

Hot topics from the Assemblies

An epigenome-wide association study of total serum immunoglobulin E concentration

Authors: Liang L, Willis-Owen SA, Laprise C, *et al.*
Nature 2015; 520: 670–674

Summary: Immunoglobulin E (IgE) serum levels are known to be associated with allergic diseases such as asthma, atopic dermatitis and hay fever. Genome-wide association studies (GWAS) have found several genetic variants associated with IgE levels. The variants identified however account for only 1–2% of the total variability for this trait and GWAS have failed to identify new targets responsible for IgE regulation. CpG islands are genetic sequences associated with the promoters of many genes and their methylation is an epigenetic regulatory mechanism of gene expression. The aim of this research was to perform an epigenome-wide study of the association between CpG island methylation and total serum IgE concentration.

The epigenome-wide association study (EWAS) was conducted using data from the Medical Research Council Asthma (MRCA) panel cohort (n=355) with replication sort using two cohorts: the Poblogaeth Asthma Prifysgol Abertawe (PAPA) study (n=149) and the Saguenay-Lac-Saint-Jean (SLSJ) of Quebec (n=160).

The study found a total of 36 CpG island loci associated with IgE levels, of which, several loci were annotated to genes characteristically expressed in eosinophils. The top three detected CpGs independently accounted for 13.5% of the variation in IgE concentration in the MRCA cohort. This is 10-fold higher than the proportion of variation explained previously by genetic variants identified by GWAS. Additionally, an association was found between high IgE concentration in asthma patients and overall low methylation levels. The data suggested the enrichment of a different subset of eosinophils in atopic asthma.

This study highlights the importance of epigenetics in the pathophysiology of allergic disease and resulted in the identification of novel predictors of serum IgE concentration, which may be of utility as new biomarkers or therapeutic targets.

Reviewed by: Miguel Pereira (UK, Assembly 6)

Has growth in electronic cigarette use by smokers been responsible for the decline in use of licensed nicotine products? Findings from repeated cross-sectional surveys

Authors: Beard E, Brown J, McNeill A, *et al.*
Thorax 2015; DOI:10.1136/thoraxjnl-2015-206801

Summary: Since their introduction in 2006, electronic cigarettes are growing in volume of sales,

while licensed nicotine products sales are globally decreasing. Although initially advertised as safer in relation to cigarettes, more and more evidence is surfacing that it is almost as harmful.

BEARD *et al.* focused on whether there was a real shift of tobacco smokers from standard cigarettes to these devices or if non-smokers take up electronic cigarettes.

They performed monthly surveys of over 14 000 smokers living in England, asking about their use of electronic cigarettes or other nicotine products and if they were smoking less regular tobacco.

Looking at their results, there was an obvious quick increase in electronic cigarette use (from 2.2 to 20%) by smokers in the beginning with little change thereafter. During this rapid increase, licensed nicotine product use rate was steady and only after 1–2 years dropped gradually (from 15.9 to 6–10%). According to the authors, the rise electronic cigarette smoking could be explained by media and social marketing selling these devices as an aid to decrease or even stop smoking.

Although this study might suggest electronic cigarette use is not associated with the decrease in licensed nicotine product sales, the reasons for this reduction were unclear: there was no significant decrease in number of people looking for smoking cessation, and nicotine advertising and marketing increased during the study period.

These data seem to confirm that these new devices may be responsible for broadening the nicotine products market, resulting in an increase of the number of people who will be affected by this addiction and also decreasing therapeutic effectiveness of individuals who want to quit smoking.

Reviewed by: João Cravo (Portugal, Assembly 6)

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Authors: Izurieta HS, Thadani N, Shay DK, *et al.*
Lancet Infect Dis 2015; 15: 293–300

Summary: This study investigated whether high-dose inactivated influenza vaccines prevented more cases of influenza-related community illness and hospital admissions than standard-dose inactivated influenza vaccines in elderly recipients (>65 years). High-dose compared with standard-dose influenza vaccines contain four times more influenza haemagglutinin antigen. The primary and secondary outcomes were influenza infection (defined as rapid influenza diagnostic test followed by oseltamivir) and hospital/emergency

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ERS 2015

department visit, respectively. Data on influenza vaccination and infection rate were collected from Medicare programmes and linked with inpatient data. Between August 2012 and January 2013, nearly 1 million high-dose and over 1.5 million standard-dose vaccinations were administered.

Post-vaccination, the standard-dose group more frequently sought medical advice for influenza-related symptoms and this resulted in increased prescribing of Oseltamivir (Tamiflu) based on rapid influenza diagnostic testing (risk difference: 0.29, 95% CI: 0.19–0.38). All participants in the high-dose vaccine group had a reduction in influenza infection, in particular those aged >85 years (0.62 *versus* 0.98 outcomes per 10 000 person-weeks in the high *versus* standard-dose cohort). Notably, the high-dose compared with the standard-dose vaccine group had a reduction in influenza-related hospital admissions (0.86 *versus* 1.10 outcomes per 10 000 persons-weeks in the high *versus* standard-dose cohort).

Previous RCTs have shown high-dose vaccinations provide better protection against influenza. This is the first study to show that high-dose influenza vaccination can reduce hospital admission rates, a very relevant endpoint globally. These results provide important information for vaccination and immunisation policymakers to consider whether high-dose influenza vaccination should become the 'gold standard' for all >65 year olds.

Reviewed by: Ashleigh Trimble (UK, Assembly 10)

Epigenetic mechanisms regulate NADPH oxidase-4 expression in cellular senescence

Authors: Sanders YY, Liu H, Liu G, *et al.*

Free Radic Biol Med 2015; 79: 197–205

Summary: Ageing, which is implicated in several chronic lung diseases such as fibrosis, is characterised by cellular senescence. Senescence is defined as a state of irreversible cell-cycle arrest and regulated, amongst others, by epigenetic factors. Senescent cells show an increased expression and activity of the reactive-oxygen species (ROS) producing enzyme, NADPH oxidase (Nox) 4. This study investigated which epigenetic mechanisms regulate Nox4 in senescent lung fibroblasts. In this study, human diploid lung fibroblasts (IMR-90) were used as a model of replicative senescence. Endpoints included analysis of histone modifications as well as the methylation status of the Nox4 gene promoter.

SANDERS *et al.* observed histone modifications of the Nox4 gene that are associated with an open chromatin structure. More specifically, the Nox4 gene in senescent cells was enriched with the active histone mark H4K16Ac whereas the repressive mark H4K20Me3 was depleted thereby promoting transcription of the Nox4 gene. Moreover, down-regulation of Mof, a specific acetyltransferase of histone H4K16, reduced Nox4 expression through decrease of the active mark H4K16Ac. No significant differences in

DNA methylation of the Nox4 promoter were found between senescent and non-senescent fibroblasts, although the expression of the DNA methyltransferase (DNMT) 1 was globally decreased in senescent cells.

These results show an important role of the acetyltransferase Mof in the modification of the histone mark H4K16Ac, thereby regulating the gene expression of Nox4. Collectively, these data provide new insights into the epigenetic activation of Nox4 and may yield new treatment options for chronic age-related diseases, such as idiopathic pulmonary fibrosis, in which Nox4 is overexpressed.

Reviewed by: Carmen Veith (The Netherlands, Assembly 3)

Natural history of typical pulmonary carcinoid tumors: a comparison of nonsurgical and surgical treatment

Authors: Raz DJ, Nelson RA, Grannis FW, *et al.*

Chest 2015; 147: 1111–1117

Summary: Carcinoid pulmonary tumours, comprising the 1–6% of all lung tumours, are composed of two types: typical and atypical. Surgical excision is the treatment of choice. Typical pulmonary carcinoids have more benign behaviour compared with atypical ones. However, their natural history and how this affects the survival of patients with contraindication for surgical removal (elderly and in high operative-risk patients) has not been studied. The authors, using data from the Surveillance, Epidemiology, and End Results Program, studied the survival of 4111 patients with biopsy specimen-proven lymph node-negative typical lung carcinoid tumour who had either no resection (306 patients) or surgical resection (sublobar resection 929 patients, lobectomy 2,876 patients). Kaplan-Meier plots were used to analyse the overall survival and disease-specific survival (DSS) and predictors of survival were identified by multivariate Cox proportional hazard models.

The observed 5- and 10-year overall survival and DSS in no surgery patients was high, 69% and 88%, respectively, but worse compared with operated patients by lobectomy (93% and 97%, respectively) or sublobar resection (92% and 98%, respectively) ($p < 0.001$). DSS was worse for all tumour size (T1–T4) in no surgery patients. Non-operative management was also associated with an increased risk for disease-specific mortality compared with lobectomy (hazard ratio 2.14, 95% CI 1.35–3.40; $p = 0.001$).

This study showed that although surgical resection of lymph node-negative pulmonary carcinoid tumours offers an increased survival, the no surgery patients have also high 5-year DSS. This finding supports the non-operative management (observation or endoscopic management in symptomatic cases) of elderly and in high operative-risk patients.

Reviewed by: Eleftheria Chaini (Greece, Assembly 11)

Hot topics are short (approx. 200 words) summaries of recent important articles in respiratory medicine written by Junior ERS members. To become a hot topic author, please contact Aran Singanayagam: e-mail: arasinga@gmail.com