Histone deacetylase 2 (HDAC2) regulate pathological response of inflammatory monocytes: a potential target of adjuvant therapies for Covid19 infection

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Summary

Histone deacetylase 2 (HDAC2) plays a key role in the regulation of inflammatory response in monocytes. Several HDAC2 inhibitory mediators have been identified including respiratory virus, Hypoxia Inducible Factor 1alpha (HIF-1α), cigarette smoke, oxidative/nitrosative stress and chronic obstructive pulmonary disease (COPD). Human monocyte/macrophagues exposed to these mediators decrease HDAC2 activity and therefore facilitate inflammatory response, via activation of the nuclear factor-kappaB (NF-κB) complex. On the other hand, the observed pathological inflammatory response, that can impair lung function, has been successfully diminished by several drug treatments including theophylline, macrolides, nortriptyline, curcumin and andrographolide. Importantly, the anti-inflammatory action of these drugs is linked to HDAC2 activation, via phosphoinositide-3-kinase-delta (PI3K-δ) inhibition. Finally, the possible cooperation of another histone deacetylase, HDAC5, in the modulation of the pathological response of inflammatory monocytes is discussed here (Figure 1).

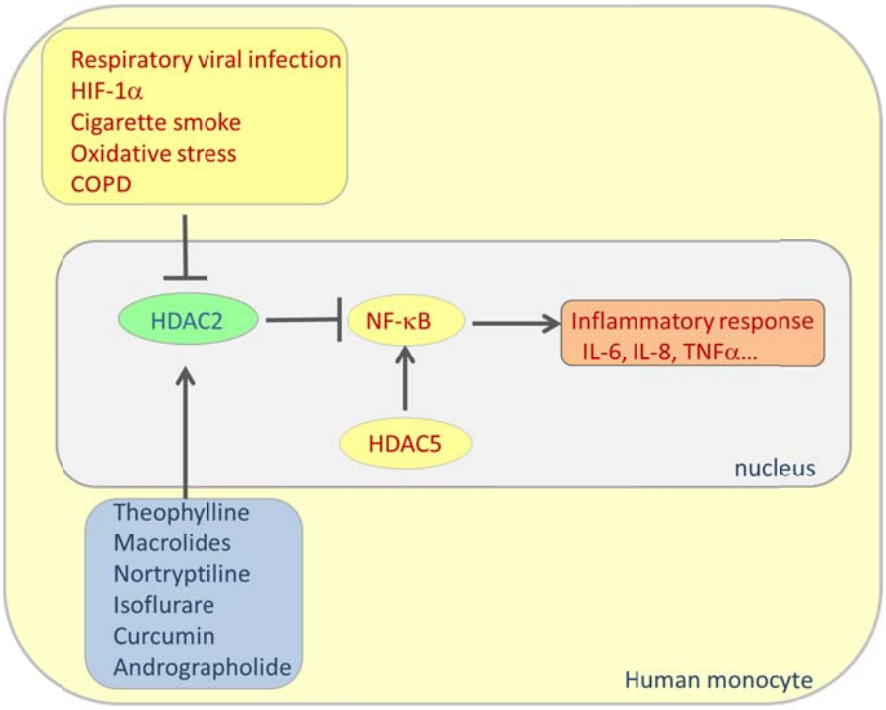

Figure 1. Representative diagram showing the influence of different HDAC2 regulators of inflammatory response of monocytes.

Introduction

Histone deacetylases (HDACs) are a superfamily of enzymes that catalyse the deacetylation of histones and influence gene expression. Of these, class I Class I (HDACs 1,2, 3, 8) are mainly ubiquitous but with nuclear localization and class II (HDACs 4, 5, 6, 7, 9, 10) are capable of shuttling between the nucleus and cytoplasm (Fuchikami et al. 2016)

Monocytes and macrophages are cells that participate mainly in the innate immune system. Monocytes circulate in the blood, but when a disturbance in tissue homeostasis occurs at any part of the body, they are capable to migrate to the affected tissue and differentiate to macrophages. Both type of cells produce proinflammatory cytokines as IL-1β, TNF-α, IL-6 and chemokines that facilitate migration (Drexhage et al. 2010).

As a class I HDAC, HDAC2 is located in the nucleus, where it can modulate inflammation in macrophages and monocytes by inhibiting the nuclear factor-kappaB (NF-κB) complex (Ito et al. 2004). In this review we are focusing on how HDAC2 participates in monocyte pathological inflammatory response. We aimed to identify a series of inflammatory mediators and therapeutic drugs exerting an opposite action on HDAC2 activity. In addition, HDAC5 is a class II HDAC and therefore it can migrate from nucleus to cytoplasm upon phosphorylation at some specific sites. While in the nucleus HDAC5 is associated to the NF-κB and facilitates transcription of inflammatory genes, HDAC5 nuclear export has been suggested to be a potential strategy to achieve anti-inflammatory action (Fuchikami et al. 2016).

Role of HDAC2 in inflammatory monocytes mediating pathological response

Firstly, we describe in Table 1 several pathological mediators of inflammatory response in monocytes that could affect to lung function. Among these, several respiratory viral infections, Hypoxia Inducible Factor 1alpha (HIF-1α), cigarette smoke, oxidative/nitrosative stress and chronic obstructive pulmonary disease (COPD) are included. These share the property of inhibiting HDAC2 activity and subsequently triggering the expression of cytokines by activating the nuclear factor-kappaB (NF-κB) complex. All the studies were carried out in humans or in human monocyte cell lines. Main findings and experimental models used were indicated.

Subsequently, we describe in Table 2 several drugs known to mediate of anti-inflammatory action in monocytes/machrophagues and therefore could be beneficial for lung function. Among these the methylxantine theophylline, macrolide antibiotics, the tricyclic antidepressant nortryptiline, the volatile anesthetics isoflurane, the phenolic compounds gallic acid and curcumine as well as the plant bioactive molecule andropragpholide are included. These drugs share the property of activating HDAC2 activity by phosphoinositide-3-kinase-delta (PI3K-δ) inhibition. HDAC2 inhibits NF-κB nuclear translocation and suppresses the expression of cytokines involved in inflammatory response. All these studies were carried out in humans or in human monocyte/macrophage cell lines with the exception of the molecule andrographolide whose effects were studied in a mouse model. The main findings and the experimental models used were specified.

Table 1. HDAC2 inhibitory mediators that induce pathological response of inflammatory monocytes and that could affect lung function.

HDAC2 inhibitors	Main findings	Model used	Reference
Influenza A Virus (IAV)	HDAC2 is a component of IAV-induced host innate antiviral response	Epithelial cell cultures	(Nagesh et al. 2017)
Rhinovirus infection	Reduced HDAC2 activity correlated inversely with virus load and inflammatory markers.	Sputum and Broncho alveolar macrophages from COPD patients	(Footitt et al. 2016)
HIV-1	HIV-1 replication correlates with reduced recruitment of HDAC2 to the IL-6 promoter, thus enhancing the pro-inflammatory cytokine IL6.	Primary macrophage cell cultures from HIV patients	(Lv et al. 2018)
COPD	Decreased HDAC2 expression and activity in COPD patients compared with healthy smokers and non-smokers	Peripheral blood mononuclear cells (PBMCs) from COPD patients	(Tan et al. 2016)
Hypoxia inducible factor 1α (HIF-1α)	HIF-1α activation decreases HDAC2 levels and amplifies inflammation: a proposed mechanism for corticoid-insensitive COPD	Lung epithelial and macrophage cell cultures and macrophagues from lung resection	(Charron et al. 2009)
Cigarette smokers extract (CSE)	CSE decreases HDAC2 expression/activity and increases inflammation	Human monocyte-macrophague cell line U937	(Meja et al. 2008; Sun et al. 2015; Li et al. 2012; Mercado, Thimmulappa, et al. 2011)
Acrolein (present in cigarette smoke)	Acrolein inactivates HDAC2 activity in macrophage-like cells by the formation of a HDAC2-acrolein adduct	Monocytes, differentiated to macrophage-like cell culture	(Randall et al. 2016)
Cigarrette smokers	Smokers had decreased HDAC2 activity and increased inflammatory cytokines	PBMCs from smokers	(Tan et al. 2016)
Oxidative/ nitrative stress	Activation of the phosphoinositide 3-kinase (PI3K) pathway that causes reduced HDAC2 activity: a proposed mechanism for corticoid-insensitive COPD	Human monocyte-macrophague cell line (U937) or human alveolar epithelial cell lines	(Meja et al. 2008; Osoata et al. 2009)

Table 2. HDAC2 activator drugs that prevent pathological response of inflammatory monocytes and that could influence lung function.

HDAC2 activator drugs	Main findings	Model used	Reference
Theophylline (methylxantine)	Theophylline increases HDAC2 activity and reduces inflammatory response induced by COPD and Haemophilus Influenziae	Alveolar macrophages (AM) from COPD patients Alveolar macrophages from COPD patients exposed ex vivo to Haemophilus influenziae	(Hodge et al. 2019) (Cosío et al. 2015)
	Theophylline increased HDAC2 by inhibiting oxidant-activated phosphoinositide-3-kinase-delta (PI3K-δ)	Peripheral blood mononuclear cells (PBMCs) from COPD patients	(To et al. 2010)
Macrolides (Eryhthromycin, clarithromycin and azithromycin)	Eryhthromycin restored HDAC2 reduction induced by CSE and in PBMCs of COPD patients	Peripheral blood mononuclear cells (PBMCs) from COPD patients Human monocyte-macrophague cell line (U937)	(Sun et al. 2015)
	Macrolides restored HDAC2 activity via PI3Kδ inhibition: Macrolides are proposed for reversion of corticoid-insensitive COPD	Human monocyte-macrophague cell line (U937)and PBMCs from COPD patients	(Kobayashi et al. 2013)
Nortriptyline	Nortriptyline restored HDAC2 activity decreased by oxidative stress and CSE via PI3Kδ inhibition: Nortriptyline is proposed for corticosteroid-insensitive COPD.	Human monocyte-macrophague cell line (U937)	(Mercado, To, et al. 2011)
Isoflurane	Isoflurane shows anti-inflammatory effects by upregulating HDAC1 and HDAC2 and subsequent inhibition of NF-κB nuclear translocation.	Human monocytic cell-line (THP-1) and primary human peripheral blood monocytes stimulated by LPS.	(Guo et al. 2020)

Table 2 (continuation)

Curcumin	Curcumin restores HDAC2 reduction and reverses inflammatory response induced by CSE in a rat COPD model.	Type II alveolar epithelial cells (AEC II) in a rat COPD model	(Gan et al. 2016)
	Curcumin maintains HDAC2 activity and reverses steroid insensitivity induced by CSE and oxidative stress in monocytes.	Human monocyte-macrophague cell line (U937)	(Meja et al. 2008)
Gallic acid (GA)	GA induces HDAC2 expression and inhibits hyperglycemic-induced cytokine production in monocytes.	Human monocytic cell-line (THP-1) exposed to hyperglycemic conditions	(Lee et al. 2015)
Andrographolide, molecule from "Andrographis paniculata"	It restores nuclear HDAC2 expression and activity via inhibition of the PI3K-δ/Akt pathway	Mouse macrophage cell line (Raw 264.7) Mouse primary lung monocytes/macrophages from mice treated with LPS/IFN-γ	(Liao, Tan, and Wong 2016)

Histone deacetylase 5 (HDAC5) could cooperate with HDAC2 in the modulation of monocyte inflammatory response

In addition, HDAC5 could also play a key role in the regulation of inflammatory response in monocytes. In the nucleus HDAC5 forms part of the NF-κB activation process in mediating pro-inflammatory response in macrophages. While overexpression has been associated with a significant increase of TNFα and MCP-1 paralleled by an activation of the NF-κB pathway, HDAC5 knockdown by siRNA resulted in the suppression of cytokine production (Poralla et al. 2015). On the other hand, some respiratory infections have shown to downregulate HDAC5 reducing the host immune response and allowing the pathogen to replicate (Zhao, Ma, and Yang 2019).

It has been suggested that drugs that can phosphorylate HDAC5 and promote its nuclear export could have a potential anti-inflammatory effect (Poralla et al. 2015). Our laboratory has shown that antidepressants that elevate noradrenaline levels in the synaptic cleft induce HDAC5 phosphorylation in neurons (Erburu et al. 2015; Muñoz-Cobo et al. 2018) and also in human monocytes (ongoing studies in our laboratory). Further studies should investigate whether a combined therapy directed to activate HDAC2 and promote HDAC5 nuclear export could synergistically cooperate to inhibit pathological response of inflammatory monocytes.

Conclusion

The mankind is nowadays suffering from the Covid19 pandemia. In some patients, this viral infection induces an exacerbated inflammatory response by monocytes and alveolar macrophages to the virus. High levels of cytokines such as IFN- γ and TNF-α and interleukins such as IL-1, IL-2 and IL-6 are secreted by these cells. At this stage, is very important to attenuate this inflammatory response for managing this disease. Indeed target directed therapies towards IL6, playing a very important role in the disease are being studied in clinical trials. Here, we would like to propose HDAC2 as a potential target of adjuvant Covid19 therapies directed to reduce the exacerbated inflammatory response.

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