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DOCK2: A Potential Target for Obesity Associated Lung Injury

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Abstract

Obesity is pandemic worldwide and closely associated with many chronic diseases including cardiovascular diseases, diabetes, cancer, and several respiratory diseases. While increasing evidence suggests that obesity is related to lung inflammatory changes, the pathophysiology underling obesity associated lung injury remains poorly understood. Recently, we reported that Dedicator of Cytokinesis 2 (DOCK2) is a potential key factor linking obesity and lung inflammatory injury and fibrosis. Dedicator of Cytokinesis 2 (DOCK2) Deficiency Attenuates Lung Injury Associated with Chronic High-Fat and High-Fructose Diet-Induced Obesity. DOCK2 deficiency not only attenuates high-fat high-fructose diet-induced obesity but also the lung inflammatory infiltration and collagen deposition in the lung of mice. The pro-inflammatory effect of TNF-α was attenuated when DOCK2 was silenced in primary human lung fibroblasts. These findings suggest that DOCK2 may serve as a novel target for obesity related lung injury and fibrosis. We discussed the major findings from this recent study and its limitations that may infer future efforts. In addition, we further discussed the emerging role of DOCK2 in lung inflammation and fibrosis in different contexts (bacterial infection, diet and chemical exposure). This min-review provides an update about the role of DOCK2 in lung injury and fibrosis and may raise interest for further understanding of the molecular mechanisms and translational impacts of DOCK2. Meanwhile, it needs to be acknowledged that much remains to be unveiled towards a comprehensive understanding of the role of DOCK2 in lung inflammation and fibrosis. We briefly discussed several aspects of research that may direct future efforts, e.g., the potential role of DOCK2 in fructose metabolism and signaling, the regulation mechanisms of DOCK2 by different inflammatory cytokines, the Rac dependent and independent role of DOCK2, and the cell-specific role of DOCK2 in obesity related lung injury and fibrosis, etc. In view of the expression of DOCK2 in both immune cells (e.g., macrophages) and non-immune cells (e.g., fibroblasts and epithelial cells), it is anticipated that the role of DOCK2 is a multiple one in obesity related lung injury. Further investigation is warranted to elucidate the role and mechanisms of DOCK2 in lung injury and fibrosis caused by diet and beyond.

Keywords: DOCK2; Obesity; Lung; Inflammation; Fibrosis

Abbreviations: DOCK2: Dedicator of Cytokinesis 2; FSP-1: Fibroblast-Specific Protein 1; GEF: Guanine Nucleotide Exchange Factor; HFD: High-Fat Diet; HFHF: High-Fat High-Fructose; TGF-β: Transforming Growth Factor-Beta; TNF-α: Tumor Necrosis Factor-Alpha

Introduction

Obesity is a pandemic worldwide [1,2]. It is closely related with many chronic diseases including cancer, cardiovascular diseases, type 2 diabetes mellitus, and several respiratory disorders [3-6]. It is generally accepted that there is a mildly increased inflammatory status in the obese people. However, the pathophysiology underling obesity associated lung injury remains poorly understood.

Dedicator of Cytokinesis 2 (DOCK2) is an atypical Guanine Nucleotide Exchange Factor (GEF) that activates Rac1 and 2. It was originally found to be exclusively expressed in hematopoietic cells. It is critical for lymphocyte migration in the response to chemo-attractant, B-cell differentiation, and certain allergic diseases, among others [7-9]. DOCK2 loss of function mutation has been identified in human patients with combined immunodeficiency and early-onset severe viral infections [10]. Increasing evidence also suggests novel functions of DOCK2 in cardiovascular diseases, cancer, and lung fibrosis [11-14]. However, the role of DOCK2 in diet induced lung injury and remodeling remains largely unclear.

Literature Review

In a recent publication [15], we report a critical role of DOCK2 in mediating lung inflammation and fibrosis induced by a High-Fat High-Fructose (HFHF) diet. Both wild-type and DOCK2 knockout C57BL/6 mice were fed a HFHF diet for 5 months. The expressions of MCP-1 and macrophage marker CD68 in the lungs were increased in the wild-type mice but not DOCK2 knockout mice fed a HFHF fed. DOCK2 expression was dramatically induced in the lung tissues of wild-type mice fed on HFHF diet. The expression of DOCK2 overlaps with the fibroblast specific marker FSP-1 (Fibroblast-Specific Protein 1), suggesting fibroblast-derived expression of DOCK2. Interestingly,

DOCK2 knockout mice were significantly protected from HFHF-induced inflammatory infiltration and collagen expression in the lung. The *in vitro* data confirmed that primary human lung fibroblasts express DOCK2 in an inducible manner by pro-inflammatory cytokines TNF-α and IL-1β. Inhibition of DOCK2 blocks the expression of MCP-1 induced by these pro-inflammatory cytokines. Together, these finding uncover a previously recognized role of DOCK2 in mediating diet-induced lung injury and remodeling.

It needs to be noted that macrophages may also play an important role in diet induced lung injury. Recently, a paper showed that DOCK2 is important for the pro-inflammatory responses of macrophages during acute injury induced by LPS. Knockdown of DOCK2 in macrophages blunts their ability to secrete pro-inflammatory cytokines. The small molecular inhibitor of DOCK2, CPYPP, also alleviates the extent of lung injury caused by endotoxemia and attenuates the secretion of pro-inflammatory cytokines caused by LPS in mice [16]. In another study, DOCK2 has also been reported to mediate antifungal innate immune response by promoting macrophage pro-inflammatory responses and ROS production [17]. On the other hand, DOCK2 has been reported to mediate pro-inflammatory cytokine expression, oxidative stress, and apoptosis induced by LPS in an alveolar epithelial cell line A549 [18]. These effects in A549 cells were attributed to the Rac activation by DOCK2 since the effects of DOCK2 knockdown were reversed by the treatment of cells with a Rac agonist, 8-Chlorophenylthio-cyclic monophosphate (8-CPT). Apparently, DOCK2 can be induced in different cell types and whether this is true for lung injury associated with diet induced obesity remains to be addressed in future studies.

The specific role of fructose in the context of diet induced lung injury remains largely unclear but deserves further investigation. A recent study has clearly demonstrated that adding fructose but not glucose into the diet disrupts the ability of the liver to handle excessive lipids [19]. The combination of high fructose and high fat likewise aggravates the severity of obesity and metabolic dysfunctions. In this manuscript, DOCK2 knockout abolished the body weight gain due to a HFHF diet. This is consistent with our previous finding that DOCK2 deficiency blocks High-Fat Diet (HFD) induced obesity through modulating adipose tissue inflammation and energy metabolism [20]. More severe lung injury might be expected in the regimen of HFHF versus HFD induced obesity although a direct comparison is beyond the scope of the manuscript. On the other hand, the potential effect of fructose on lung inflammatory injury and DOCK2 induction remains unaddressed. Previous studies have implicated fructose in tissue fibrosis especially in the activation of the TGF-β signaling [21,22]. TGF-β has been shown to induce DOCK2 expression in different cell types [13, 14]. It remains to be tested, however, whether fructose also induces DOCK2 expression and fibrosis in the lung in the context of HFHF diet induced obesity.

Of note is the observation of pro-fibrotic changes in the lung that is associated with a chronic HFHF diet. Collagen expression was increased in the lungs of mice fed a HFHF diet. This finding was supported by previous studies [23]. Further, DOCK2 knockout attenuates these pro-fibrotic changes induced by a HFHF diet. Indeed, both high-fat diet and high fructose can induce the expression of TGF-β [21,22,24,25], the most potent inducer of tissue fibrosis including the lung. In addition, HFD also enhances TGF-β levels in the lung tissues of mice challenged with bleomycin and arguments pulmonary fibrosis [26]. Elevated levels of TGF-β in the lung have been reported in obese human, mice, and rats [23]. Interestingly, we recently reported that TGF-β induces DOCK2 expression in human lung fibroblasts and that DOCK2 knockout significantly attenuates fibroblast to myofibroblast transition and pulmonary fibrosis development induced by bleomycin [13]. Taken together, it seems that DOCK2 may be involved not only in pulmonary inflammatory infiltration but also in the pro-fibrotic phase of the lung associated with a chronic HFHF diet.

The manuscript also showed that DOCK2 knockdown mitigates the PI3K/AKT and NF-κB signaling pathways that are activated by TNF-α in primary human lung fibroblasts. This helps explain how DOCK2 mediates the pro-inflammatory responses. It remains challenging to answer, however, whether DOCK2 contributes to the pro-fibrotic changes in the lung through directly mediating TGF-β signaling as reported [14], or an indirect one through mediating chronic inflammation, or both. In addition, a transcriptional regulation of DOCK2 by TNF-α was observed in primary human lung fibroblasts. Recently, we found that TGF-β induces DOCK2 expression in primary human lung fibroblasts partly through stabilizing DOCK2 protein [13]. Whether a post-translational mechanism is existent in TNF-α-induced DOCK2 up-regulation remains to be tested.

Discussion

It would be interesting to test whether the role of DOCK2 in mediating obesity related lung injury is Rac dependent or independent. DOCK2 is implicated in different pathological process by activating Rac, mainly in immune cells [12]. Beyond immune cells, the role of DOCK2 is less studied, although increasing evidence suggests that adipocytes, epithelial cells, and stromal cells can express DOCK2 in certain conditions [11-13]. In obesity related lung injury, whether the effect of DOCK2 is also dependent on Rac activation remains largely unclear. One reason lies in the lack of specific DOCK2-Rac inhibitors. A naturally occurring inhibitor of DOCK2 has been identified, i.e, cholesterol sulfate, which binds to the catalytic domain of DOCK2 and thus suppresses its GEF activity towards Rac activation [27]. It is not commercially available though. CPYPP remains the only commercially available inhibitor of DOCK2-Rac activity. Unfortunately, this inhibitor also inhibits DOCK180, DOCK5 and DOCK9 to a less extent [28]. Therefore, there is an urgent need to develop specific DOCK2 inhibitors to test targeting of DOCK2 in obesity related lung injury and other diseases as well.

Conclusion

To sum up, the recent manuscript identifies DOCK2 as a critical regulator for obesity related lung injury and remodeling. DOCK2 modulates the pro-inflammatory phenotype of lung fibroblasts caused by HFHF. Targeting DOCK2 may provide a novel strategy for treatment of lung injury and remodeling associated with diet. Further investigation is deserved to test Rac dependent and independent functions of DOCK2 in this context. The generation of conditional DOCK2 knockout mice is also warranted to dissect the cell specific roles of DOCK2 in lung injury and remodeling associated with diet induced obesity.

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Conflicts of Interest

The authors declare no conflict of interest.

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