Structural and functional changes in the airways of acute and chronic murine models of asthma.

Rhys Evans[1,2], Kenneth Broadley[1], Will Ford[1], Emma Kidd[1], Tony Nials[2]. [1]Cardiff University, Cardiff, United Kingdom, [2]GlaxoSmithKline, Stevenage, Herts, United Kingdom.

Asthma is a chronic inflammatory disease characterised by airway inflammation, airway hyperresponsiveness (AHR), reversible airway obstruction and airway remodelling[1]. Most animal models of asthma focus on acute allergen challenges and airway remodelling is absent[2]. This study compared airways histology with function and inflammation in acute and chronic ovalbumin (OA) challenge murine models.

Groups of six BALB/c male mice (20-25g) were sensitised with i.p. OA (100µg) and $Al(OH)_3$ (100mg) on days 1 and 5. The acute group was challenged with nebulised OA (0.5%, 1h) twice (4 h apart) on day 15. The chronic group was challenged from day 15 with OA (2%) 3 times a week for 6 weeks (18 challenges). Controls received saline at the same times. Lung function was assessed by plethysmography (enhanced pause - P_{enh}). AHR to inhaled methacholine (MCh) (30mg/ml for acute; 10mg/ml for chronic) was assessed by measuring P_{enh} pre- and 24h-post-final OA challenge. Lung differential cell counts and histology followed the final MCh challenge.

Compared to controls, an early (0-6h) bronchoconstriction (increase in P_{enh}) was observed in both acute OA (64.6±2.7 vs 20.4±5.0%) and chronic OA (55.8±7.8 vs 23.1±8.5%) challenged mice. A late phase bronchoconstriction was seen 7-12 hours following acute (55.8±3.7 vs 21.5±3.8%) and chronic OA (47.5±10.1 vs 1.7±4.3%) challenge. Post-OA, MCh increased P_{enh} compared to controls in the acute (1203.9±115.6 vs 2.2±3.3%) and chronic OA (362.6±16.1 vs -10.3±2.2%) groups, suggesting AHR. Compared to controls, % eosinophils increased in the acute (15.7±0.7 vs 0.4±0.2%) and chronic OA (12.5±1.0% vs. 0.2±0.1%) mice. Structural changes were only observed in the bronchioles of chronic OA challenged mice. Thus, airway-associated collagen deposition (51.5±5.2 vs 14.2±4.4%) and mucin-associated goblet cells (13.6±2.6 vs. 2.8±0.7au) both increased compared to controls.

Acute and chronic OA challenged mice showed airways functional and inflammatory changes but airway remodelling was only observed in the chronic OA group suggesting it may be a better pre-clinical model of asthma.

[1] McMillan, S.J. and Lloyd, C.M. (2004).Clinical and Experimental Allergy, 34:497-507.
[2] Kumar, R.K., Herbert, C. and Foster, P.S. (2008). Current Drug Targets, 9:485-494.

RLE supported by a BBSRC/GSK studentship. We thank Dr. T Nials for helpful advice.