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Title: Maternal genetic asthma predisposition affects signaling networks in lungs of neonatal offspring

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Body: Introduction: Exposure-induced deregulation of microRNAs (miRs) during early critical developmental periods has been proposed to contribute to the propagation of asthma risk in later life. Aim: We asked if maternal genetic asthma predisposition is sufficient to affect pulmonary miR and also mRNA profiles in offspring that do not bear the genetic asthma risk. To address this question, we used female mice with a heterozygous deficiency for Tbx21 as they develop spontaneous airway remodeling and airway hyperreactivity (Finotto et al., Science, 2002; 295:336). Methods: Female C57BL/6J Tbx21+/- mice were mated with wild type (wt) males. Neonatal lungs from wt pups of dams with (Tbx21+/-, n=8) and without (wt, n=8) genetic asthma predisposition were removed within 24h after birth and total mRNA including small RNAs was extracted. RNA from individual animals was subjected to microRNA (ABI, TaqMan® Array microRNA cards) and mRNA (Affymetrix Mouse Gene ST 1.0® arrays) expression profiling. Counter-regulated miRNA-mRNA pairs were further analyzed for pathway enrichment using in silico tools (GePS, IPA). Results: After adjustment for gender differences 57 miRNAs and 2599 mRNAs were differentially regulated. Within these, 39 miRNAs paired to 1456 mRNA targets according to expression regulation. Enrichment analysis showed that developmentally important pathways (e.g. growth factor and BMP-signaling) are affected by exposure to maternal asthma predisposition even in the absence of genetic risk in the pups. Conclusion: These data show that maternal genetic asthma predisposition affects pulmonary miR and mRNA profiles during an early developmental stage and might therefore influence lung development.