Epithelial integrins in mucosal immune and inflammatory responses

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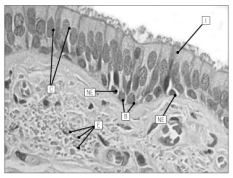
Dr. Ulanova's Lab Research Projects

- **Molecular mechanisms of innate immunity and inflammation in the lung**
- **Integrins as molecular targets to treat severe pulmonary infections caused by *P. aeruginosa***

Bronchial epithelium



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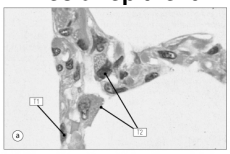
Alveolar epithelium



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Receptors expressed:

ICAM-1, MHC class I and II, integrins, TNF-R, TLR1-6, and TLR9, IL4-R, IL9-R, EGF-R, PAR2, CD23, CD40, Histamine receptors, Fcn-R

Soluble products:

IL-1, IL-6, IL-8, IL-11, eotaxin, MCP-1, MCP-3, RANTES, TNF, G-CSF, GM-CSF, M-CSF, TGF-β, lipid metabolites, nitric oxide…

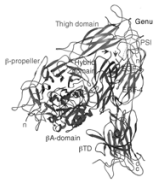
Integrins

A large family of heterodimeric transmembrane receptors

Molecular sensors

Signaling properties: mediate cellular responses to changes in microenvironment

Provide co-stimulatory signals



Crystal structure of αVβ3 integrin (extracellular part)

Two protein subunits encoded by different genes

Large extracellular part

Short transmembrane and intracellular domains

Airway epithelial cell integrins

- **Eight different αβ heterodimers**
- **Regulate cell growth, differentiation, survival, and cytokine production**
- **Signaling is poorly understood**

Previous research at U of A:

- **In lung epithelial cells, β1 integrins provide co-stimulatory signals regulating inflammatory responses**

Ulanova et al: Am J Physiol, 2005, 288:L497-507

Ulanova et al: Biochem Biophys Res Commun, 2006, 351: 431-437

Hypothesis:

Integrin receptors can be used as therapeutic targets in lung inflammation

Integrins as receptors for respiratory pathogens

Some pathogens use integrins as receptors for epithelial cell invasion

Examples: *Pseudomonas aeruginosa, Bordetella pertussis, Yersinia, Listeria monocytogenes, Shigella flexneri, Mycobacterium tuberculosis, M.leprae*

Some viruses: rotavirus, adenovirus, echovirus

Pseudomonas aeruginosa

Major cause of ventilator-associated pneumonia in ICU with high mortality rate

Major pulmonary pathogen in CF

***P. aeruginosa* infections: out-of-control inflammation causing tissue damage**

Mechanisms of inflammatory responses in LEC are poorly understood

Rumbak M. Bone's Atlas of Pulmonary and Critical Care Medicine. Edited by James Crapo, James D. Crapo. ©2005 Current Medicine LLC.

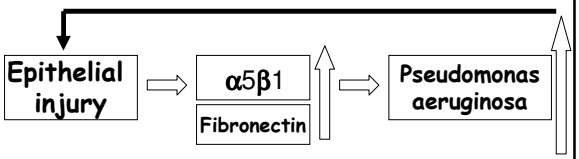
Severe acute pulmonary disease post surgery.

Pseudomonas aeruginosa were isolated from the sputum.

Diagnosis: hospital-acquired pneumonia.

Pseudomonas aeruginosa: **binding β1 integrins and fibronectin**

Result: adhesion to airway epithelium & invasion



Pro-inflammatory signaling?

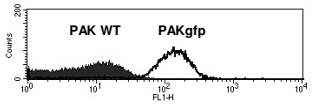
Can blocking of integrin-bacteria interactions inhibit inflammation?

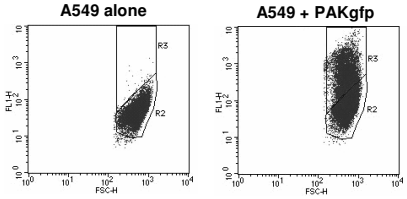
Project:

Role of epithelial integrins in inflammatory responses caused by *P.aeruginosa*

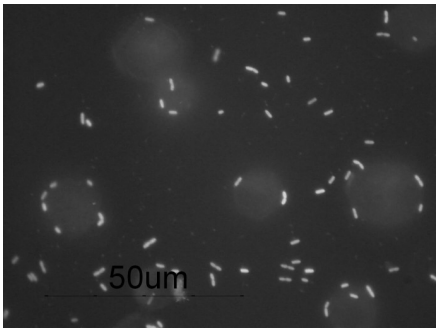
Chromosomal *P. aeruginosa* gfp labeling using a mini Tn7 transposon

Detection: by flow cytometry



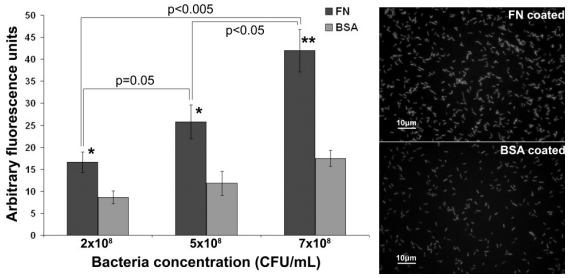


Chromosomal gfp labeling of *P. aeruginosa*

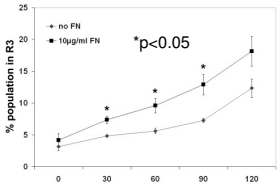


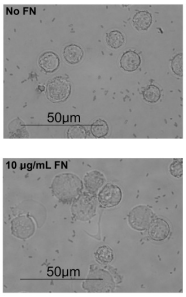
Adhesion of *P. aeruginosa*-gfp to A549 cells

P. aeruginosa adhere to fibronectin

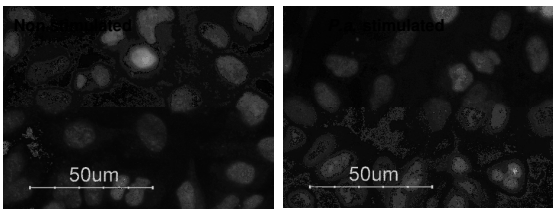


Fibronectin mediates *P. aeruginosa* adhesion to epithelial cells

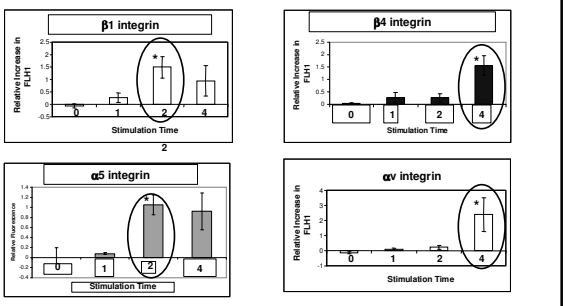




Stimulation of lung epithelial cells with *P. aeruginosa* ⇨ nuclear translocation of p65 NF-κB

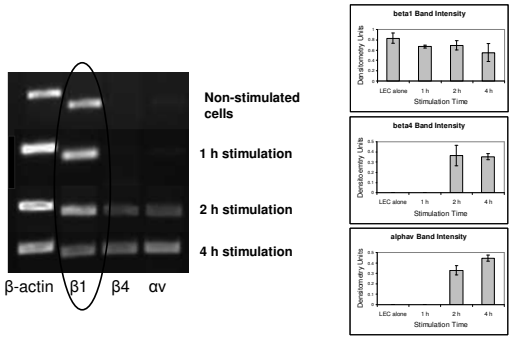


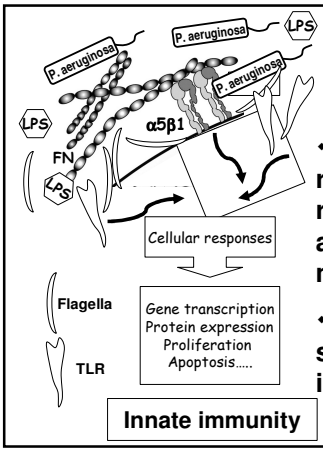
Effect of *P. aeruginosa* on the surface expression of integrins



* p<0.05 Mann-Whitney U Test

Effect of *P. aeruginosa* on integrin mRNA expression





Bigger picture:

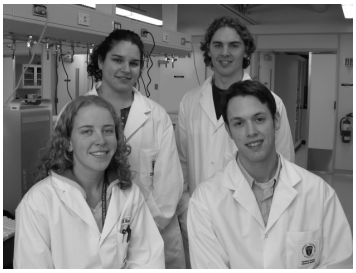
- ❖ **Integrins as receptors that recognize pathogen-associated molecular patterns**
- ❖ **Integrins play a significant role in innate immunity**

More questions…

Which specific pathogen-associated molecules are recognized by integrins?

What does this mean for the host?

What will determine the balance between host defense and inflammation leading to tissue damage and disease?



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