

Article Type: Editorial

Title:

MicroRNA-155: microtuning the allergic concert

Preliminary author list:

Fabiola Cortinas-Elizondo¹, Stephan von Gunten¹

¹Institute of Pharmacology, University of Bern, Bern, Switzerland

Corresponding Author:

Stephan von Gunten, MD, PhD, MME, Institute of Pharmacology, University of Bern, INO-F, Inselspital, CH-3010 Bern, Switzerland. Phone +41 (0)31 632 32 81, Fax +41 (0)31 632 49 92. E-mail: stephan.vongunten@pki.unibe.ch.

Key words: microRNA, miR-155, purinergic receptors, allergy, inflammation

MicroRNAs (miRNAs) are small non-coding single-stranded RNAs that play a critical role in the regulation of gene expression by repressing the translation and inducing degradation of mRNAs. Given their diversity and their efficacy as post-transcriptional

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.12673

This article is protected by copyright. All rights reserved.

regulators, miRNA expression has wide-ranging implications on cellular functions. Dysregulation of this modulatory system can compromise immune homeostasis, leading to medical conditions, including allergic disease. Several studies have identified altered miRNA expression profiles in asthma, allergic rhinitis, eosinophil esophagitis and atopic dermatitis (1-4). For example, it has been recently shown in *Allergy*, that miR-19a is highly expressed in samples of severe asthmatic patients, and enhances the proliferation of bronchial epithelial cells by targeting the TGF β R2 gene (4). Another miRNA, miR-23b, has been shown to promote tolerogenic activity of OVA-stimulated dendritic cells (DCs) by inhibiting Notch1 and NF-kB signaling pathways (5).

In the current issue of *Allergy*, Zech et al. provide evidence that miR-155 is essential in DCs for the initiation and maintenance of allergic airway inflammation (6). Using a DC-driven murine model, it was demonstrated that miR-155 deficiency of DCs resulted in a marked decrease of common features of allergic airway inflammation, i.e. airway eosinophilia, production of Th2-cytokines, peribronchial inflammation, as well as a reduced bronchial hyperresponsiveness. miR-155 expression was upregulated in OVA- and HDM-pulsed DCs and its deficiency resulted in an impaired maturation of DCs. Consequently, when co-culturing OVA-primed miR-155^{-/-} DCs with OVA-specific naive T cells they failed to orchestrate a full Th2 response, as seen by a reduction in IL-4, IL-5 and IL-13 cytokine production.

Previously, functional and mechanistic studies have been performed to elucidate the role of miR-155 in allergic airway inflammation. For example, it has been reported that miR-155 is required for a proper function of B and T lymphocytes and DCs, as indicated by attenuated immune responses in miR-155 deficient mice, characterized by

impaired antibody secretion, T cell proliferation and cytokine production (7). Moreover, it was shown that miR-155 is essential in regulating CD4⁺ T cell activation by targeting c-Maf, a potent transactivator of the *IL-4* promoter, resulting in attenuated Th2 cell responses *in vivo* (7). Furthermore, recent data showed that miR-155 is able to modulate allergen-induced Th2 responses in the lung by targeting the transcription factor PU.1 (2) and *S1pr1* (8). Additionally, it has been demonstrated that miR-155 plays a pivotal role in FCεRI-mediated activation of mast cells by regulating components of the PI3Kγ signaling pathway (9).

In this issue, Zech *et al.* provide further insights on the molecular mechanisms of miR-155 activity in allergic airway inflammation, by showing a novel crosstalk of miR-155 and ATP-type 2 purinergic receptors (P2R) signaling in DCs (Fig. 1) (6). It has been previously reported that extracellular ATP, released into the airways, contributes to the initiation and maintenance of allergic airway inflammation via signaling through P2R on DCs (10). For instance, ATP-P2RY2 signaling promotes recruitment of DCs and eosinophils into the lung (11), whereas ATP-P2RX7 mediates IL-1β maturation and release (12). Now, Zech *et al.* performed an *in silico* prediction of miR-155 targets and identified potential binding sites of miR-155 on *Entpd1* and *Entpd3*, members of the ectonucleotidase family responsible for ATP degradation (6). In accordance, *Entpd1* and *Entpd3* expression levels were upregulated in lung tissue and DCs of miR-155^{-/-} mice, which presented an increased local ATPase activity compared to wild type animals. In concordance, the increased ectonucleotidase activity of miR-155^{-/-} mice affected their ATP-induced P2RY2- and P2RX7-signaling in DCs, resulting in their disturbed migration and reduction in IL-1β secretion.

We have recently highlighted the potential of pleiotropic immunomodulatory molecules, such as glucocorticoids, vitamin D, or intravenous immunoglobulin (IVIg), that target diverse cellular players or pathways involved in the complex pathogenesis of allergic inflammation (13). Likewise, miRNA-based therapeutic strategies seem promising in view of the accumulating evidence pointing towards a role of specific miRNAs in the modulation of multiple molecular processes associated with the pathogenesis or maintenance of atopic diseases. Yet, further mechanistic studies, such as the one by Zech et al. in this issue of *Allergy*, are required to fully explore the repertoire of relevant miRNAs and to dissect the specific disease-associated pathways and networks that are modulated by these molecules.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Yang Y, Zhang N, Lan F, Van Crombruggen K, Fang L, Hu G, et al. Transforming growth factor-beta 1 pathways in inflammatory airway diseases. *Allergy* 2014;**69**:699-707.
2. Malmhäll C, Alawieh S, Lu Y, Sjostrand M, Bossios A, Eldh M, et al. MicroRNA-155 is essential for T(H)2-mediated allergen-induced eosinophilic inflammation in the lung. *J Allergy Clin Immunol* 2014;**133**:1429-1438.
3. Sonkoly E, Janson P, Majuri ML, Savinko T, Fyhrquist N, Eidsmo L, et al. MiR-155 is overexpressed in patients with atopic dermatitis and modulates T-cell proliferative

responses by targeting cytotoxic T lymphocyte-associated antigen 4. *J Allergy Clin Immunol* 2010;**126**:581-589.

4. Haj-Salem I, Fakhfakh R, Berube JC, Jacques E, Plante S, Simard MJ, et al. MicroRNA-19a enhances proliferation of bronchial epithelial cells by targeting TGFbetaR2 gene in severe asthma. *Allergy* 2015;**70**:212-219.

5. Zheng J, Jiang HY, Li J, Tang HC, Zhang XM, Wang XR, et al. MicroRNA-23b promotes tolerogenic properties of dendritic cells in vitro through inhibiting Notch1/NF-kappaB signalling pathways. *Allergy* 2012;**67**:362-370.

6. Zech A, Ayata KC, Pankratz F, Meyer A, Baudiss K, Cicko S, et al. MicroRNA-155 modulates P2R-signaling and Th2-priming of dendritic cells during allergic airway inflammation in mice. *Allergy*; In press.

7. Rodriguez A, Vigorito E, Clare S, Warren MV, Couttet P, Soond DR, et al. Requirement of bic/microRNA-155 for normal immune function. *Science* 2007;**316**:608-611.

8. Okoye IS, Czesio S, Ktistaki E, Roderick K, Coomes SM, Pelly VS, et al. Transcriptomics identified a critical role for Th2 cell-intrinsic miR-155 in mediating allergy and antihelminth immunity. *Proc Natl Acad Sci U S A* 2014;**111**:E3081-3090.

9. Biethahn K, Orinska Z, Vigorito E, Goyeneche-Patino DA, Mirghomizadeh F, Foger N, et al. miRNA-155 controls mast cell activation by regulating the PI3Kgamma pathway and anaphylaxis in a mouse model. *Allergy* 2014;**69**:752-762.

10. Idzko M, Hammad H, van Nimwegen M, Kool M, Willart MA, Muskens F, et al. Extracellular ATP triggers and maintains asthmatic airway inflammation by activating dendritic cells. *Nat Med* 2007;**13**:913-919.

11. Muller T, Robaye B, Vieira RP, Ferrari D, Grimm M, Jakob T, et al. The purinergic receptor P2Y2 receptor mediates chemotaxis of dendritic cells and eosinophils in allergic lung inflammation. *Allergy* 2010;**65**:1545-1553.
12. Ferrari D, Pizzirani C, Adinolfi E, Lemoli RM, Curti A, Idzko M, et al. The P2X7 receptor: a key player in IL-1 processing and release. *J Immunol* 2006;**176**:3877-3883.
13. von Gunten S, Cortinas-Elizondo F, Kollarik M, Beisswenger C, Lepper PM. Mechanisms and potential therapeutic targets in allergic inflammation: recent insights. *Allergy* 2013;**68**:1487-1498.

FIGURE LEGEND

Figure 1 Putative role of miR-155 in allergic airway disease. Upon allergen challenge miR-155 expression is upregulated in dendritic cells (DCs). miR-155 augments extracellular ATP levels by reducing ATPase activities, presumably by targeting transcripts of endonucleotidases (Entpd1 and Entpd3). Enhanced ATP-induced P2RY2 and P2XR7 signaling promotes DC lung recruitment and allergic inflammation. Conversely, miR-155 deficiency results in increased ATP degradation and reduced allergic inflammation, likely as a consequence of decreased purinergic receptor signaling. Illustration by Aldona von Gunten.

