal organization. Kawasaki et al. examined the interaction of APC with the RAC-specific guanine nucleotide exchange factor, Asef, and showed that truncated APC stimulates Asef-mediated activities, such as motility and E-cadherin-associated cell adhesion.

VASCULAR LEAK SYNDROME

Genetic engineering of an immunotoxin to eliminate pulmonary vascular leak in mice.


Vascular leak system (VLS) is often a dose-limiting side effect of immunotoxins and cytokines used to treat relapsed lymphoma or myeloma. The authors previously identified a disintegrin-like amino-acid motif common to both these biological therapies. Smallshaw et al. have now mutated this motif in a ricin toxin A chain immunotoxin, and have shown that it is more effective than the non-toxin toxin but did not cause VLS in mouse models.


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HIGHLIGHTS

Receptor relay

c-SRC is a common oncogenic partner of the epidermal growth-factor receptor (EGFR), as both c-SRC and EGFR are overexpressed in human malignancies such as breast cancer. However, the mode of oncogenic cooperation between these two proteins has been unclear. Now, Yosef Yarden and colleagues report that c-CBL — a ubiquitin ligase that is known to be a regulator of EGFR endocytosis — is the "middle leg" in the relay of oncogenic signalling between c-SRC and EGFR.

To investigate whether c-SRC affects the expression of EGFR, the receptor was co-expressed with different forms of c-SRC in receptor-negative Chinese hamster ovary (CHO) cells. Both wild-type c-SRC and an active-mutant form resulted in increased levels of expression of EGFR, in contrast to a kinase-defective mutant, which led to decreased EGFR expression levels. As the active form of c-SRC was shown to have no effect on receptor synthesis (mRNA levels) or maturation, the authors propose that c-SRC stabilizes the mature cell-surface form of EGFR. c-CBL ubiquitylates EGFR, which results in its endocytosis and degradation and, therefore, receptor desensitization in response to growth-factor signalling. Could effects on c-CBL be responsible for the change in expression of EGFR in response to c-SRC? Ectopic expression of c-CBL increased the removal of EGFR from the surface of SYF cells (which lack SRC, YES and FYN), but this receptor endocytosis was inhibited by the co-expression of an active-mutant c-SRC. The authors found that c-SRC prevents the c-CBL-EGFR interaction (which is required for receptor ubiquitylation), specifically downregulates the expression of c-CBL and recruits c-CBL to vesicles. So, how does c-SRC decrease the level of expression of c-CBL? Expression of active-mutant c-SRC leads to polyubiquitylation of c-CBL, which targets this protein for degradation by the proteasome. This process does not occur for a RING-finger closely related compound that does not inhibit HH signalling had no effect on SCLC cells. Cyclopamine also inhibited growth of three different SHH- and GLI1-expressing SCLC xenografts in nude mice, but not of NSCLC or colon cancer xenografts.

Activation of HH signalling has been previously associated with medulloblastoma. The HH pathway regulates cerebellar progenitor differentiation, and in this brain tumour it is believed to allow malignant cells to maintain progenitor-like fates. Similarly, SCLC might represent a malignancy that arises from an airway epithelial progenitor and has maintained its HH signalling capabilities, as these cells continue to express SHH and lack PTCH mutations. Drugs designed to inhibit HH signalling could therefore have therapeutic effects in patients with SCLC.

Kristine Novak

References and links


WEB SITE Stephen Baylin’s lab: http://www.hopkinsmedicine.org/graduateprograms/cmmb/baylin.html

TUMORIGENESIS

Back in time

A number of developmental signalling pathways have been shown to be reactivated during tumour formation — the Hedgehog (HH) pathway seems to be the latest member of this growing list. HH signalling mediates pattern formation during embryogenesis, and has recently been shown to regulate epithelial–mesenchymal interactions during lung development. In Nature, Watkins et al. now report that HH signalling also promotes lung tumour development.

Sonic Hedgehog (SHH) — a secreted ligand for the HH receptor patched (PTCH) — is a signalling switch expressed by a variety of differentiation subpopulations of cells throughout the embryo. Loss of Shh function results in severe lung defects in mice. Unlike skin and colon, the adult airway epithelium only proliferates in response to injury. In a search for factors that activate airway epithelial-cell proliferation after injury, Watkins et al. observed increased expression of both Shh and its transcriptional effector GlI1 in an adult mouse model of acute airway repair.

This was surprising, as this pathway had been previously only associated with embryonic lung epithelial cells, where it signals adjacent lung mesenchyme to regulate branching morphogenesis. Watkins et al. next looked to see if Shh was upregulated in lung tumours. They examined different tumour types, and found that 5 of 10 human small-cell lung carcinoma (SCLC) samples expressed SHH and GLI1. Only 9 of 40 non-SCLC (NSCLC) tumour samples expressed SHH, however, and only 4 of these also expressed GLI1. These findings indicate that the HH signalling pathway is reactivated in lung cancer cells — predominantly in SCLC.

But is ligand-driven HH pathway activation required for SCLC formation? Antibody inhibition of SHH prevented the growth of cultured SCLC cells. Furthermore, treatment of nine SCLC cell lines that expressed both SHH and GLI1 with cyclopamine — an alkaid inhibitor of the HH pathway — induced both growth arrest and apoptosis. Cyclopamine had no effect on growth of NSCLC cells, and a more SCLC-like form of c-SRC was shown to have no effect on receptor synthesis (mRNA levels). So, how does c-SRC decrease the level of expression of c-CBL? Expression of active-mutant c-SRC leads to polyubiquitylation of c-CBL, which targets this protein for degradation by the proteasome. This process does not occur for a RING-finger closely related compound that does not inhibit HH signalling had no effect on SCLC cells. Cyclopamine also inhibited growth of three different SHH- and GLI1-expressing SCLC xenografts in nude mice, but not of NSCLC or colon cancer xenografts.

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Kristine Novak
mutant of c-CBL (lacking ubiquitin-ligase activity), which indicates that c-SRC activates a self-ubiquitylating function of c-CBL. However, the RING-finger mutant is still susceptible to the degradative effects of c-SRC, so it is probable that alternative, ubiquitin-independent mechanisms for the degradation of c-CBL are also used.

These data indicate the following mechanism of oncogenic cooperation. Increased expression of c-SRC or expression of a constitutively active form leads to the destruction of c-CBL (through self-ubiquitylation or other means). In turn, reduced levels of c-CBL mean that EGFR ubiquitylation and endocytosis (receptor desensitization) are inhibited and growth-factor signalling is increased, thereby potentiating EGF-induced mitogenesis.

Winging your way to cancer with wingless

The WNT oncogene — first identified as wingless in Drosophila — is known to have a role in tumour development, so could it be a useful therapeutic target? Lewis Chodosh and colleagues, reporting in the 15 February issue of Genes & Development, investigate this using a conditional mouse model of breast cancer and show that loss of Wnt1, even in advanced cancer, can result in tumour regression.

Transgenic mice were generated that expressed Wnt1 in mammary tissue only in the presence of doxycycline. Induction of Wnt1 resulted in expression of Myc — a Wnt1 transcriptional target — and an increase in ductal sidebranching by 96 hours. Prolonged exposure to Wnt signalling by continuously administering doxycycline resulted in the development of invasive mammary tumours — mostly adenocarcinomas — in 90% of mice within 1 year; control mice remained tumour-free over this period. Similar to human breast cancers, which frequently metastasize to the lung, 3 of 10 mice with overt Wnt-induced mammary tumours had lung metastases at the time of sacrifice.

The long latency for tumour development indicates that other genetic alterations are required for tumour formation, and this might lessen the therapeutic effect of inhibiting Wnt1. However, removal of doxycycline after mammary tumour formation resulted in complete regression in 94% of cases within approximately 2 weeks. Analysis of gene expression in tumours grafted onto syngeneic mice confirmed that expression of both Wnt1 and Myc was significantly decreased by 36–54 hours after doxycycline withdrawal.

Even more genetic changes must occur for a tumour to acquire the ability to metastasize; but, interestingly, metastatic lesions that had been explanted onto host mice were still sensitive to doxycycline withdrawal and transgene downregulation — all seven that were investigated regressed completely within 2–4 weeks.

So, do any genetic lesions influence this regression? Loss of p53 frequently occurs in human breast cancers and has previously been shown to increase the aggressiveness of Wnt1-induced mammary tumours. Many Wnt-induced tumours that lack p53 were still able to regress fully following doxycycline withdrawal, indicating that p53 itself is not required for tumour regression. However, loss of a single Trp53 allele did markedly reduce the number of tumours that regress completely — 40% failed to regress to a non-palpable state (compared with 6% of tumours in Trp53 wild-type mice) and rapidly resumed growth despite the continued absence of Wnt1 transgene expression. This might have been due to the spontaneous loss of heterozygosity for Trp53, and resulting chromosomal instability that was observed by FACS analysis in tumours arising in Trp53+/− mice.

For Wnt1 inhibition to be an effective cancer treatment, it must be able to induce long-term regression. Almost a third of mammary tumours regressed within a year, and both the extent and rate of regression was accelerated in Trp53+/− mice, a group in which almost 80% of tumours had recurred by 30 weeks.

So, p53 loss increases tumour recurrence in animals whose tumours have fully regressed, and so decreases disease-free survival. Wnt inactivation exerts a selection pressure for loss of p53 and this, in turn, could impair the effectiveness of drugs that target this pathway. Nevertheless, this report does show that developing inhibitors of Wnt could be an effective anticancer strategy that is worth pursuing.
**HIGHLIGHTS**

**Two are worse than one**

Most cases of breast cancer are dependent on oestrogen for tumour progression, and treatment with tamoxifen, which modulates the oestrogen receptor (ER), has been successful in considerably reducing deaths from breast cancer. However, many patients become resistant to tamoxifen and C. Kent Osborne and colleagues now show that overexpression of an oestrogen receptor co-activator, AIB1, together with high expression of a member of the epidermal growth-factor-receptor family, ERBB2 (also known as HER2/neu), in ER-positive breast cancer patients is associated with resistance to tamoxifen.

Osborne et al. examined tumour samples from 316 breast cancer patients with long-term follow-up. In the 187 patients who had received adjuvant tamoxifen, AIB1 expression was associated with poorer prognosis and shorter disease-free survival (DFS). ERBB2 signalling through MAPK (mitogen-activated protein kinase) activates both the ER and AIB1, and some studies have indicated that high ERBB2 expression is associated with tamoxifen resistance, so do ERBB2 and AIB1 interact to affect the response of a tumour to tamoxifen? The authors found that untreated patients with high ERBB2, regardless of the level of expression of AIB1, had worse prognosis than those with low ERBB2.

However, high ERBB2 plus high AIB1 in patients who had received adjuvant tamoxifen was an even worse prognostic factor. DFS in these patients was 42% versus 70% in patients with any other combination of ERBB2 and AIB1 expression.

So, these results confirm laboratory findings that ER co-activators can enhance the ER-agonist activity of tamoxifen — the drug is less effective in patients with high AIB1 levels. The role of AIB1 in tamoxifen resistance might explain why correlations in previous studies in which only ERBB2 was measured in tamoxifen-treated patients have been inconsistent.

**TUMOUR SUPPRESSORS**

**Sticky situation**

Tumour invasion is commonly associated with increased cell migration and extracellular-matrix destruction. In a search for genes that are disrupted during tumour formation, Vijay Yajnik et al. discovered that loss of intercellular contact structures called ‘adherens junctions’ can also contribute to tumour invasiveness.

Yajnik et al. used representational difference analysis (RDA) — a screening method for detecting homozygous deletions in genomic DNA — to identify genes that were deleted during tumour progression in the NF2+/− Trp53+/− mouse cancer model, which gives rise to tumours with high metastatic potential. One of the genes that is lost in osteosarcomas from these mice encodes Dock4, a member of the CDM family of proteins. These proteins are regulators of the small GTPases that control cell mobility, cell adhesion and invasion. Analysis of human cancer samples revealed that inactivating Dock4 mutations were also present in a variety of human cancer cells, but not in any of the 200 control samples tested.

Yajnik et al. showed that reconstitution of mouse osteosarcoma cells with Dock4 led to pronounced morphological changes. These cells developed a flattened morphology and grew to a lower cell density at confluence than the parent cell line, indicating contact inhibition. Dock4 re-expression also caused the cells to form adherent junctions — strong mechanical attachments between adjacent cells.

Formation of such cellular structures is typically regulated by the activity of small GTPases. Yajnik et al. found that re-expression of Dock4 was correlated with activation of the Rap GTPase, but not with Rac, Rho or Cdc42 GTPase activity. Furthermore, co-expression of Dock4 with a dominant-negative form of Rap prevented adherens junction formation and contact inhibition in osteosarcoma cells. Mouse osteosarcoma cells engineered to re-express Dock4 were less likely than their parent cells to produce colonies in soft agar, and produced much smaller tumours when injected into mice. These tumours also failed to infiltrate surrounding tissues, indicating that adherens junctions can somehow prevent tumour-cell invasiveness.

Further research is required to determine the mechanisms by which Rap controls adherens junction formation, and how these cellular structures regulate cell migration.

**References and links**


**WEB SITE** C. Kent Osborne’s lab: http://www.breastcenter.tmc.edu/index.htm

**References and links**


**WEB SITE** Daniel Haber’s lab: http://www.mgh.harvard.edu/depts/CancerCenter/haber.html
Acting on active AKT

Improving early detection, decreasing tobacco smoking and developing better therapies are all important strategies for combating lung cancer, but drug-targeted lung cancer prevention is another option. Ho-Young Lee and colleagues now show that AKT — a downstream component of the phosphatidylinositol 3-kinase (PI3K) pathway, which is important in regulating cell proliferation and apoptosis — is constitutively active in an in vitro lung carcinogenesis progression model. They further report that deguelin — a natural plant product — inhibits activated AKT in this model system, so showing potential as a lung cancer chemoprevention agent.

Ho-Young Lee and colleagues used normal, immortalized, premalignant and malignant human bronchial epithelial (HBE) cell lines. Deguelin inhibited cell proliferation — cells accumulated in the G2-M phase of the cell cycle — and induced apoptosis in the premalignant and malignant cell lines in a dose- and time-dependent manner, but had no adverse effects on normal or immortalized HBE cells. Levels of activated phosphorylated AKT were higher in the transformed cells than in normal cells and, at concentrations that might be attainable in vivo, the authors showed that deguelin decreased levels of phosphorylated AKT without affecting the total levels of the protein. Deguelin also decreased PI3K activity by about half, although it took longer to do so than inhibition of AKT, indicating that deguelin may inhibit AKT activity through both PI3K-dependent and -independent mechanisms.

So, is the AKT pathway a specific target of deguelin? Treatment with deguelin did not affect the activity of other components of kinase pathways, such as mitogen-activated protein kinase (MAPK), extracellular signal-related kinase 1/2 (ERK1/2) or JUN N-terminal kinase (JNK). In addition, when one of the premalignant cell lines was infected with an adenovirus expressing constitutively active AKT and treated with deguelin, inhibition of growth and triggering of apoptosis was much reduced.

As deguelin belongs to a class of agents that are used as insecticides, which have been associated with cardiac and other toxicities in humans, thorough evaluation of possible toxic effects will be key to the development of the compound for lung cancer prevention. Constitutive activation of AKT occurs frequently in non-small-cell lung cancer in humans, so we await further investigation of how deguelin inhibits AKT with interest.

Ezzie Hutchinson

References and links


WEB SITE Waun Ki Hong’s lab: http://www.mdanderson.org/departments/thoracic_hnmo/