EBioMedicine 69 (2021) 103479

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

A new cytokine target for chronic obstructive pulmonary disease?

Jürgen Bernhagen[a,b,c,*]

[a] Chair of Vascular Biology, Institute for Stroke and Dementia Research (ISD), Klinikum der Universität München (KUM), Ludwig-Maximilians-University (LMU), 81377 Munich, Germany
[b] Munich Cluster for Systems Neurology (SyNergy), 81377 Munich, Germany
[c] Munich Heart Alliance, 80802 Munich, Germany

ARTICLE INFO

Article History:
Received 23 June 2021
Accepted 24 June 2021
Available online 10 July 2021

Chronic obstructive pulmonary disease (COPD) is an airway disease that is associated with obstructive airway wall remodelling and emphysematous tissue damage. Chronic inflammation and defective epithelial repair are causes of the disease. With cigarette smoking being the major risk factor for COPD, it is a leading cause of hospital admissions and death worldwide [1]. There is an unmet therapeutic need for COPD, since there are no effective disease-modifying treatments. Inflammatory cytokines are drivers of chronic airway inflammation, but anti-inflammatory therapeutic strategies (e.g. against TNF-α, IL-8, CCL2, or IL-1β), have shown little or no effect on COPD. Since the destruction of small airways is a major contributor to peripheral airway resistance in COPD, lung regeneration by repair-augmenting cytokines may be a promising alternative therapeutic approach [2].

In their *EBioMedicine* article, Barbro Melgert's group [3] reported on a previously unrecognized lung epithelial repair function of the macrophage migration-inhibitory factor (MIF) family protein D-dopachrome tautomerase (D-DT; also termed MIF-2) in COPD and identified atypical chemokine-receptor-3 (ACKR3) as a novel receptor for D-DT. D-DT/ACKR3 may represent a novel repair-augmenting cytokine axis in COPD.

MIF was discovered 55 years ago. It's functions have long remained unclear, but a wealth of evidence from molecular and structural studies, and *in vivo* disease models has re-defined MIF as an important pleiotropic inflammatory cytokine and atypical chemokine (ACK) with a role in inflammatory conditions, cardiovascular diseases, acute lung injury, and cancer [4, 5]. However, MIF and its receptor CD74 have a beneficial role in alveolar repair through increasing the proliferation of alveolar type-II (ATII) cells, a regenerative cell-type in the lung that can replenish damaged type-I (ATI) cells, and the low-expressing MIF-promotor polymorphism $CATT_5$ is associated with increased COPD severity in humans [6, 7].

Melgert's group investigated the role of MIF homolog D-DT on epithelial lung repair and interrogated the mechanism [3]. D-DT was found to be prominently expressed in lung tissue, mostly in ATII cells. Using a clonogenic and staurosporine-induced apoptosis assay, they found that D-DT promotes A549 cell proliferation and protects these cells from apoptosis. This was found to be mediated by an activation of the ERK1/2 and AKT kinase survival pathways. Moreover, similarities with effects elicited by the homeostatic chemokine CXCL12 provided them with a hint for the receptor mechanism. CXCL12 is the cognate ligand of the chemokine-receptor CXCR4, and together with CXCL11, also a ligand for ACKR3, an atypical chemokine-receptor formerly termed CXCR7. MIF binds to CXCR2, CXCR4, and ACKR3 [5. 8], but whether D-DT binds to the MIF chemokine-receptors was unknown. In fact, only CD74, which is hardly expressed in A549 cells, had been identified as a receptor for D-DT [9]. Using a plate-based receptor-binding assay and coimmunoprecipitation, Melgert's group found that D-DT binds to ACKR3, while no interaction with CXCR4 was observed. Consequently, in the presence of a blocking nanobody against ACKR3, D-DT failed to prevent apoptosis in A549 cells, while it's effect was amplified in ACKR3-overexpressing cells. In contrast, a CD74-blocking antibody did not interfere with D-DT's signaling effects, underscoring the specificity of the D-DT/ACKR pathway. Of note, the pro-proliferative capacity of D-DT on ATII cells was recapitulated in alveolar-type organoids derived from primary murine lung tissue. Importantly, D-DT was also able to induce epithelial growth in organoids from lung tissue of patients with GOLD stage I-IV COPD and this effect was attenuated by the ACKR3 nanobody. Together with the notion that ATII expression of D-DT in COPD tissue was lower than in healthy lung tissue and that D-DT was preferentially expressed in ATII-B cells, which are more mature than ATII-A cells, these data suggest a regenerative role for the D-DT/ACKR3 axis for lung epithelial cells from patients with COPD.

The current study [3] identifies the D-DT/ACKR3 ligand/receptor axis as a novel cytokine target in COPD. For both MIF and D-DT, dichotomous roles in disease have previously been observed. While MIF is generally viewed to have pro-inflammatory, disease-exacerbating activities, it also shows tissue-protective roles in cardiac ischemia, metabolic liver-disease and alveolar repair. D-DT promotes

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103412.
* Corresponding author.
E-mail address: juergen.bernhagen@med.uni-muenchen.de

https://doi.org/10.1016/j.ebiom.2021.103479

endotoxemia, multiple sclerosis, and tumorigenesis, but has protective roles in cardiac ischemia, heart failure, and adipose-tissue inflammation. Melgert's group suggests a protective role for D-DT in COPD, an effect linked to D-DT signaling through its novel receptor ACKR3. The study has implications for harnessing the pro-repair role of D-DT as a therapeutic strategy in COPD.

Still, important questions need to be addressed: 1) Is ACKR3 the only D-DT receptor in the lung? D-DT shares with MIF features of its N-like loop, suggesting it might be able to interact with CXCR4. Song et al. did not detect D-DT binding to CXCR4, but the applied plate-based binding assay may have blocked epitopes required for CXCR4 binding; a contribution of CXCR4 to the effects of D-DT in COPD may thus not be ruled out; 2) Are receptor complexes involved? the current study did not obtain evidence for an involvement of CD74, but MIF promotes ATII proliferation through CD74 [10] and CD74/ACKR3 complexes mediate MIF effects on lymphocytes; 3) Is a D-DT-based biologic strategy feasible? Issues related to delivery mode and pharmacokinetics would need to be resolved, and the use of D-DT in COPD patients carefully timed; 4) to this end, can a D-DT treatment scheme circumvent D-DT's known inflammatory and tumorigenic effects in the lung? [6]; 5) Lastly, the expression of D-DT in ATII cells suggests an autocrine/paracrine mode of action for D-DT, questioning whether exogenous D-DT would be effective. Inhalement would be an option, but the development of a pharmacological augmentation strategy for endogenous pulmonary D-DT could be an alternative. MIF20 is a small-molecule agonist of MIF enhancing its CD74-binding affinity by augmentation [5], and it would be tempting to speculate whether similar compounds would work for the D-DT/ACKR3 axis.

Contributors

The author did the reference search and wrote the commentary.

Declaration of Competing Interest

The author is an inventor on patent applications describing anti-MIF strategies, but otherwise declares no conflict of interest.

Acknowledgements

This work was supported by Deutsche Forschungsgemeinschaft (DFG) Grant SFB1123-A3 and by DFG under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy—ID 390857198) (to J. B.).

References

[1] Barnes PJ. Targeting cytokines to treat asthma and chronic obstructive pulmonary disease. Nat Rev Immunol 2018;18(7):454–666.
[2] Ng-Blichfeldt JP, Gosens R, Dean C, Griffiths M, Hind M. Regenerative pharmacology for COPD: breathing new life into old lungs. Thorax 2019;74(9):890–7.
[3] Song S, Liu B, Habibie H, et al. D-dopachrome tautomerase contributes to lung epithelial repair via atypical chemokine receptor 3-dependent Akt signaling. EBioMedicine 2021;68:103412.
[4] Calandra T, Roger T. Macrophage migration inhibitory factor: a regulator of innate immunity. Nat Rev Immunol 2003;3(10):791–800.
[5] Sinitski D, Kontos C, Krammer C, Asare Y, Kapurniotu A, Bernhagen J. Macrophage migration inhibitory factor (MIF)-based therapeutic concepts in atherosclerosis and inflammation. Thromb Haemost 2019;119(4):553–66.
[6] Sauler M, Leng L, Trentalange M, et al. Macrophage migration inhibitory factor deficiency in chronic obstructive pulmonary disease. Am J Physiol Lung Cell Mol Physiol 2014;306(6):L487–96.
[7] Zhang C, Ramsey C, Berical A, et al. A functional macrophage migration inhibitory factor promoter polymorphism is associated with reduced diffusing capacity. Am J Physiol Lung Cell Mol Physiol 2019;316(2):L400–5.
[8] Bernhagen J, Krohn R, Lue H, et al. MIF is a noncognate ligand of CXC chemokine receptors in inflammatory and atherogenic cell recruitment. Nat Med 2007;13(5):587–96.
[9] Merk M, Zierow S, Leng L, et al. The D-dopachrome tautomerase (DDT) gene product is a cytokine and functional homolog of macrophage migration inhibitory factor (MIF). Proc Natl Acad Sci U S A 2011;108(34):E577–85.
[10] Rajasekaran D, Zierow S, Syed M, Bucala R, Bhandari V, Lolis EJ. Targeting distinct tautomerase sites of D-DT and MIF with a single molecule for inhibition of neutrophil lung recruitment. FASEB J 2014;28(11):4961–71.