Neutrophil-Mediating Lung Diseases and Integrin α subfamily, α4 and α9

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ABSTRACT

Neutrophil-mediating acute lung injury like aspiration pneumonia is a serious problem in the elderly. Although integrin β2 plays an important role in neutrophil-mediating lung diseases, integrin β2-independent neutrophil transmigration pathways have also been reported. Several members of the integrin a subfamily (α2β1, α3β1, α4β1, α5β1, α6β1 and α9β1) are known to be expressed on neutrophils, and up-regulated by activation. And these integrins on systemic neutrophils might mediate migration into the site of pulmonary inflammation. Especially, integrin α9β1 and integrin α4β1 have been also shown to mediate adhesion to vascular cell adhesion molecule (VCAM)-1. In this draft, author focused lung diseases and the involvement of integrin α9 and α4. And the future direction as the therapeutic strategy against neutrophil-mediating lung injury was also discussed.

Key words: Integrin α9β1; Integrin α4β1; Neutrophil

Neutrophil-mediating acute lung injury like aspiration pneumonia is a serious problem in the elderly. Although integrin β2 plays an important role in neutrophil-mediating lung diseases, integrin β2-independent neutrophil transmigration pathways have also been reported. Several members of the integrin a subfamily (α2β1, α3β1, α4β1, α5β1, α6β1 and α9β1) are known to be expressed on neutrophils, and up-regulated by activation. And these integrins on systemic neutrophils might mediate migration into the site of pulmonary inflammation. Especially, integrin α9β1 and integrin α4β1 have been also shown to mediate adhesion to vascular cell adhesion molecule (VCAM)-1. In this draft, author focused lung diseases and the involvement of integrin α9 and α4. And the future direction as the therapeutic strategy against neutrophil-mediating lung injury was also discussed.

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subfamily of integrin α subunits[8]. Furthermore, both α4β1 and α9β1 have a receptor against vascular cell adhesion molecule-1 (VCAM-1) as a ligand[9]. In this draft, author focused lung diseases and the involvement of integrin α9 and α4. And I discussed the future direction as the therapeutic strategy against neutrophil-mediating lung injury.

**INTEGRIN α4β1**

Integrin β1and β7 are known as the partners of integrin α4. Integrin α4β1 constitutively expressed on the cell surface of lymphocytes, monocytes, eosinophils, and neutrophils, and is known to be up-regulated by stimuli including inflammatory cytokines[6,7]. Since the expression level of integrin α4β1 on human neutrophil is very weak comparing with that of mouse, human neutrophil was supposed not to express integrin α4β1 before. After that, many papers have been reported about the expression of α4β1 on human neutrophils[6,7]. In animal model, integrin α4β1 involved in mice pneumonia by Streptococcus pneumoniae[11]. Integrin α4β1 on neutrophils has a role in adhesion and migration to move into the site of inflammation, and integrin α4β1 mediate integrin β2-independent neutrophil accumulation[11]. Not only in animal model, but also human septic cases showed up-regulation of integrin α4β1 on neutrophils[10,13]. On the other hand, increased expression of integrin α4β1 on neutrophils was not recognized in early stage of acute respiratory distress syndrome (ARDS) cases in another paper[12]. They discussed that increased expression level of adhesion molecule might be delay, several hours later. Although literatures about molecular mechanism of involvement of integrin α4β1 on neutrophils were limited and not fully elucidated, these evidences showed the possibility of integrin α4β1 mediating human neutrophil pulmonary inflammation.

**INTEGRIN α9β1**

Integrin α9β1 also expressed on human neutrophils and VCAM-1 on the surface of vascular endothelial cells, and integrin α9β1 plays an important role in the extravasation of neutrophils to the site of inflammation[11]. Author reported increased expression levels of integrin α9β1 and CD11b on circulating neutrophils and elevated serum IL-17A in elderly aspiration pneumonia cases[15]. Previously, the possibility of cross-talking signaling pathways playing a role in modifying migration between integrin β2 and integrin β1 has been already reported[12], but the signal pathway of integrin α9β1 is not well understood. Recently, it was reported that integrin α9β1/VCAM-1 interaction could be trigger to the activation of signal pathway to modulate neutrophil apoptosis and mediating inflammation[15,16]. And during the process, integrin α9β1 on human neutrophils depends on the activated mitogen-activated protein kinase[16] and phosphoinositol 3-kinase[15] pathway. Although mechanism of signal transduction of integrin α9β1 may be different from that of integrin α4β1, integrin α9β1 on human neutrophils also mediate lung injury in a certain condition.

**REFERENCES**

4. Taooka Y, Chen J, Yednock T, Sheppard D: The integrin α9β1 mediates adhesion to activated endothelial cells and transendothelial neutrophil migration through interaction with in lung fibrosis[17]. Zhao X et al[17] demonstrated that platelet derived growth factor BB (PDGF-BB) induces focal adhesion kinase (FAK) activation and lung fibroblast migration after receiving PDGF-BB stimulation. FAK associated with integrin β1 and PDGF-BB stimulated lung fibroblasts, then FAK activation and β1 integrin mediated fibroblast migration. About pulmonary fibrosis, activating transforming growth factor (TGF) b regulated by integrin avβ6 is also well known[18]. Various kinds of integrin related cancer invasion and lung fibrosis, and further detailed examination is necessary.

**FUTURE DIRECTION**

From the point of above description, inhibiting integrin α4/VCAM-1 and/or integrin α9/VCAM-1 interaction might attenuate neutrophilic lung inflammation at least in a certain condition. As the therapeutic options to inhibit integrin α4/α9, functional blocking anti-integrin α4β1 or α9β1 monoclonal antibody, disintegrin, and small molecules inhibiting intracellular signal transduction are supposed to be candidates. As anti monoclonal antibody inhibiting integrin α4β1, commercial-based drug, natalizumab (Biogen-Idec, Durham, NC, USA) is already available against multiple sclerosis in many countries[19]. The major adverse effect of natalizumab is immunosuppression. Specific inhibition of neutrophilic lung injury without immunosuppression should be expected, when against severe pneumonia patients for their treatment. In this meaning, natalizumab is not sufficient for treatment of sepsis cases. As disintegrin derived from venomous vipers, Marcinkiewicz C et al reported that functional inhibitor of integrin α9, named EC3 and EC6 inhibited α9β1-mediated adhesion to VCAM-1 and of neutrophil migration in vitro experiment[20]. And the peptide containing a novel MLDG motif shared by both of these disintegrins also inhibited α9β1- and α4β1-mediated adhesion to VCAM-1. They also reported that disintegrin might provide a basis for the development of potent drugs that could be used to inhibit emigration of neutrophils into pulmonary inflammation[19]. Furthermore, paxillin inhibitors are also promising candidate. Integrin α4 cytoplasmic domain enhances cell migration and spreading, which effects depend on interaction with the adaptor protein, paxillin, and to migrate circulating neutrophils into the site of inflammation[19,22]. This interaction is critical for integrin dependent cell adhesion, spreading, and migration as it provides a needed connection to the actin cytoskeleton[22]. And Rose DM discussed that α4-paxillin interaction was a potentially therapeutic target in controlling leukocyte trafficking[22].

So far, mechanism between integrin α4/α9 and neutrophil migration is not well elucidated, and the further study would be necessary. But author supposes they are promising therapeutic strategy against neutrophil-mediating lung injury in the future.


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