Linking protein to chronic obstructive pulmonary disease could lead to indication of disease and novel treatments

Biochemists from The University of Texas Health Science Center at Houston (TX, USA) report that they have linked the osteopontin (OPN) protein to chronic obstructive pulmonary disease (COPD). This work could eventually lead to new approaches to the treatment of the disease.

Michael Blackburn, the study's senior author and professor in the Department of Biochemistry and Molecular Biology at the University of Texas Medical School at Houston used a mouse model to demonstrate that they could prevent COPD features by genetically removing OPN. They then analyzed COPD patients' airways and found that OPN was elevated, indicating that a similar approach may be applicable in humans.

COPD is an under-diagnosed progressive lung disease which causes difficulties with breathing and deterioration in the quality of life, and it may lead to death. The World Health Organisation (WHO) predicts that COPD will become the third leading cause of death worldwide by 2030. Over 12 million Americans are diagnosed with COPD, which is reported as the fourth-leading cause of death according to the National Heart, Lung and Blood institute. COPD includes two major conditions – emphysema and chronic obstructive bronchitis.

Dr Blackburn described the significance of the study, "This is an important cross-over study. Because we can show osteopontin is elevated in people with COPD, this suggests that osteopontin could serve as both an indicator of disease progression and a therapeutic target."

The recent study stems from Balckburn's research involving adenosine, which can control the process of inflammation in wound healing. It also activates a cell surface receptor, A2B, which is associated with COPD. Dr Blackburn has spent the last decade focusing on research aimed at blocking the A2B receptor.

The researchers induced COPD features in mice, comparing the symptoms experienced by mice with OPN and those who had it genetically removed. It was found that mice without OPN had less inflammation and lung disease.

"This paper reveals exciting new information on the pathogenetic mechanisms involved in the development of chronic obstructive pulmonary disease and emphysema," commented Richard J Castriotta, professor and director of the Pulmonary, Critical Care and Sleep Medicine Division at the UT Medical School at Houston and medical director of the Sleep Disorder Center at Memorial Hermann – Texas Medical Center.

Owing to their work linking OPN to COPD, Blackburn and his team believe that they may have uncovered a protein that could lead to a more targeted approach to treating emphysema.

"As a physician scientist, one goal of drug development is to offer more specific drug targets to treat the disorder, and osteopontin provides a specific target that may be associated with fewer side effects," explains Schneider.

"This paper adds a new element, osteopontin, to the mix by discovering its significant role in the development of COPD with emphysema ... It's still too early to be used clinically, but there may be a place for osteopontin in the future as an indicator of lung disease in progress that leads to COPD and emphysema," Castriotta remarked on the future developments of this study.

Source: Schneider DJ, Lindsay JC, Zhou Y, Molina JG, Blackburn MR: Adenosine and osteopontin contribute to the development of chronic obstructive pulmonary disease. FASEB J. *DOI: 10.1096/fj.09-140772 (2009) (Epub ahead of print).*

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New vaccine shows potential for chronic obstructive pulmonary disease patients at risk of pneumonia

A new vaccine may be superior in preventing pneumonia in patients with COPD compared with the current vaccine.

Pneumonia affects COPD patients and can often cause exacerbations of the disease. It is recommended that individuals who suffer from COPD should receive the 23-valent pneumococcal polysaccharide vaccination (PPSV23). However, debate exists over the immunogenicity and protective efficacy of the antibodies produced by this vaccine.

Mark Dransfield and his colleagues from the University of Alabama at Birmingham, AL, USA set out to discover the efficacy of a new vaccine, PCV7. The new vaccine works by conjugating the pneumococcal polysaccharide antigen to a stronger antigen, the diphtheria toxin. In this way, it is hoped that the conjugated vaccine will provoke a stronger immune response.

"Conjugated vaccines were originally intended for young children who respond poorly to polysaccharide antigens", explained Dr Dransfield. "We wanted to see whether they could have a similar effect in the COPD patient population in whom immune responses may also be blunted".

A total of 120 individuals with moderate to severe COPD were randomized in an open-label trial that demonstrated that both the old vaccine and the new conjugated vaccine were well-tolerated, but PCV7 vaccine administration resulted in a superior immune response on several measures of immunogenicity.

In patients who received the PCV7 vaccine, the proportion of individuals who displayed a twofold increase in serotype-specific IgG antibodies was higher than in those receiving PPSV23 in five of the seven serotypes tested. Moreover, 1 month after the vaccination, the blood from the PCV7-receiving group killed pneumococci more effectively in six of seven serotypes tested.

There is also another vaccine in development that contains the capsule of 13 pneumococcal serotypes (PCV7 has seven).

Dr Dransfield hopes that "future research will confirm the superior immunogenicity of PCV13 in COPD … We also want to determine the relative duration of the immune response following PPSV23 and conjugate vaccination, and to identify the immunologic correlates of protection against both invasive and noninvasive pneumococcal disease. We believe our data provide the rationale for further study of the clinical efficacy of protein-conjugate pneumococcal vaccines in the high-risk COPD population."

Source: Dransfield MT, Nahm MH, Han MK et al.*: Superior immune response to protein-conjugate versus free pneumococcal polysaccharide vaccine in chronic obstructive pulmonary disease.* Am. J. Respir. Crit. Care Med. *180. 499–505 (2009).*

'Compelling evidence' for beneficial statin use in chronic obstructive pulmonary disease

Canadian researchers have reported that there is 'compelling evidence' for an advantage in using statins for COPD. However, the evidence has not been deemed strong enough to develop statin indications beyond vascular protection.

John Swiston, from the University of British Columbia, Canada, and his team of researchers reported that statins do not only have a role in lowering high cholesterol. The scientists from Vancouver believe that statins also have anti-inflammatory and immunomodulatory pleiotropic effects that are beneficial in COPD.

Dr Swiston and his team performed a systematic review in which they analyzed nine studies that evaluated the effect of statins in patients with COPD. Both individually and collectively, the studies demonstrated that statins were beneficial in various COPD-specific outcomes including lung function, exercise capacity, exacerbation and mortality. However, eight of the studies were retrospective cohorts, case–control studies or epidemiologic analyses. Only one was an interventional randomized controlled trial.

Although the results are promising, the researchers have pointed out that owing to the lack of randomized controlled trials there is not enough data to support changes in the clinic.

According to Dr Swiston, "Multiple observational studies in the setting of biological plausibility paints a compelling picture, but is not sufficient to justify routine clinical use of statins for COPD patients"

"However, the current literature is sufficient to ethically and financially justify large, well-designed randomized controlled prospective studies. These types of studies, if properly carried out, will provide stronger evidence either supporting or refuting the utility of statins as part of medical therapy for COPD", he added.

The authors conclude that a therapeutic intervention that positively affects outcomes in this way could benefit the individual, social and economic consequences of the disease.

Source: Janda S, Park K, FitzGerald JM, Etminan M, Swiston J: Statins in COPD: a systematic review. Chest *136(3), 734–743 (2009).*

Almirall are to file once-daily aclidinium bromide for chronic obstructive pulmonary disease in Europe

The pharmaceutical company, Almirall (Barcelona, Spain), have revealed that they wish to file a Marketing Authorization Application (MAA) with the European Medicines Agency (EMEA) for Eklira® (aclidinium bromide), which is a long-acting muscarininc antagonist. The drug is to be administered once-daily for the maintenance of bronchodilator treatment and the control of COPD symptoms.

The filing will be supported by a large clinical programme. There will be two 12-month studies (ACCLAIM/COPD I and II), a rate-of-onset study and an exercise endurance and lung hyperinflation study. The programme accounted for more than 2000 patients across the globe.

The ACCLAIM/COPD Phase III studies demonstrated aclidinium to consistently achieve a sustained statistical significant difference compared with placebo in trough forced expiratory volume in 1 second (FEV_1). These results were maintained throughout the 12-month treatment period. It also significantly increased the proportion of individuals who demonstrated a clinically relevant improvement in health-related quality of life compared with placebo. Furthermore, aclidinium delayed the time to patients' first moderate or severe exacerbation.

Assessed in approximately 2500 subjects, the safety and tolerability of the drug was similar to placebo. This included 1647 patients who were treated for 1 year. Potential anticholinergic adverse effects were only observed in a small percentage of patients: dry mouth was experienced by 0.7% of the aclidinium group and 1.2% of the placebo group.

"COPD patients are characterized by their heterogeneity in symptoms and today there are relatively few treatment options available for patients living with this debilitating disease. Based on the results of the clinical program, I think that aclidinium bromide can provide a clinically meaningful improvement in bronchodilation, symptoms and health-related quality of life and will provide a worthwhile alternative for patients", commented Professor Paul Jones from St George's Hospital, University of London, UK.

Two other clinical studies also achieved success. One assessed the rate of onset of bronchodilation and the other evaluated exercise endurance and lung hyperinflation in patients with moderate to severe COPD. A single dose was shown to have a bronchodilation effect comparable to the current drug on the market and significant improvement in exercise endurance time.

It is hoped that Eklira will be a new treatment option for COPD patients.

Source: Almirall, www.almirall.com/webcorp2/cda/comunicacion_detalle_noticia.jsp?id=1225

Individualizing chronic obstructive pulmonary disease treatment by predicting risk of death

An index scale has been developed to help physicians predict a patient's risk of dying from COPD. The scale is called the 'ADO index' and it can aid physicians in assessing the severity of the illness to determine the appropriate treatment level.

The current assessment used by chest physicians is the BODE index. It is based on body-mass index, airflow obstruction, dyspnea and exercise capacity. The problem with this assessment is because in the primary care setting, where treatment options are usually managed, exercise capacity cannot be measured very easily.

Milo A Puhan, associate professor in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health (MD, USA) and his colleagues developed a simplified BODE index and the ADO index, which included age, dyspnea and airflow obstruction. They compared the BODE index predictions with the 3-year risk of all-cause mortality in 232 patients from Switzerland. The new ADO index and the updated BODE index were then confirmed with a cohort of 342 patients from Spain.

"The burden from COPD is so enormous that we need to reach out to any doctors who care for COPD patients. The ADO index can be used in any setting, and we hope that it will serve as a basis for more individualized treatment selection in the near future," stated Dr Puhan.

The results of the study demonstrated that the updated BODE and new ADO indices were able to accurately predict 3-year mortality, and matched this observation in the Spanish cohort with little difference between predicted and observed mortality when compared with the original BODE index. The old test did not perform well when predicting 3-year risk of mortality. It made a 36% under-prediction in the Swiss cohort and a 39% over-prediction in the Spanish cohort.

Source: Puhan MA, Garcia-Aymerich J, Frey M et al.*: Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index.* Lancet *374(9691), 667–668 (2009).*

Treatment for chronic obstructive pulmonary disease should start early, study says

It has been shown that treatment with inhaled tiotropium at an earlier stage of COPD can lessen the decline of lung function. Marc Decramer from the University Hospital, University of Leuven, Belgium, and his colleagues made their conclusions based on the UPLIFT study. The study shows that treatment should begin at an earlier stage.

The UPLIFT study in fact investigated patients at all disease stages, but the authors in this paper performed a subgroup analysis of prespecified patients specifically at Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II (moderate disease). A total of 2739 patients had GOLD stage II at randomization. Pre- and post-bronchodilator spirometry was performed with the study drug and the short-acting bronchodilators, ipratropium and salbutamol. The mean post-bronchodilator FEV_1 volume was 1.63 l, 59% of the predicted value. A total of 2376 participants qualified for final analysis and of these, 1218 patients received tiotropium and 1158 received placebo. This was over a period of 4 years.

The results demonstrated that the rate of reduction of mean post-bronchodilator FEV_1 per year was 12% less in the tiotropium group when compared with the placebo group. Pre-bronchodilaltor mean FEV_1 was similar between the two groups. Health status in the tiotropium group was better for those receiving tiotropium, risk of exacerbations was reduced by 18% and hospital admission owing to exacerbation also dropped by 26%

The authors conclude that "In patients with GOLD stage II COPD, long-term treatment with tiotropium seemed to reduce the rate of decline of post-bronchodilator FEV_1 and the risk of exacerbations. Since we also found that lung function and health-related quality of life were better in the tiotropium group than in the control group throughout the trial, treatment of COPD should begin in symptomatic patients with moderate disease."

Source: Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP: Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet *(2009) (Epub ahead of print).*