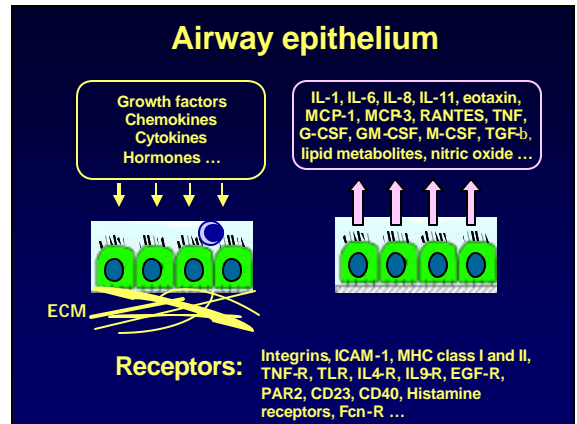


Novel aspects of pro-inflammatory signaling in lung epithelium

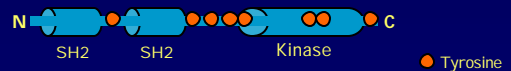
Marina Ulanova, MD, PhD
 Medical Sciences Division, Northern Ontario School of Medicine



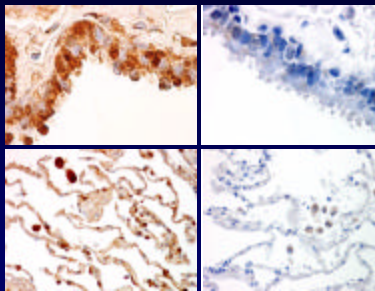
Molecular components of inflammatory responses as potential therapeutic targets

Syk Non-receptor protein tyrosine kinase

- 📌 Critical component of immunoreceptor signaling in leukocytes (T- and B-lymphocytes, macrophages, mast cells, neutrophils)
- 📌 Host response and inflammation



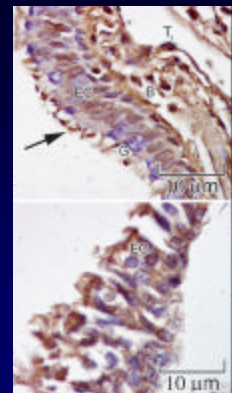
Syk is expressed in human lung epithelium



Syk Isotype control

Adult human lung

Lung of 22-week old human fetus

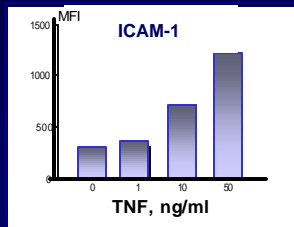
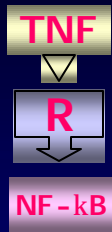


What is the functional role of Syk in airway epithelium?

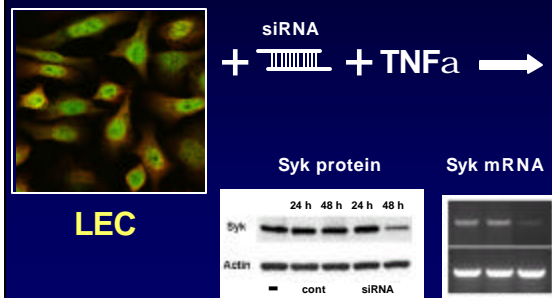
TNF α

- Principal mediator of acute inflammatory responses to microbial pathogens
- Major source in the lung: activated alveolar macrophages
- Critical in host defence
- When overproduced, contributes to acute lung injury and septic shock

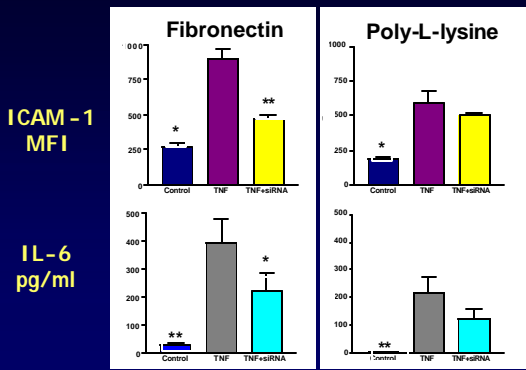
TNF stimulation of epithelial cells results in up-regulation of ICAM-1 expression



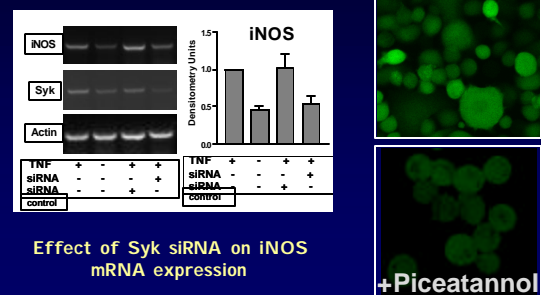
Inhibition of Syk using siRNA
Effect on TNF responses



Syk siRNA \rightarrow TNF-induced ICAM-1 and IL-6



Syk inhibition \rightarrow TNF-induced iNOS expression and NO production



📌 Inhibition of Syk downregulates TNF-induced inflammatory responses

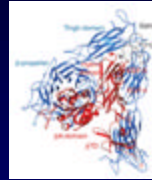
ICAM1
IL-6
iNOS and NO
MAPK
NF- κ B

📌 Syk as a molecular target for therapy of lung inflammatory disorders

📌 Dependence on integrin receptor engagement

Integrins

📌 A large family of transmembrane receptors



📌 In lung epithelial cells: 8 different $\alpha\beta$ heterodimers

📌 Molecular sensors

📌 Mediate responses to changes in the microenvironment

📌 Provide co-stimulatory signals

Integrin receptors as therapeutic targets

Integrins as receptors for respiratory pathogens

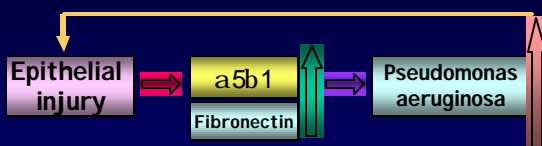
Some pathogens use integrins as receptors for epithelial cell invasion

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

Some viruses: rotavirus, adenovirus, echovirus

Pseudomonas aeruginosa: binding β 1 integrins and fibronectin

Result: adhesion to airway epithelium & invasion



Pro-inflammatory signaling?

Can blocking of integrin-bacteria interactions inhibit inflammation?

New Research Program at NOSM

📌 Integrins as molecular targets to treat severe pulmonary infections caused by *P. aeruginosa*

📌 Using specific small molecular inhibitors