Circulating Mirnas Associated With Both Bronchodilator Response and Airways Hyperresponsiveness in Asthma

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RATIONALE: Asthma is a multifactorial and heterogenous disease where highly stable circulating miRNAs are candidate biomarkers and potential therapeutic targets. In this study, we hypothesized that miRNAs may play a role as master regulators of airway smooth muscle tone in asthma. We tested this hypothesis by investigating the overlap of miRNAs associated with baseline bronchodilator response versus those with airways hyperresponsiveness as measured by PC20 in the Childhood Asthma Management Program (CAMP). METHODS: In this analysis miRNA were sequenced from baseline serum samples of 492 CAMP children. We selected 489 samples with measures of both baseline PC20 (log transformed to normalize the distribution) and bronchodilator response. We filtered the miRNA for those present with at least 5 read counts in 50 percent of the samples resulting in analysis of 258 miRNAs. To identify differentially expressed miRNAs, we performed linear regression using the edgeR and limma R packages for this analysis, for visualizing the directionality of the associations of miRNA with bronchodilator response and PC20, we plotted a linear regression scatter plot using their normalized count values. RESULTS: We selected significant miRNAs on the basis of a nominal $p < 0.05$. We also evaluated the directionality (up-regulated vs. down-regulated), prioritizing associations in the opposite direction for the two phenotypes. Overall, we found 21 significant associated miRNAs with bronchodilator response (BDR) where 13 miRNAs are up-regulated and 8 miRNAs are down-regulated, and 35 with PC20, with 14 miRNAs up-regulated and 21 miRNAs down-regulated. We found 6 miRNAs significantly associated with both airway smooth muscle phenotypes: hsa-miR-320d (p=0.027 in BDR and p=0.010 in PC20); hsa-miR-873-3p (p=0.046 in BDR and p=0.021 in PC20); hsa-miR-320c (p=0.012 in BDR and p=0.003 in PC20); hsa-miR-29a-3p (p=0.037 in BDR and p=0.034 in PC20); hsa-miR-106b-5p (p=0.004 in BDR and p=0.029 in PC20); hsa-miR-320b (p=0.003 in BDR and p=0.005 in PC20). Of these, miR-320d and miR-29a-3p have been previously associated with inflammatory processes. CONCLUSIONS: miRNAs may modulate overall airway tone underlying multiple asthma phenotypes. These may form the basis for further mechanistic interrogation of pathways underlying airway smooth muscle function in asthma.

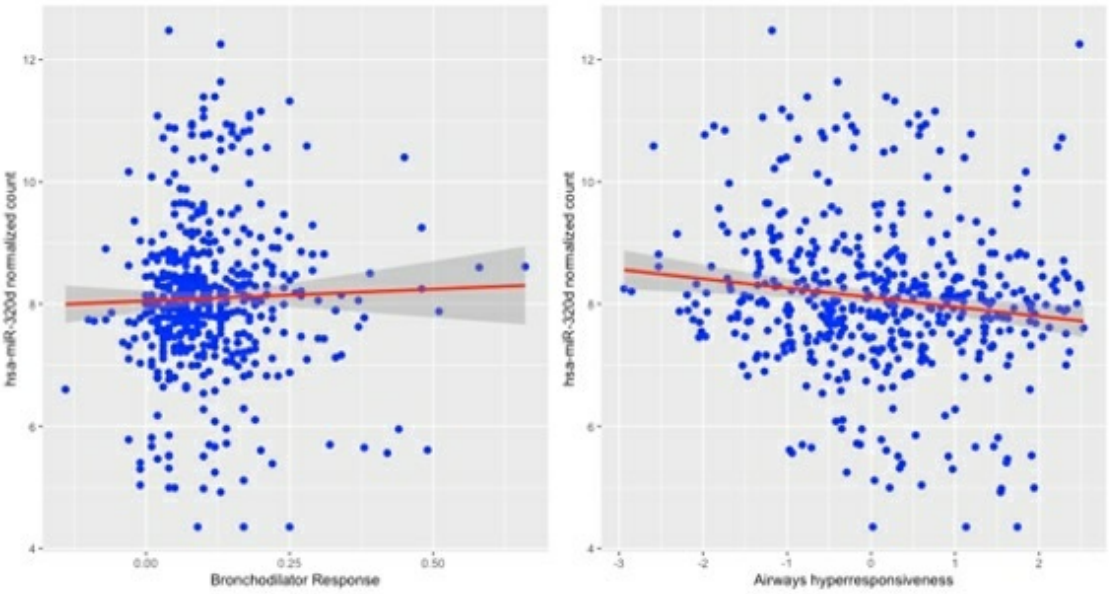

Figure: Scatter plot shows relative expression of miR-320d as significantly up-regulated in bronchodilator response and down-regulated in airways hyperresponsiveness.

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