Discoveries

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Break the Cigarette

As with most addictions, smoking and tobacco addictions are immensely challenging behaviours to change. For years, various pharmacological and non-pharmacological methods to reduce and discontinue smoking have been tried, with limited success.

Recently, Johnson and Stout published a remarkable study in Nature Structural and Molecular Biology on the pharmacology of a drug called Methoxsalen.[1] This drug has been clinically proven to decrease smoking. The mechanism of action proposed in this study is that methoxsalen interacts with and blocks the action of cytochrome P450 2A6 which degrades nicotine. The binding pattern and specific action is detailed in the study. Cytochrome P450 2A6 also breaks down carcinogens found in tobacco to more harmful chemicals that can cause cancer.

People who have nicotine addiction continue to smoke to maintain high nicotine levels in the brain. By preventing nicotine breakdown Methoxalen could help people reduce their craving for nicotine and stop smoking. Understanding this drug interaction will help guide future studies aimed at improving inhibitor design. Ultimately, this may lead to better drugs aimed at decreasing nicotine dependence that at the same time could also reduce the risk of tobacco-related cancers.

1. Yano JK, Hsu MH, Griffin KJ, Stout CD, Johnson EF. Structures of human microsomal cytochrome P450 2A6 complexed with coumarin and methoxsalen. Nat Struct Mol Biol 2005;12:822-3.

Tiotropium for COPD

Niewoehner et al[1] recently published results from one of the largest randomized, double blind, placebo-controlled study that evaluated the effectiveness of a long-acting inhaled anticholinergic bronchodilator, tiotropium, in reducing COPD exacerbations and exacerbation-related health care utilization. More than 1800 patients with moderate to severe COPD were randomized to either once-daily tiotropium (18 μg) or placebo for 6 months. Patients otherwise received usual care, except for other anticholinergic bronchodilators. The coprimary end points were the percentage of patients with a COPD exacerbation and the percentage of patients with a COPD-related hospitalization.

Tiotropium significantly reduced the percentage of patients experiencing one or more exacerbations compared with placebo (27.9% vs. 32.3%, respectively), although it did not significantly reduce all-cause hospitalization rates. The authors are hopeful that exacerbations and COPD-related health burden may be significantly reduced in patients with moderate to severe COPD. They do caution, however, that since participants were enrolled from Veteran medical centers 99% were men, and the follow-up period extended for only 6 months. A longer follow-up period is needed to soundly confirm these results.

1. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 20056;143:317-26.

Prophylactic Rescue

Tachyarrhythmias are common after heart surgery and are associated with increased morbidity. Several studies have investigated the prophylactic role of amiodarone in decreasing the incidence of postoperative atrial tachyarrhythmias. However, due to inconclusive results and lack of adequate power to detect changes in cardiovascular morbidity, length of stay, or mortality, the evidence remains cloudy. To clarify these data, Aasbo et al.[1] conducted a meta-analysis of ten such double-blind, randomized, placebo-controlled trials involving 1744 patients collectively, which reported the incidence of supraventricular arrhythmia, atrial fibrillation, or atrial flutter as the primary end point.

Amiodarone therapy was found to decrease the incidence of atrial fibrillation or flutter (relative risk, 0.64 [95% CI, 0.55 to 0.75]), ventricular tachycardia and fibrillation (relative risk, 0.42 [CI, 0.28 to 0.63]), stroke (relative risk, 0.39 [CI, 0.21 to 0.76]), and length of stay (weighted mean difference, -0.63 day [CI, -1.03 to -0.23 days]). Three studies found significantly more adverse events with amiodarone therapy, including nausea permitting continuation of therapy, bradycardia of unclear clinical significance, and increased intensive care monitoring and support.

Conclusively, amiodarone may benefit some patients undergoing heart surgery. However, the authors suggest that a multicenter, randomized, double-blind trial with cardiovascular outcomes that compare amiodarone with placebo in patients already receiving a β-blocker is needed. This is specifically because not all studies evaluated here used concomitant β-blockade, and regimens were not uniform among trials.

1. Aasbo JD, Lawrence AT, Krishnan K, Kim MH, Trohman RG. Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: a meta-analysis. Ann Intern Med 2005;143:327-36.

Therapy-related disease

A breakthrough study published in Science in September this year by O'Donovan and colleagues in the UK may explain the prevalence of skin cancer in long-term survivors of organ transplantation.[1] Oxidative stress and mutagenic DNA lesions formed by reactive oxygen species (ROS) are linked to human malignancy. Several clinical treatments are known to induce chronic oxidative stress and may therefore carry a risk of therapy-related cancer. The authors tested their hypothesis that immunosuppression by azathioprine (Aza) may be one such treatment. Aza works by incorporating its metabolite 6-thioguanine (6-TG) into the patients' DNA. They successfully demonstrate that biologically relevant doses of ultraviolet A (UVA) generate ROS in cultured cells with 6-TG-substituted DNA (which also escapes DNA repair). Thus 6-TG and UVA are synergistically mutagenic. A preliminary analysis revealed that in five of five cases, Aza treatment was associated with a selective UVA photosensitivity.

1. O'Donovan P, Perrett CM, Zhang X, Montaner B, Xu YZ, Harwood CA, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science 2005;309:1871-4.

Gene Invasion

Joan Massague and colleagues from the Cancer Biology and Genetics Program (New York) have published two spectacular studies on breast cancer metastasis. The first one was published in Nature (July 2005) and elucidates the role of genes that mediate breast cancer metastasis to the lung but not other organs.[1] The second study was published in PNAS (September 2005) and it describes the role of the Smad pathway in human breast cancer bone metastases.[2]

The Nature study demonstrates that one subset of the genes involved in lung metastases promote primary tumour growth, and a second subset affects the cancer's virulence at the metastatic site. Strikingly, these genes are over expressed in breast tumours that later spread to the lung, but not in those that spread to the bone. Equally interesting was the finding that patients with the gene signature for lung metastasis had a worse prognosis than other patients. The results of this work could help tailor treatment options for patients according to their gene signature by refining the prognosis of breast cancer.

Smad transcription factors are typical tumor suppressors that inhibit cell proliferation. Smad mutations disable this tumor-suppressive pathway in certain cancers, but breast cancer cells frequently evade the cytostatic action of TGF-beta while retaining Smad function. This landmark study provides evidence for active Smad signaling in human and mouse bone-metastatic lesions. Genetic depletion experiments further demonstrate that Smad4 contributes to the formation of osteolytic bone metastases and is essential for the induction of IL-11, a gene implicated in bone metastasis in a mouse xenograft model system. The authors show that activator protein-1 is a key participant in Smad-dependent transcriptional activation of IL-11 and its over expression in bone-metastatic cells. These crucial findings provide functional evidence for a switch of the Smad pathway, from tumor-suppressor to prometastatic, in the development of breast cancer bone metastasis. This study adds much value to our understanding of the biology of cancer.

1. Minn AJ, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, et al. Genes that mediate breast cancer metastasis to lung. Nature 2005;436:518-24.

2. Kang Y, He W, Tulley S, Gupta GP, Serganova I, Chen CR, et al. Breast cancer bone metastasis mediated by the Smad tumor suppressor pathway. Proc Natl Acad Sci U S A 2005;102:13909-14.