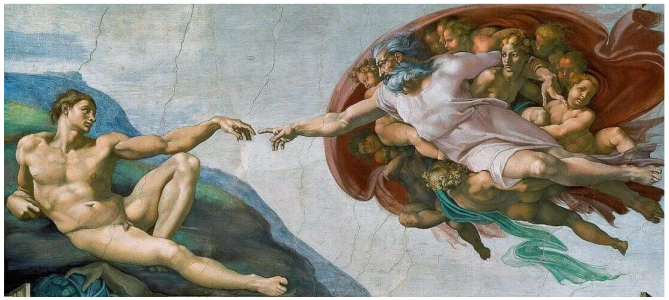
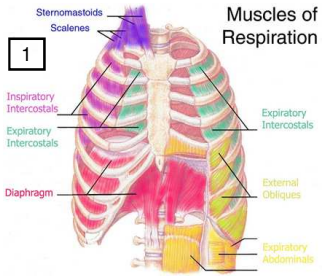


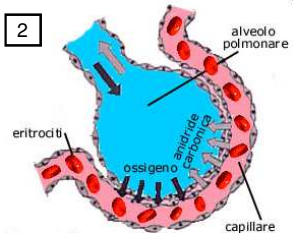
Determinanti della funzione respiratoria



Ventilazione alveolare:
- gabbia toracica
- muscolatura respiratoria
- pervietà vie aeree
- stimolo nervoso
- contenuto di O_2 dell'aria

Diffusione alveolo-capillare:
- superficie di scambio
- spessore membrana alveolo-capillare
- perfusione polmonare (V/Q)

2

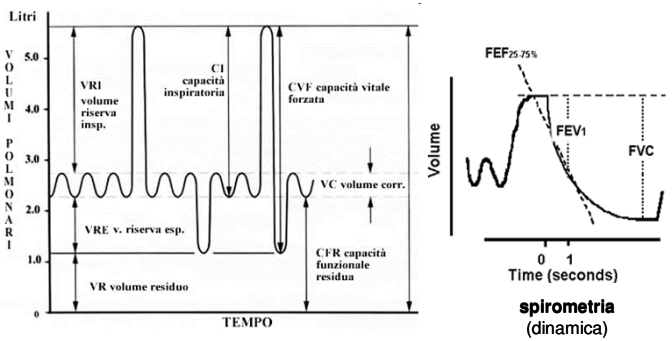


Trasporto ematico gas respiratori:
- velocità di transito sangue nel capillare alveolare
- trasporto O_2 nel sangue

3

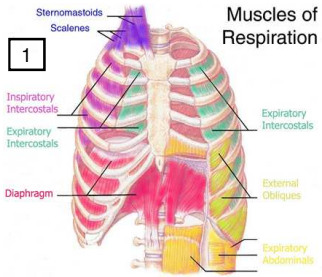
4 **Respirazione in senso stretto!**
- Diffusione O_2 alle cellule e mitocondri
- riduzione dell'O_2 ad H_2O e fosforilazione ossidativa

ventilazione: misura dei volumi statici polmonari



spirometria
(dinamica)

Determinanti della funzione respiratoria



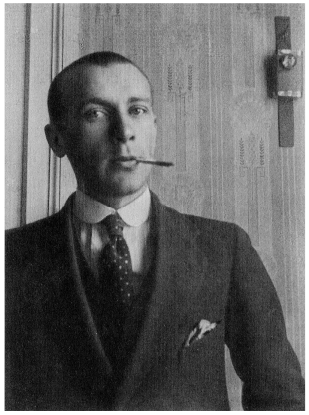
Ventilazione alveolare:
- gabbia toracica
- muscolatura respiratoria
- pervietà vie aeree
- stimolo nervoso
- contenuto di O_2 dell'aria

Ipoventilazione

riduzione degli scambi gassosi tra atmosfera e aria alveolare

- gabbia toracica
  lesioni ossee che compromettono la meccanica respiratoria (es. traumi, fratture costali, schiacciamento)
- muscolatura respiratoria
  miopatie, paralisi dei muscoli respiratori
- impervietà vie aeree
  ostruzione da corpi estranei o altro (p.e. compressione)
  broncocostrizione

Causa ipossiemia (<O_2 nel sangue arterioso) e ipercapnia (>CO_2)



Mikhail Bulgakov in the 1910s, during his university years. Photo before 1916. Unknown author. Via Wikimedia. Public Domain.

Bulgakov qualified in 1916 and at age twenty-four found himself in sole charge of a country clinic 32 miles from the nearest town, the roads to which were frequently impassable. Czarist Russia, despite its ramshackle absolutist monarchy, had a rural medical service (provided by the local government "zemstvo" councils and financed from local taxation) that many countries would envy today. Bulgakov found himself treating the local peasants, in charge of a facility with beds, an operating theatre, a staff of two midwives, and a feldsher (physician's assistant). In the collection of short stories he wrote about his early isolation in that country clinic (A Country Doctor's Notebook), he dwelt often on the terrors induced by the combination of total clinical responsibility and utter inexperience.

In the story "The Steel Windpipe," he tells of the arrival at the clinic of a three year-old girl, Lidka, with diphtherial croup, close to death—**her throat already choked with membrane**. The mother and grandmother are appalled when he tells them (with enormous silent misgivings about his competence) that only an operation—to cut open the windpipe and insert a silver tube—will save the child's life.

Already injected with camphor as an analgesic, the little girl was laid on the operating table by a midwife who strapped her down, washed her throat, and painted it with iodine. The surgery began:

I picked up the scalpel, still wondering what on earth I was doing. It was very quiet. With the scalpel I made a vertical incision down the swollen white throat. Not one drop of blood emerged. Again I drew the knife along the white strip which protruded beneath the split skin. Again not a trace of blood. Slowly, trying to remember the illustrations in my textbooks, I started to part the delicate tissues with the blunt probe. At once dark blood gushed from the lower end of the wound, flooding it instantly and pouring down her neck. The feldsher started to staunch it with swabs but could not stop the flow. Calling to mind everything I had seen at university, I set about clamping the edges of the wound with forceps, but this did no good either.

I went cold and my forehead broke out in a sweat. **I bitterly regretted having studied medicine** and having landed myself in this wilderness. In angry desperation I jabbed the forceps haphazardly into the region of the wound, snapped them shut and the flow of blood stopped immediately. We swabbed the wound with pieces of gauze; now it faced me clean and absolutely incomprehensible. There was no windpipe anywhere to be seen. This wound of mine was quite unlike any illustration. I spent the next two or three minutes poking about in the wound, first with the scalpel and then with the probe, searching for the windpipe. […] I despaired of finding it. 'This is the end,' I thought. […] 'She will die with her throat slit open and I can never prove that she would have died anyway.' The midwife wiped my brow in silence. 'I ought to put down my scalpel and say: I don't know what to do next'. As I thought this I pictured the mother's eyes. I picked up the knife again and made a deep undirected slash into Lidka's neck. The tissues parted and to my surprise the windpipe appeared before me.

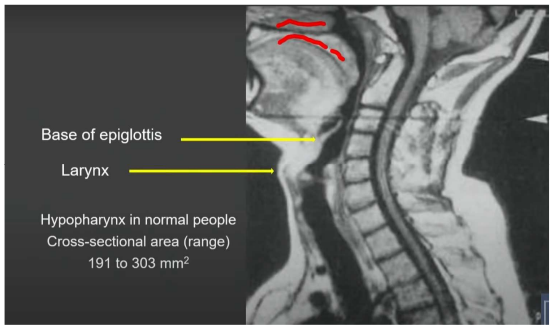
'Hooks!' I croaked hoarsely.

The feldsher handed them to me. I pierced each side with a hook and handed one of them to him. Now I could see one thing only: the greyish ringlets of the windpipe. […] I plunged the scalpel into the trachea and then inserted a silver tube. […] Silence reigned. I could see Lidka turning blue. […] **The child suddenly gave a violent convulsion, expelled a fountain of disgusting clotted matter through the tube, and the air whistled into her windpipe**.

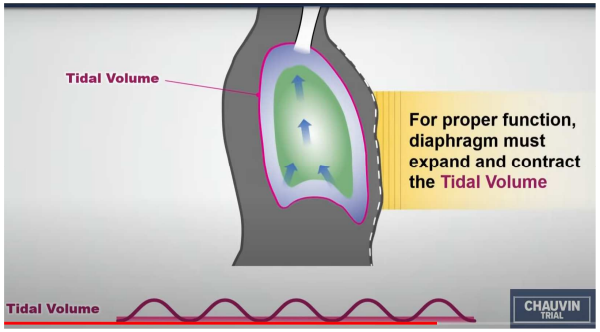
In due course, the silver tube was removed and Lidka made a full recovery. The rumour spread that Lidka had received a steel throat instead of her own and people travelled to her village just to look at her. The clinic's practice boomed and, with around 110 patients to be seen every day, Bulgakov found himself working an eleven hour shift.

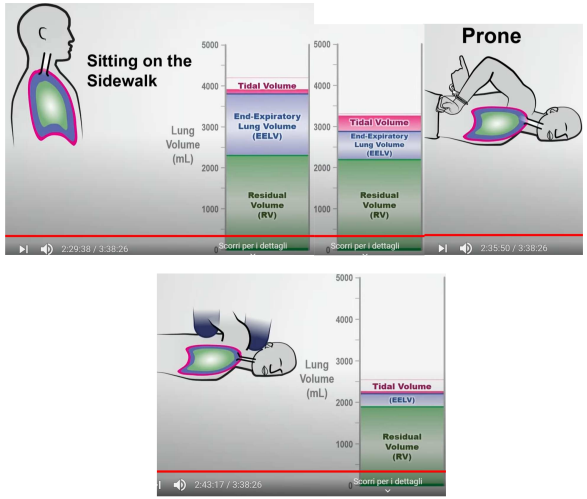
Michael Bloor (2021) https://hekint.org/2017/01/31/mikhael-bulgakovs-the-steel-windpipe-in-a-country-doctors-notebook/

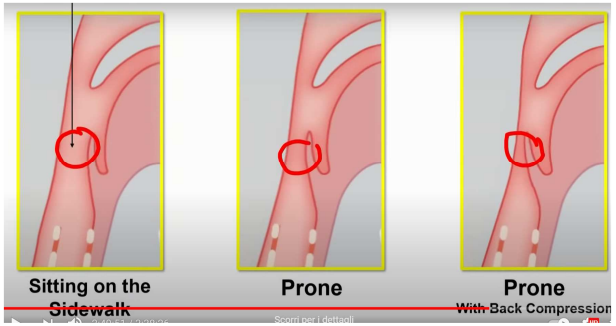
Dalla testimonianza del Dr. Martin Tobin
al processo per la morte di George Floyd

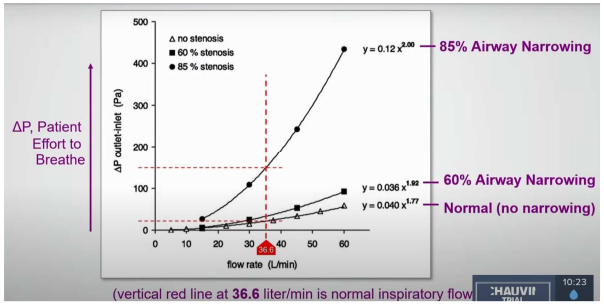


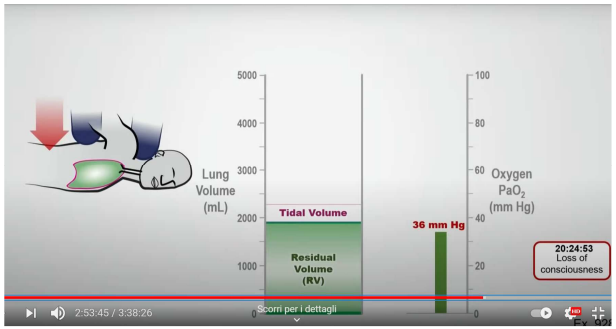
https://www.youtube.com/watch?v=pAjSVKtn5Aw

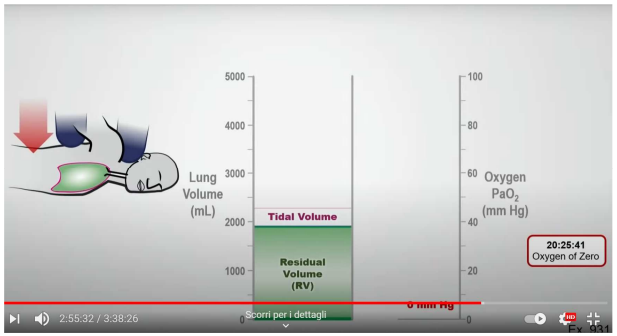



Sitting on the Sidewalk
Prone
Lung Volume (mL)
Tidal Volume
End-Expiratory Lung Volume (EELV)
Residual Volume (RV)
5000
4000
3000
2000
1000
2:29:38 / 3:38:26
Scorri per i dettagli
2:35:50 / 3:38:26
2:43:17 / 3:38:26

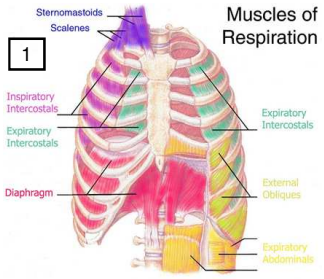

Sitting on the Sidewalk
Prone
Prone
With Back Compression
Scorri per i dettagli


ΔP, Patient Effort to Breathe
Δ no stenosis
60 % stenosis
85 % stenosis
ΔP outlet-inlet (Pa)
flow rate (L/min)
y = 0.12 x^2.00
y = 0.036 x^1.92
y = 0.040 x^1.77
85% Airway Narrowing
60% Airway Narrowing
Normal (no narrowing)
(vertical red line at 36.6 liter/min is normal inspiratory flow)
10:23


Lung Volume (mL)
Tidal Volume
Residual Volume (RV)
36 mm Hg
Oxygen PaO2 (mm Hg)
20:24:53
Loss of consciousness
2:53:45 / 3:38:26
Scorri per i dettagli



Determinanti della funzione respiratoria



Ventilazione alveolare:
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- impervietà vie aeree
  ostruzione da corpi estranei o altro (p.e. compressione)
  broncocostrizione
- ridotto/assente stimolo nervoso
  sindromi neurologiche
- riduzione O_2 nell'aria
  alta quota, ambienti chiusi

Causa ipossiemia (<O_2 nel sangue arterioso) e ipercapnia (>CO_2)

Science **371**, 52–57 (2021) 1 January 2021

STEM CELLS

Airway stem cells sense hypoxia and differentiate into protective solitary neuroendocrine cells

Manjunatha Shivaraju[1,2,3], Udbhav K. Chitta[4], Robert M. H. Grange[5], Isha H. Jain[6,7,8]*, Diane Capen[9], Lan Liao[10], Jianming Xu[10], Fumito Ichinose[5], Warren M. Zapol[5], Vamsi K. Mootha[6,7,8], Jayaraj Rajagopal[1,2,3]†

Airway neuroendocrine (NE) cells were first identified as epithelial cells that store and secrete amines and peptides from membrane-bound vesicles, mirroring the process of neurotransmitter release from neurons. Indeed, both neurons and airway NE cells secrete serotonin and calcitonin gene–related peptide (CGRP) (*1*, *2*). However, the physiologic functions of solitary NE cells are largely unknown. One study of human solitary NE cells in vitro suggests that they function as airway chemosensory cells in vivo (*12*). Human solitary NE cells secrete CGRP in culture, and it is hypothesized that this neuropeptide links epithelial stimulus detection to the modulation of stem cell behavior (*12*).

solitary NE cells display rapid turnover and are regularly replaced by basal stem cells (*15*, *16*).

We have shown that hypoxia-induced murine solitary NE cells are necessary for repairing hypoxia-induced epithelial damage. The mechanism invokes the secretion of a protective paracrine signal. We speculate that the diffuse distribution of solitary NE cells throughout the human airway, in contrast to the discrete location of murine NEBs at airway bifurcations, forms the basis of a distributed tissue-wide protection system in which effective epithelial repair can be fostered throughout the length of the airway tree.

Oxygen therapy is used in the setting of respiratory failure in many diseases associated with NE cell excess, ranging from severe asthma to cystic fibrosis to COPD, but oxygen has also been associated with multiple forms of toxicity (*30*). If hypoxia-induced solitary NE cells are indeed protective in disease states, supportive oxygen therapy might result in unintended consequences by reducing the physiologic stimulus for generating protective NE cells. By contrast, in neuroendocrine hyperplasia of infancy (NEHI), where NE cell excess appears to be a primary pathology, supplemental oxygen might act as a primary therapy by triggering a reduction in pathologic NE cell numbers. Indeed, some

In this study, we have identified a conserved tissue-level response to a fundamental form of stress, oxygen deprivation. In this instance, sentinel stem cells detect hypoxia and produce a specific protective cell type that is needed to mitigate the effects of the hypoxia. Although we have identified CGRP as a protective airway solitary NE cell factor, NE cells can secrete a host of other neuropeptides and amines. Thus, we speculate that different forms of pulmonary injury might engender varied protective NE cell responses. It will be of great interest to assess whether other organ-specific stem cells more generally execute their own specific protective behaviors when triggered by hypoxia. It will also be important to determine whether the stem cells of other organs respond to local hypoxia by generating their own distinctive populations of protective NE cells.

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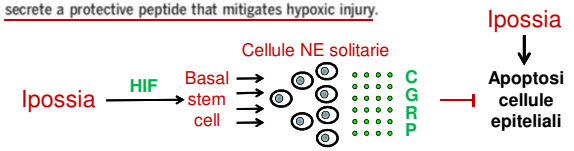
Neuroendocrine (NE) cells are epithelial cells that possess many of the characteristics of neurons, including the presence of secretory vesicles and the ability to sense environmental stimuli. The normal physiologic functions of solitary airway NE cells remain a mystery. We show that mouse and human airway basal stem cells sense hypoxia. Hypoxia triggers the direct differentiation of these stem cells into solitary NE cells. Ablation of these solitary NE cells during hypoxia results in increased epithelial injury, whereas the administration of the NE cell peptide CGRP rescues this excess damage. Thus, we identify stem cells that directly sense hypoxia and respond by differentiating into solitary NE cells that secrete a protective peptide that mitigates hypoxic injury.



Developmental Cell

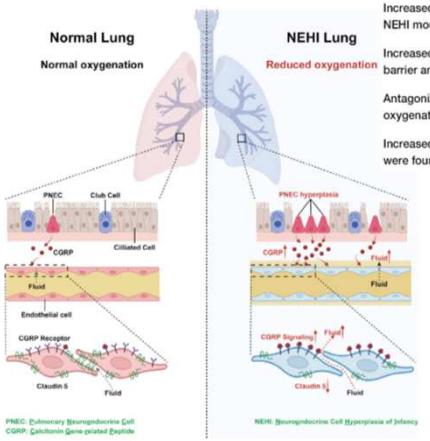
CellPress

Article

Excess neuropeptides in lung signal through endothelial cells to impair gas exchange

Jinhao Xu,[1,2] Le Xu,[1] Pengfei Sui,[3] Jiyuan Chen,[4] Esteban A. Moya,[5] Patrick Hume,[6] William J. Janssen,[6] Jason M. Duran,[7] Patricia Thistlethwaite,[8] Aaron Carlin,[9] Peter Gulleman,[10] Brandon Banaschewski,[11] Mary Kate Goldy,[11] Jason X.-J. Yuan,[4] Atul Malhotra,[6] Gloria Pryhuber,[12] Laura Crotty-Alexander,[4,13] Gail Deutsch,[14] Lisa R. Young,[10,11] and Xin Sun[1,2,15,*]

Although increased neuropeptides are often detected in lungs that exhibit respiratory distress, whether they contribute to the condition is unknown. Here, we show in a mouse model of neuroendocrine cell hyperplasia of infancy, a pediatric disease with increased pulmonary neuroendocrine cells (PNECs), excess PNEC-derived neuropeptides are responsible for pulmonary manifestations including hypoxemia. In mouse postnatal lung, prolonged signaling from elevated neuropeptides such as calcitonin gene-related peptide (CGRP) activate receptors enriched on endothelial cells, leading to reduced cellular junction gene expression, increased endothelium permeability, excess lung fluid, and hypoxemia. Excess fluid and hypoxemia were effectively attenuated by either prevention of PNEC formation, inactivation of CGRP gene, endothelium-specific inactivation of CGRP receptor gene, or treatment with CGRP receptor antagonist. Neuropeptides were increased in human lung diseases with excess fluid such as acute respiratory distress syndrome. Our findings suggest that restricting neuropeptide function may limit fluid and improve gas exchange in these conditions.



Increased PNECs are responsible for poor gas exchange in a NEHI mouse model

Increased PNECs and CGRP led to impaired endothelial barrier and excess fluid

Antagonizing CGRP signaling improved barrier and oxygenation in NEHI mouse mutants

Increased neuropeptides and reduced endothelial junctions were found in ARDS lungs

NEHI

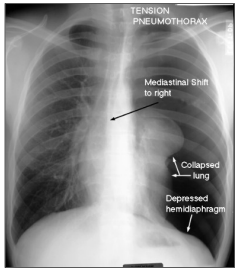
Iperplasia delle cellule neuroendocrine dell'infanzia

Xu et al., 2022, Developmental Cell *57*, 839–853
April 11, 2022 © 2022 Elsevier Inc.
https://doi.org/10.1016/j.devcel.2022.02.023

Determinanti della funzione respiratoria

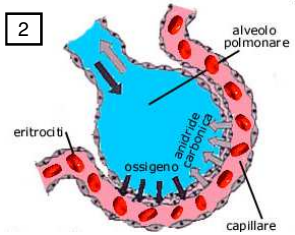
Riduzione della *superficie di scambio:*

- rimozione del polmone (chirurgia)
- infarto polmonare
- tumori polmonari
- collasso del polmone (es. pneumotorace)



Diffusione alveolo-capillare:
- superficie di scambio
- spessore membrana alveolo-capillare
- perfusione polmonare (V/Q)

2

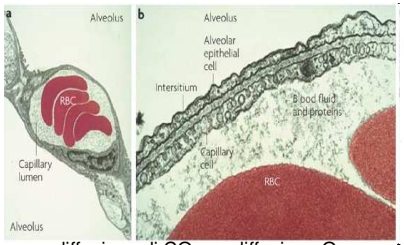


La capacità residua del parenchima polmonare sano può permettere di tollerare riduzioni della superficie di scambio aria/sangue (la superficie di scambio alveolare è >> di quella minima necessaria). Notare però che alterazioni della superficie di scambio alveolare causano squilibrio fra ventilazione e perfusione aggravando la riduzione di O_2

Determinanti della funzione respiratoria

Aumento di spessore della membrana alveolo-capillare:

- fibrosi polmonare
- accumulo di liquido nell'interstizio
  - edema polmonare
  - esposizione a radiazioni
  - esposizione a tossici, farmaci

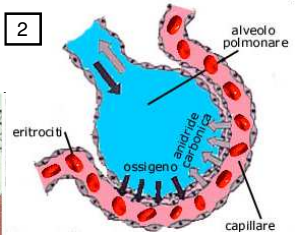


diffusione di CO_2 >> diffusione O_2 →

Nature Reviews | Drug Discovery

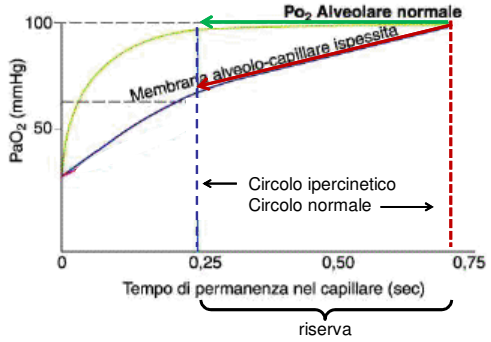
Diffusione alveolo-capillare:
- superficie di scambio
- spessore membrana alveolo-capillare
- perfusione polmonare (V/Q)

2



ispessimento membrana alveolo-capillare ha effetto maggiore sulla diffusione di O_2

ossigenazione del sangue lungo il capillare polmonare



Durante l'esercizio l'estrazione di O_2 e la velocità del flusso di sangue capillare aumentano. Se la diffusione attraverso la membrana alveolo-capillare è compromessa, il tempo di transito ridotto non permette una ossigenazione adeguata della Hb

Determinanti della funzione respiratoria

Diminuita perfusione alveolare:

- riduzione del flusso sanguigno alveolare (embolia, stasi) → aumento spazio morto funzionale
- condizioni in cui si ha esclusione di ventilazione di porzioni del polmone (ostruzione bronchi – alveoli) → aumento shunt; deviazione del flusso sanguigno in porzioni di polmone intatte

Diminuita velocità di transito del sangue nel capillare alveolare:

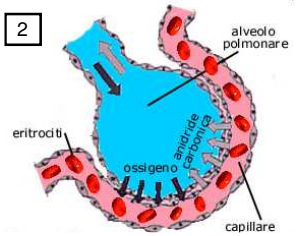
- insufficienza cardiaca (riduzione della gittata): riduzione della perfusione globale dei polmoni

Deficit del trasporto di ossigeno nel sangue:

- anemie: riduzione capacità di trasporto totale di O_2
- stati ipercinetici
- emoglobinopatie

Diffusione alveolo-capillare:
- superficie di scambio
- spessore membrana alveolo-capillare
- perfusione polmonare (V/Q)

2



Trasporto ematico gas respiratori:
- velocità di transito sangue nel capillare alveolare
- trasporto O_2 nel sangue

3

Sindromi respiratorie

I meccanismi sopra descritti si combinano a causare una serie di sindromi che in base al meccanismo prevalente o esclusivo si possono raggruppare in:

- **Ostruttive**: da patologie che alterano la resistenza al flusso nelle vie aeree
- **Restrittive**: da patologie che riducono la distensibilità del parenchima polmonare o l'espansibilità della gabbia toracica
- **Ipodiffusorie**: da prevalente alterazione della membrana alveolo-capillare
- **Da squilibrio V/Q**: da prevalente mismatch fra ventilazione e flusso sanguigno nei capillari alveolari

Immunopatologia

Danno prodotto da meccanismi immunologici

- **Ostruttive**
  - **Asma bronchiale**
  - Broncopneumopatia cronica ostruttiva (bronchite cronica, enfisema)
  - Bronchiectasie
  - Fibrosi cistica
  - Bronchiolite
- **Restrittive parenchimali**
  - Sarcoiodosi
  - Fibrosi polmonare idiopatica
  - Pneumoconiosi
  - Malattia interstiziale da farmaci o radiazioni
- **Restrittive extraparenchimali**
  - Neuromuscolari (paralisi del diaframma, miastenia gravis, sindrome di Guillan-Barré, distrofie muscolari, lesioni del midollo cervicale)
  - Affezioni gabbia toracica (cifoscoliosi, obesità, spondilite anchilosante)

- **Polmoniti e broncopolmoniti**

Infettive

Haemophilus influenzae
Streptococcus pneumoniae
Staphilococcus aureus
Legionella pneumophila
Mycobacterium tubercolosis
Chlamidia pneumoniae
Mycoplasma pneumoniae

Virus (SARS-CoV, MERS-CoV, SARS-CoV-2)

Funghi

Non infettive

gas nocivi
sostanze chimiche irritanti
tossici volatili

Classificazione delle reazioni immunopatologiche secondo Coombs

Reazione	Meccanismo	Conseguenze	Esempio di malattia
Tipo 1 anafilattica Ipersensibilità immediata	Mediata da IgE	Sviluppo di infiammazione acuta	Asma bronchiale Shock anafilattico
Tipo 2 citotossica	Mediata da immunità umorale e/o citotossica	Danno cellulare diretto	Febbre reumatica
Tipo 3 da immunocomplessi	Deposizione di immunocomplessi	Attivazione del complemento	Glomerulonefrite post-streptococcica
Tipo 4 ipersensibilità ritardata	Mediata da linfociti T con liberazione di citochine citotossiche	Danno cellulare da citochine citotossiche	Tubercolosi Febbre tifoide

Tipo 1, anafilattica
ipersensibilità immediata

Reazione a rapido sviluppo (secondi, minuti)
mediata da anticorpi della classe IgE

Anafilassi, dal greco ανά (indietro) e φύλαξις (protezione)

Parola coniata nel 1902 da Charles Richet (1850-1935) e Paul Portier (1866-1962) per indicare il *contrario della protezione*

Contrario di *profilassi, che favorisce la protezione*

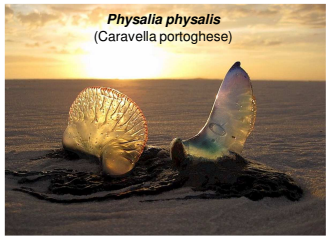


FIG 3. Postage stamp issued by Monaco in 1953 to commemorate the 50th anniversary of the discovery of anaphylaxis. Pictured are *Physalia (left)*, Prince Albert *(upper right)*, Richet and Portier *(lower right)*, the Prince's yacht Hirondelle II *(center)*, and the Oceanographic Institute of Monaco *(background)*. Gift of Charles May, 1985.

Tipo 1, anafilattica
ipersensibilità immediata

Reazione a rapido sviluppo (secondi, minuti)
mediata da anticorpi della classe IgE

Anafilassi, dal greco ανά (indietro) e φύλαξις (protezione)

Parola coniata nel 1902 da Charles Richet (1850-1935) e Paul Portier (1866-1962) per indicare il *contrario della protezione*

Contrario di *profilassi, che favorisce la protezione*

Asma bronchiale

Malattia caratterizzata da uno stato infiammatorio cronico su base immunologica

Dal greco άσθμα, respirazione difficile. Il termine indica il sintomo, ***dispnea espiratoria accessionale***, che può anche dipendere da altre cause: asma cardiaco, asma tossico (uremia)

Nell'asma bronchiale, distinguiamo

una componente **immediata** IgE-mediata → Crisi asmatica acuta

una componente **ritardata e prolungata** → Rimodellamento bronchiale

→ **Ostruzione bronchiale** acuta e cronica

Patogenesi

- Sensibilizzazione ad allergeni: polveri di casa (acari), pollini, muffe
- Predisposizione familiare: atopia
- Modalità di contatto con l'allergene: piccole dosi, via inalatoria (favorisce la formazione di IgE)

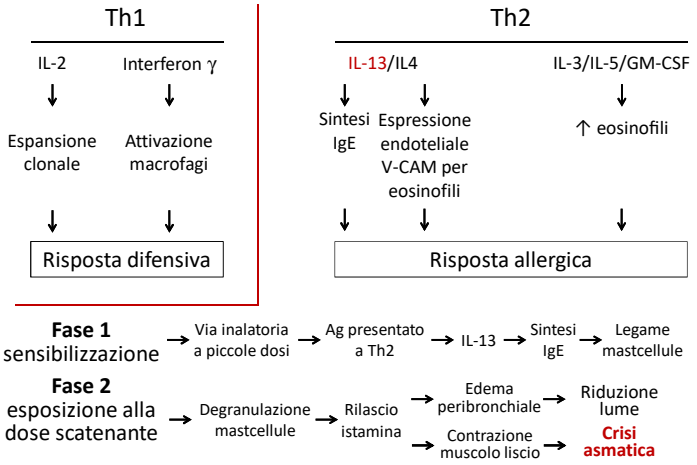
Ipotesi

- Igiene domestica: la mancata esposizione ai patogeni ambientali durante lo sviluppo del sistema immunitario porterebbe alla maturazione anomala del sistema immunitario con shift Th1→Th2
- Inquinamento: calo dell'incidenza dopo il 1989 nei paesi dell'Est europeo

Dal punto di vista epidemiologico

- La probabilità di sviluppare asma bronchiale è inversamente correlata con il grado di diversità biologica (batteri, funghi) nelle polveri di casa
- La colonizzazione batterica intestinale durante l'infanzia è protettiva contro lo sviluppo di asma bronchiale
- Alcune infezioni virali favoriscono, mentre altre proteggono dallo sviluppo di asma

Ruolo dei linfociti T helper

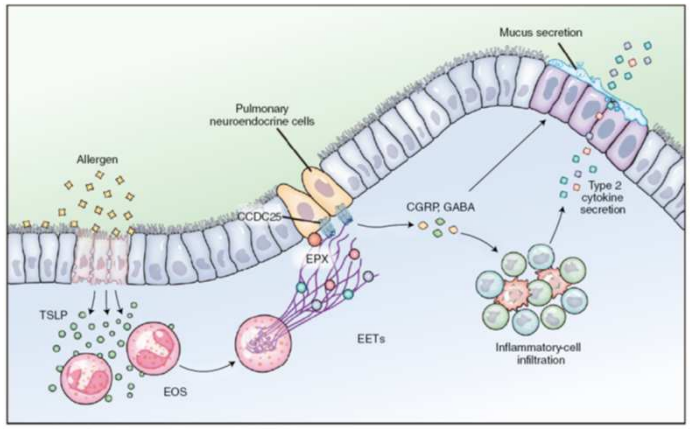


NATURE CELL BIOLOGY | VOL 23 | OCTOBER 2021 | 1060–1072 | www.nature.com/naturecellbiology

Eosinophil extracellular traps drive asthma progression through neuro-immune signals

Yiwen Lu[1,2,9], Yijiao Huang[1,3,9], Jiang Li[1,2,9], Jingying Huang[1,2,9], Lizhi Zhang[1,3,9], Jingwei Feng[1,2], Jiaqian Li[1,2], Qidong Xia[1,2], Qiyi Zhao[4,5,6], Linjie Huang[1,3,7], Shanping Jiang[1,3,7] ✉ and Shicheng Su[1,2,4,8] ✉

Eosinophilic inflammation is a feature of allergic asthma. Despite mounting evidence showing that chromatin filaments released from neutrophils mediate various diseases, the understanding of extracellular DNA from eosinophils is limited. Here we show that eosinophil extracellular traps (EETs) in bronchoalveolar lavage fluid are associated with the severity of asthma in patients. Functionally, we find that EETs augment goblet-cell hyperplasia, mucus production, infiltration of inflammatory cells and expressions of type 2 cytokines in experimental non-infection-related asthma using both pharmaceutical and genetic approaches. Multiple clinically relevant allergens trigger EET formation at least partially via thymic stromal lymphopoietin in vivo. Mechanically, EETs activate pulmonary neuroendocrine cells via the CCDC25–ILK–PKCα–CRTC1 pathway, which is potentiated by eosinophil peroxidase. Subsequently, the pulmonary neuroendocrine cells amplify allergic immune responses via neuropeptides and neurotransmitters. Therapeutically, inhibition of CCDC25 alleviates allergic inflammation. Together, our findings demonstrate a previously unknown role of EETs in integrating immunological and neurological cues to drive asthma progression.



i. Schematic summarising the major discoveries of this study. Allergens induce TSLP, which triggers the formation of EETs in asthmatic airways. The EET-DNA activates PNECs, which is potentiated by the eosinophil granule protein EPX. Subsequently, PNECs amplify type 2 immune responses via neuropeptides and neurotransmitters such as CGRP and GABA.

NATURE CELL BIOLOGY | VOL 23 | OCTOBER 2021 | 1052–1059 | www.nature.com/naturecellbiology

Eosinophils set DNA traps in allergic asthma

The underlying molecular and cellular mechanisms for asthma remain incompletely understood. A new study now shows that eosinophils release DNA traps that stimulate pulmonary neuroendocrine cell-mediated amplification of the allergic asthma response.

Barsha Dash and Xin Sun

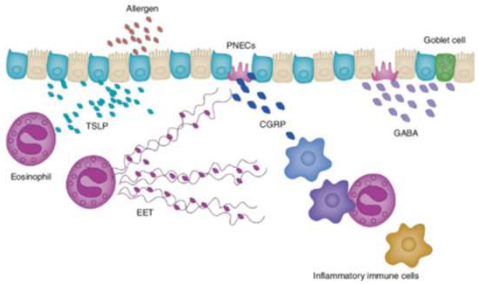
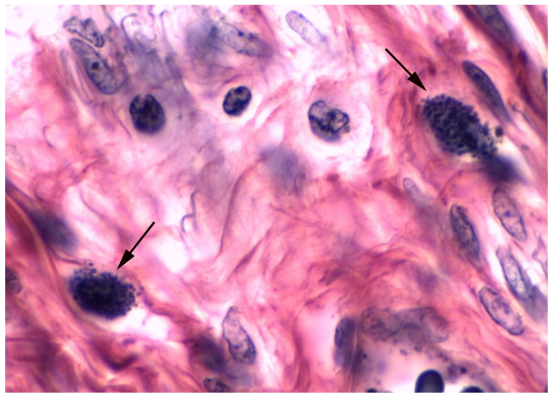
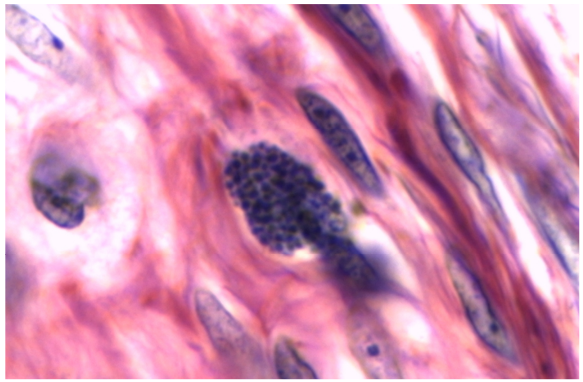


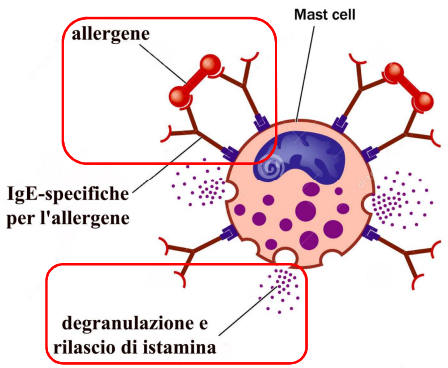
Fig. 1| **Allergen EET release by eosinophils reinforces PNEC-mediated type 2 immunity.** Allergens stimulate the release of thymic stromal lymphopoietin (TSLP) from airway epithelial cells, which elicit eosinophils to release DNA traps. These, in turn, are sensed by PNECs that secrete CGRP to activate and recruit inflammatory immune cells, and GABA for goblet cell production of mucus.

Mastcellule

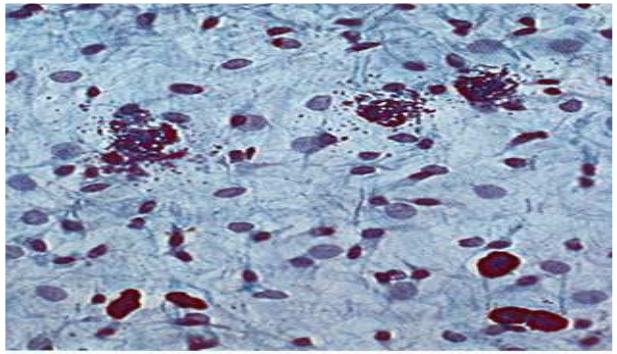




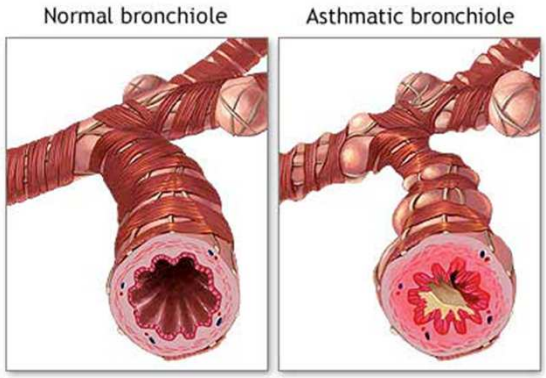
Fase 2 Esposizione alla dose scatenante



La degranulazione delle mastcellule *in vivo*



Asma bronchiale



Lucio Anneo Seneca (4 a.C.-65 d.C.)
Epistulae ad Lucilium, 54, 1-4

L'attacco del male è di breve durata; simile ad un temporale, passa, di solito, dopo un'ora. Chi, infatti, potrebbe sopportare a lungo quest'agonia? Ormai ho provato tutti i mali e tutti i pericoli, ma nessuno per me è più penoso. E perché no? In ogni altro caso si è malati: in questo ci si sente morire. Perciò i medici chiamano questo male *meditazione della morte*: talvolta, infatti, la mancanza di respiro provoca il soffocamento.

L'istamina agisce con meccanismo recettoriale

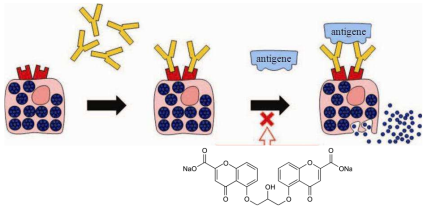
- H1: cellule muscolari lisce bronchiali, vascolari, intestinali, cellule endoteliali
- H2: cellule muscolari lisce vascolari, cellule parietali gastriche, utero
- H3: Sistema Nervoso Centrale
- H4: cellule del sistema emopoietico, tratto gastrointestinale, fibroblasti dermici

Non solo istamina

Dal polmone di cavie morte per shock anafilattico era isolabile una sostanza che induceva la contrazione lenta della muscolatura liscia ileale, detta «slow reacting substance of anaphylaxis» (SRS-A). Oggi sappiamo che si tratta del leucotriene B4.

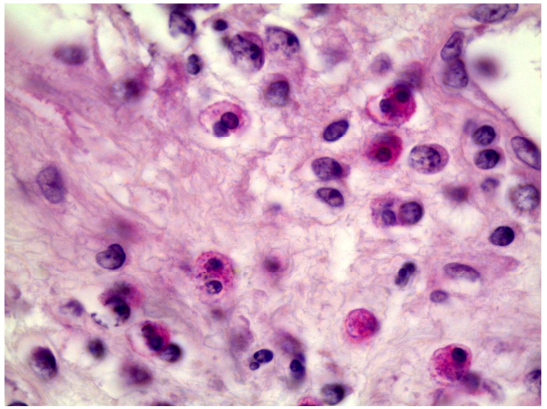
Terapia della crisi asmatica

- Simpaticomimetici broncodilatatori
- Cortisone
- L'aspirina non serve (non blocca la sintesi dei leucotrieni)
- Stabilizzatori di membrana

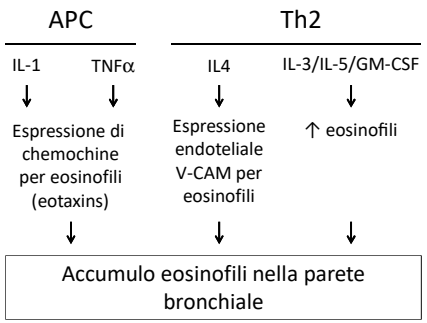


Sodio cromoglicato
(uso topico)

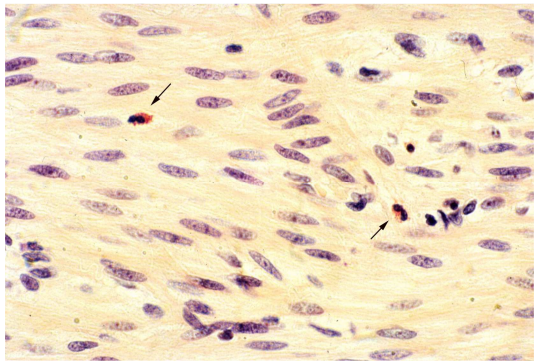
Eosinofili in corso di lisi



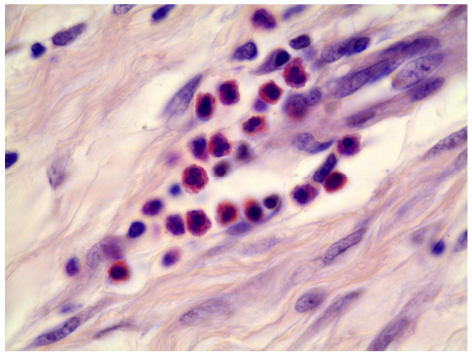
Patogenesi del danno cronico

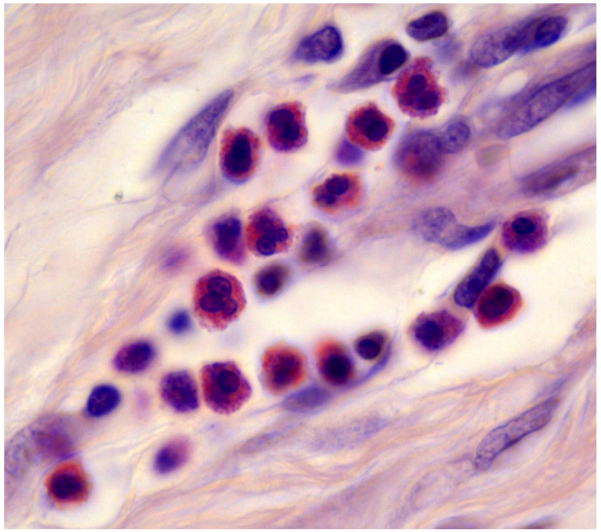


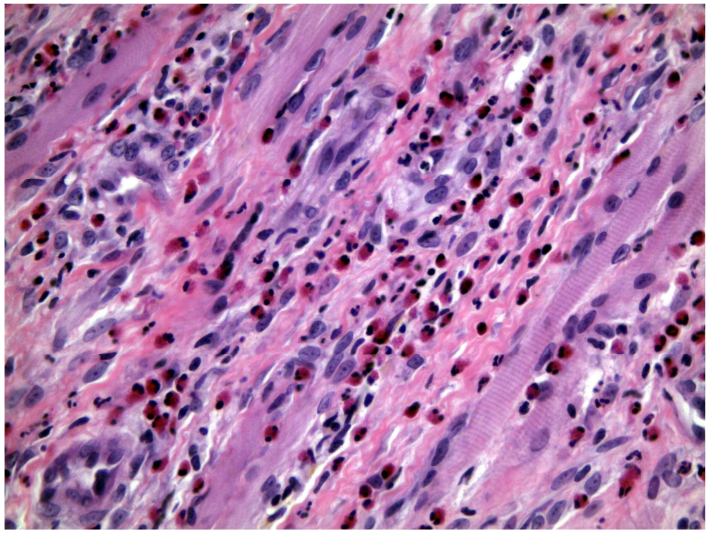
Eosinofili nella muscolatura liscia intestinale

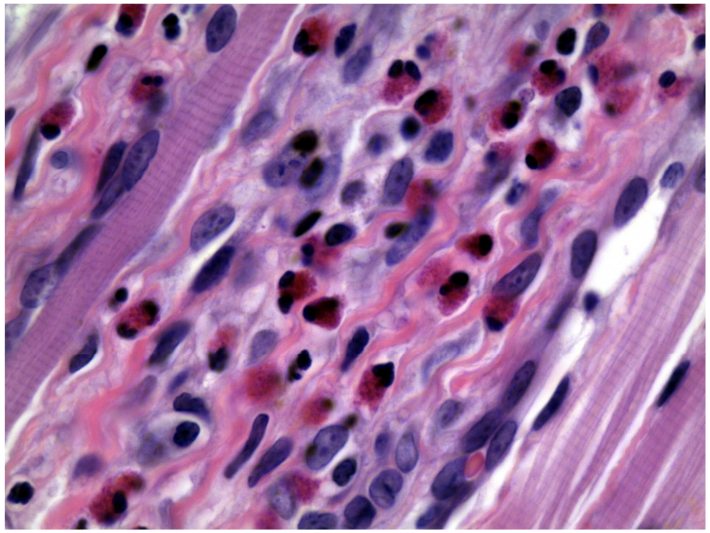


Blood eosinophilia

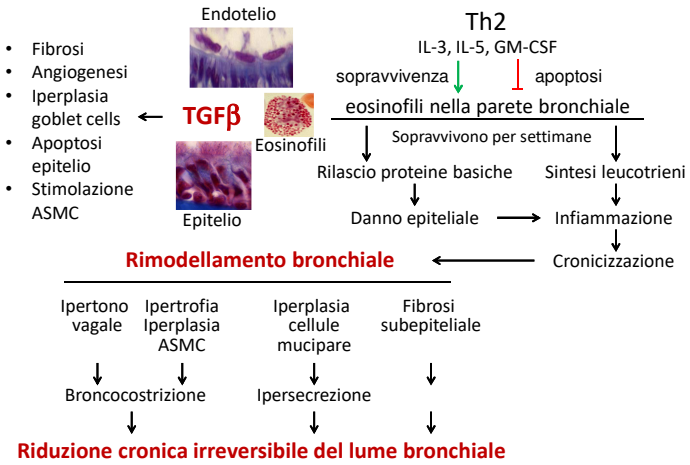








Patogenesi del danno cronico



Bronchite cronica ed enfisema polmonare

sono due processi distinti, ma compaiono quasi sempre in diversa misura negli stessi soggetti con

Ostruzione cronica delle vie aeree

il meccanismo patogenetico che conduce ad ostruzione è diverso nelle due condizioni:

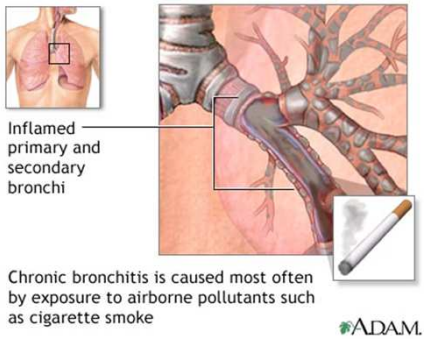
nella bronchite prevale l'ostruzione da ipersecrezione di muco e ipertrofia della mucosa bronchiale.

nell'enfisema, prevale la riduzione della distensione elastica delle vie bronchiali per distruzione dei setti alveolari.

Bronchite cronica

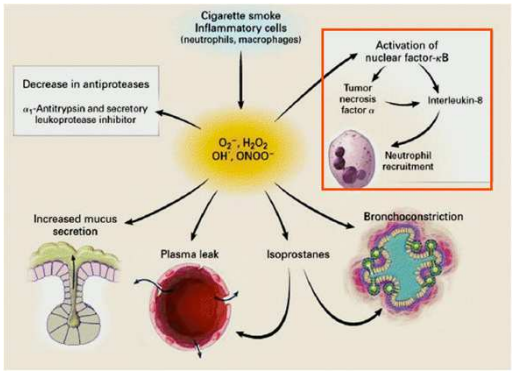
patologia infiammatoria cronica dei bronchi

associata a eccessiva produzione di muco tale da causare tosse con espettorazione per almeno **tre mesi** all'anno per **due anni** consecutivi

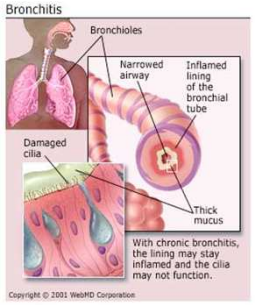


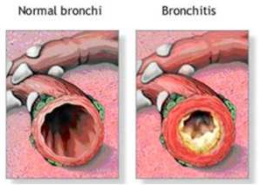
Bronchite cronica: meccanismo fisiopatologico

- iperproduzione muco
- inibizione motilità delle cellule ciliate
- infiltrazione infiammatoria sottomucosa
- iperplasia cellule muscolari lisce



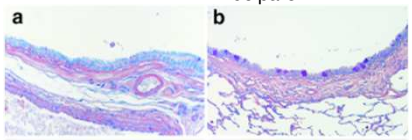
ostruzione bronchiale → ritenzione di aria negli alveoli ostruiti → danno meccanico e distruzione parete alveolare





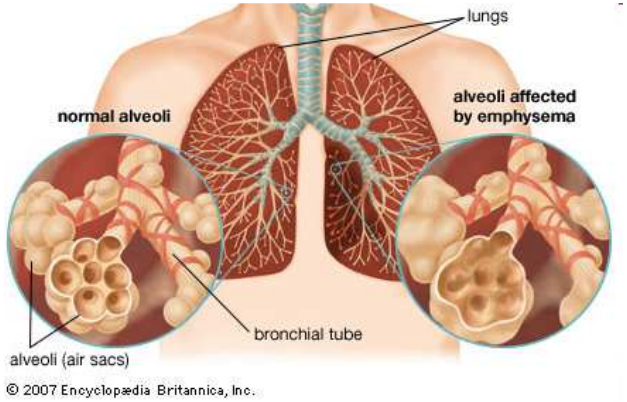
normale

iperplasia delle cellule mucipare



enfisema polmonare

enfisema: distensione degli spazi aerei situati distalmente ai bronchioli terminali con distruzione dei setti alveolari



enfisema polmonare: meccanismi

lesione irreversibile dello stroma elastico polmonare

↓

distensione del tess polmonare

↓

diminuito ritorno elastico = aumento volume residuo

↓

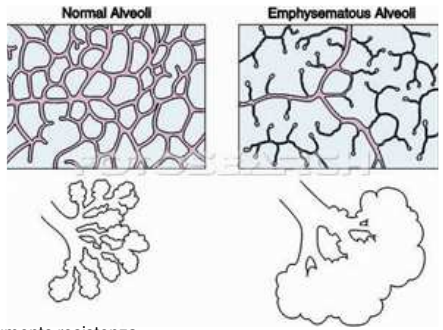
riduzione della superficie della membrana alveolo capillare

↓

ridistribuzione del flusso sanguigno

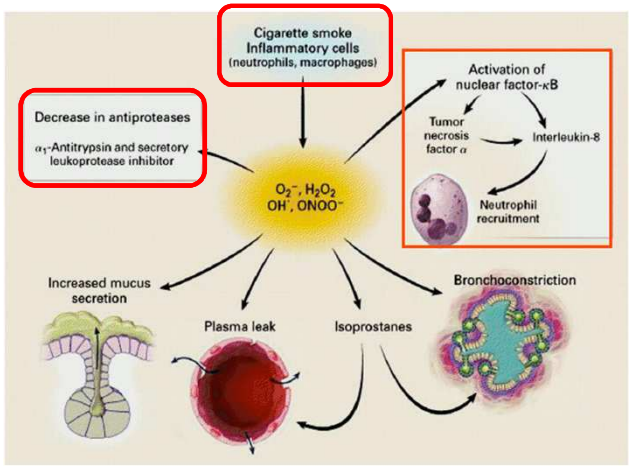
↓

shunt = squilibrio V/Q



aumento resistenza capillari polmonari → aumento lavoro VDx

Fumo di sigaretta



Deficit di α1-antitripsina

- La α1-antitripsina viene attivata nella fase acuta della risposta infiammatoria
- Il gene è *SERPINA1* ed esistono almeno tre alleli (M, Z ed S)
- **le variant SS e ZZ causano misfolding con deficit di attività antiproteasica e danno epatico e polmonare**
- L'integrità strutturale dei setti alveolari dipende dalla presenza di sufficiente attività α1-antitripsinica

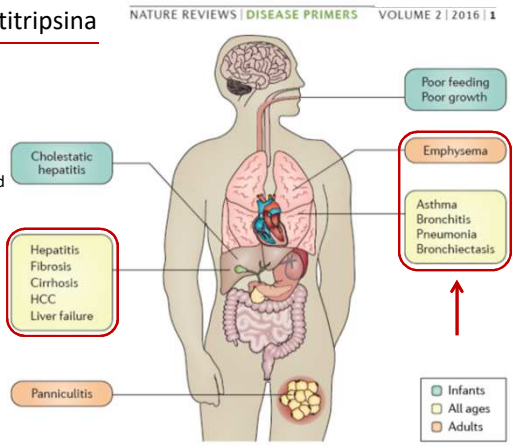
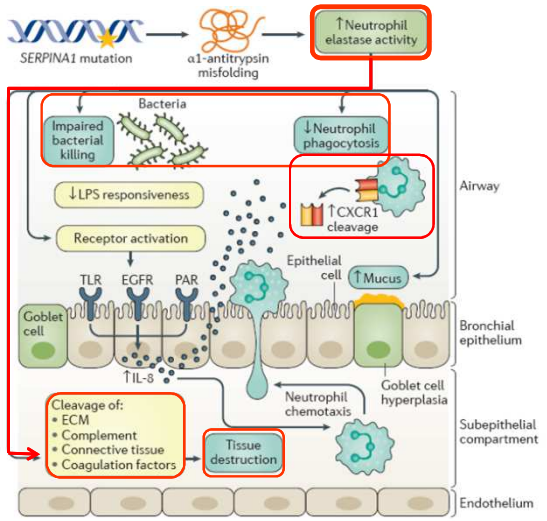


Figure 1 | **Clinical manifestations of the PI*ZZ genotype.** About 15% of infants with the PI*ZZ genotype have, or develop, clinically relevant liver disease, which, in children, carries a risk of death of between 2% and 3%[181,182]. The levels of serum aminotransferases



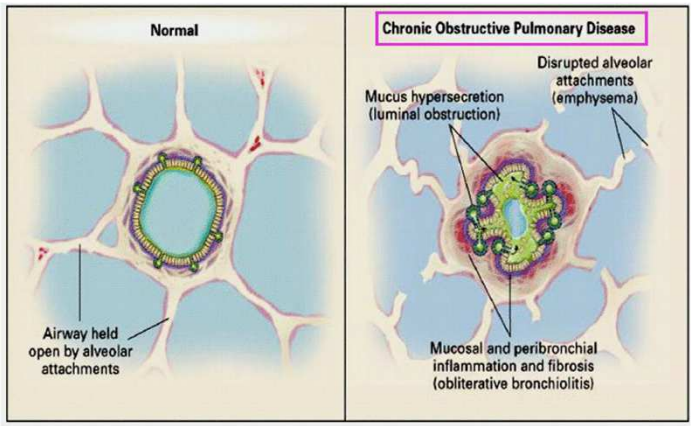
NATURE REVIEWS | DISEASE PRIMERS VOLUME 2 | 2016 | 1

α1-Antitrypsin deficiency

Catherine M. Greene[1], Stefan J. Marciniak[2], Jeffrey Teckman[3], Ilaria Ferrarotti[4], Mark L. Brantly[5], David A. Lomas[6], James K. Stoller[7] and Noel G. McElvaney[1]

Figure 4 | **Intrapulmonary consequences of unopposed neutrophil elastase activity.** Neutrophil elastase is normally inhibited by α1-antitrypsin. However, in the lungs of patients with α1-antitrypsin deficiency, unopposed neutrophil elastase activity can affect innate immunity by cleaving CXC-chemokine receptor 1 (CXCR1), decreasing neutrophil phagocytosis and lipopolysaccharide (LPS) responsiveness, and impairing bacterial killing. Neutrophil elastase can also cause tissue destruction by cleaving various protein substrates and can activate bronchial epithelial cell surface receptors, leading to transcriptional upregulation of IL-8, which leads to neutrophil recruitment into the airway lumen. Goblet cell hyperplasia and increased production of mucus also occur as a result of unopposed neutrophil elastase activity. ECM, extracellular matrix; EGFR, epidermal growth factor receptor; PAR, protease-activated receptor; TLR, Toll-like receptor. Adapted with permission from REF. 60, Taylor & Francis Ltd, http://www.informaworld.com.

evoluzione delle sindromi ostruttive polmonari



polmonite e broncopolmonite

Polmonite: infiammazione delle parti distali del parenchima polmonare } alveoli, interstizio, bronchioli

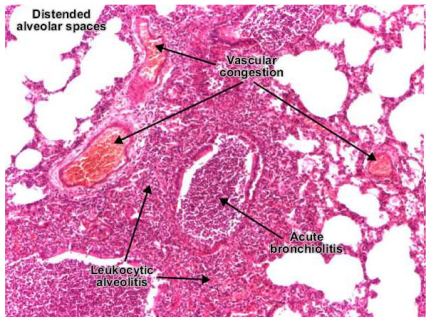
sede del processo patologico

- **Polmonite lobare**

Interessa interamente un lobo polmonare

- **Broncopolmonite**

Interessa diffusamente il polmone con focolai multipli



- **Polmoniti e broncopolmoniti**

Infettive

Haemophilus influenzae
Streptococcus pneumoniae
Staphilococcus aureus
Legionella pneumophila
Mycobacterium tubercolosis
Chlamidia pneumoniae
Mycoplasma pneumoniae

Virus (SARS-CoV, MERS-CoV, SARS-CoV-2)

Funghi

Non infettive

gas nocivi
sostanze chimiche irritanti
tossici volatili

polmonite e broncopolmonite

Meccanismi

- diminuzione del parenchima funzionante
- alterazione V/Q
- alterazione microcircolo (secondarie a ipoventilazione e ipoperfusione)

Evoluzione: Dipende!

Si può andare dalla *restitutio ad integrum* ad una evoluzione che dipende dall'agente eziologico e dalla risposta dell'ospite, per esempio ascessi e successiva fibrosi e/o formazione di bronchiectasie (piogeni), formazione di granulomi con necrosi (bacillo di Koch), ispessimento della membrane alveolare (forme tossiche)

Bronchiectasia: dilatazione anormale ed irreversibile dei bronchi

Può essere localizzata o diffusa

Conseguenza dell'infiammazione delle componenti strutturali della parete bronchiale

P. aeruginosa, H. influenzae, S. aureus

secernono proteasi ed altre tossine che danneggiano l'epitelio respiratorio e impediscono la clearance muco-ciliare

Interstitial lung disease (ILD)

Also known as diffuse parenchymal lung disease (DPLD), refers to a group of lung diseases affecting the interstitium. It concerns alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and perilymphatic tissues.

- **Inhaled substances**
  - *Inorganic*
    - Silicosis
    - Asbestosis
    - Berylliosis
  - *Organic*
    - Hypersensitivity pneumonitis
- **Drug-induced**
  - Antibiotics
  - Chemotherapeutic drugs
  - Antiarrhythmic agents
  - Statins
- **Connective tissue disease**
  - Systemic sclerosis
  - Polymyositis
  - Dermatomyositis
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
- **Infection**
  - Atypical pneumonia
  - *Pneumocystis pneumoniae* (PCP)
  - Chlamydia trachomatis
  - Respiratory Syncytial Virus
  - **SARS-CoV**
  - **MERS-CoV**
  - **SARS-CoV-2**
- **Idiopathic**
  - Sarcoidosis
  - **Idiopathic pulmonary fibrosis**
  - Hamman-Rich syndrome
  - Antisynthetase Syndrome
- **Malignancy**
  - Lymphangitic carcinomatosis

British Journal of Pharmacology (2008) 153, 1367–1378

www.brjpharmacol.org

REVIEW

LifeSciences2007

Procoagulant signalling mechanisms in lung inflammation and fibrosis: novel opportunities for pharmacological intervention?

RC Chambers

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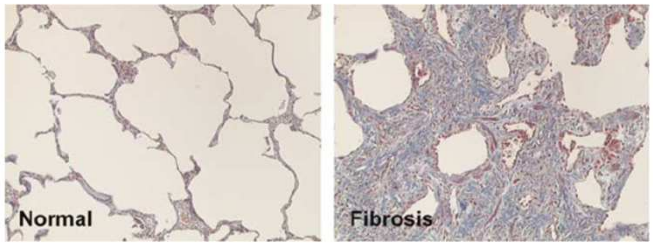


Figure 1 Alveolar architecture of normal and fibrotic lung. Images show the stark contrast in alveolar architecture in the normal and fibrotic lung. In the fibrotic lung, the open alveolar architecture is obliterated and replaced with dense fibrotic tissue. (Histology slides courtesy of Dr Robin McAnulty, Centre for Respiratory Research, University College London.)

Eur Respir Rev 2008; 17: 109, 130–137
DOI: 10.1183/09059180.00010905

Abnormal wound healing responses in pulmonary fibrosis: focus on coagulation signalling

R.C. Chambers

ABSTRACT: **The normal response of tissue to injury involves a sequence of overlapping events, which need to occur in a timely and controlled manner for successful tissue repair and restoration of normal function. Failure to control the healing process can lead to considerable tissue remodelling and the replacement of functional tissue with permanent fibrous scar tissue.**

It is proposed that pulmonary fibrosis arises from repetitive, widespread epithelial injury. However, the nature of the insult for the most common and most fatal form of pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), is currently unknown and the pathogenetic pathways leading to IPF remain to be fully elucidated. Increasing evidence suggests that abnormalities in a number of pathways involved in the wound healing response may play central roles.

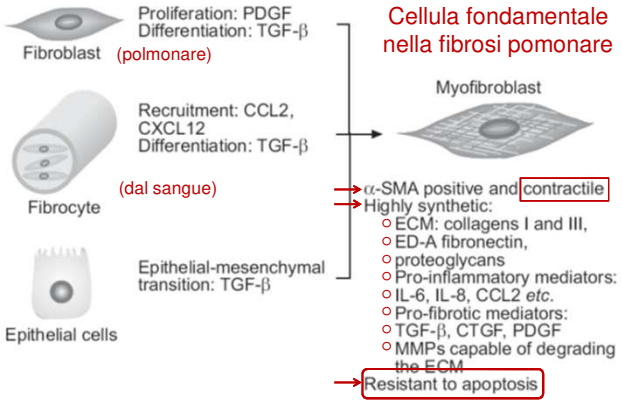
The present article will briefly review the pathways involved in wound healing focusing on the control of fibroblast/myofibroblast function and the coagulation cascade acting *via* the family of signalling receptors, the proteinase activated receptors, which influence a range of cellular responses implicated in the development of pulmonary fibrosis.

Understanding the involvement of these pathways in the aberrant wound repair-response in pulmonary fibrosis may lead to the identification of new targets and strategies for therapeutic intervention.

KEYWORDS: **Coagulation cascade, lung, myofibroblasts, proteinase-activated receptor**

The normal response of tissue to injury involves the initiation of a highly coordinated wound repair-programme aimed at restoring normal tissue function. Some of the earliest responses involve the activation of the coagulation cascade, inflammatory cell recruitment and the formation of a provisional matrix to prevent blood loss, infection and promote subsequent wound healing responses. Successful wound repair and the re-establishment of an intact epithelium requires spatially and temporally regulated epithelial and mesenchymal cell responses. Epithelial cell proliferation, migration and differentiation must be coordinated with mesenchymal cell recruitment, proliferation, differentiation with extracellular matrix (ECM) remodelling, and subsequent apoptosis of myofibroblasts [1]. Dysregulation of this orchestrated wound repair-response can result in pathological scar formation and excessive deposition of collagen and other ECM proteins.

The pathogenetic mechanisms leading to pulmonary fibrosis and, in particular, idiopathic pulmonary fibrosis (IPF) remain poorly understood. However, current evidence suggests that IPF arises as a consequence of chronic, widespread epithelial injury leading to the development of the classical picture of patchy interstitial fibrosis alternating with areas of mild inflammation and normal lung. The failure of classical anti-inflammatory and immunosuppressive therapy to impact on the course of this condition supports the notion that IPF results from chronic epithelial injury and dysregulated or inappropriate repair rather than chronic inflammation. The distinctive presence of fibroblastic foci and excessive ECM deposition are thought to lead to the characteristic thickening of alveolar septae and the collapse of normal lung architecture (honeycombing). However, the role of inflammation in driving fibrosis remains at the centre of an interesting debate. The present article will discuss some of the potential mechanisms controlling fibroblast function, with a particular emphasis on coagulation signalling pathways, and what implications this may have for future therapy.



REVIEW
Leukemia (2006) 20, 1331–1340
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Tissue factor as an effector of angiogenesis and tumor progression in hematological malignancies

C López-Pedrera[1], N Barbarroja[1], G Dorado[2], E Siendones[1] and F Velasco[1]

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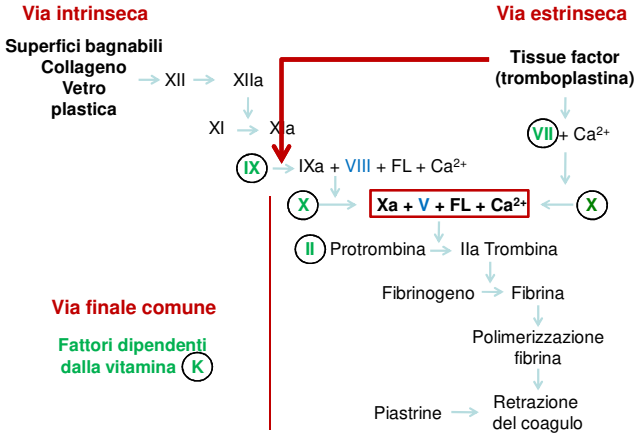
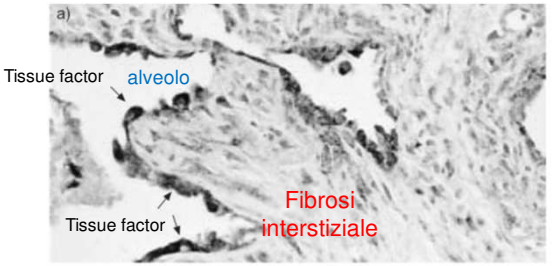
Tissue factor (TF) is a 47 kDa transmembrane glycoprotein, found on the surface of various cells and is the principal initiator of the coagulation cascade. The TF protein consists of 295 amino acids, from which 32 amino acids serve as a signal peptide for intracellular transport. The mature peptide consists of 263 amino acids with an extracellular domain (residues 1–219) that contribute to the binding of its natural ligand, the FVII(a): a membrane spanning domain (residues 220–242) necessary for stabilization of the molecule, and a cytoplasmic domain (residues 243–263), playing a key role in intracellular signaling.[1,2] Structurally, TF belongs to the class II cytokine receptor superfamily, sharing a significant degree of homology with the interferon class of receptors. Moreover, the fact that the intracellular part of TF contains two putative phosphorylation sites suggests a role for this protein in intracellular processes.[3] TF is a key player in blood coagulation; one of the consequences of the disruption of the vessel wall is the exposure of TF-expressing cells located in the underlying cell layers to the bloodstream, thus enabling binding of activated factor VII to TF. This protein complex then initiates the extrinsic coagulation pathway, thereby initiating the formation of a blood clot. In the last few years, it has become clear also that TF-mediated conversion of FIX to FIXa is pivotal for the activation of the intrinsic coagulation pathway. Thus, TF ensures that the extrinsic and intrinsic pathways operate simultaneously.[1,3] In the adult organism, TF is constitutively expressed in a variety of extravascular tissues. In addition, TF expression can be transiently upregulated by growth factors and cytokines in intravascular cells as endothelial cells and monocytes.[4] TF expression itself is under cell-type-specific control through different transcriptional pathways, which is also reflected by different activation patterns in response to different stimuli. In addition to its regulation of the clotting cascade, TF has recently been shown to participate in a variety of physiological processes distinct from hemostasis, including embryogenesis, inflammation, cellular signaling, cell migration, tumor growth, metastasis and angiogenesis.[4,5] Furthermore, recent investigations have revealed that intracellular activities induced by FVII(a) bound to cell surface TF may well be related to these events.[5–7] In addition, TF can often exerts its role independently from binding to its natural ligand, FVII(a)[8] (Figure 1).

3. Fase emocoagulativa





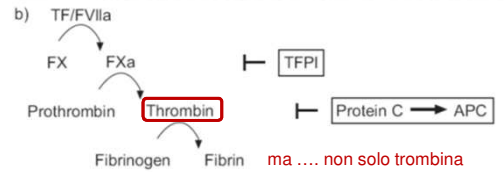
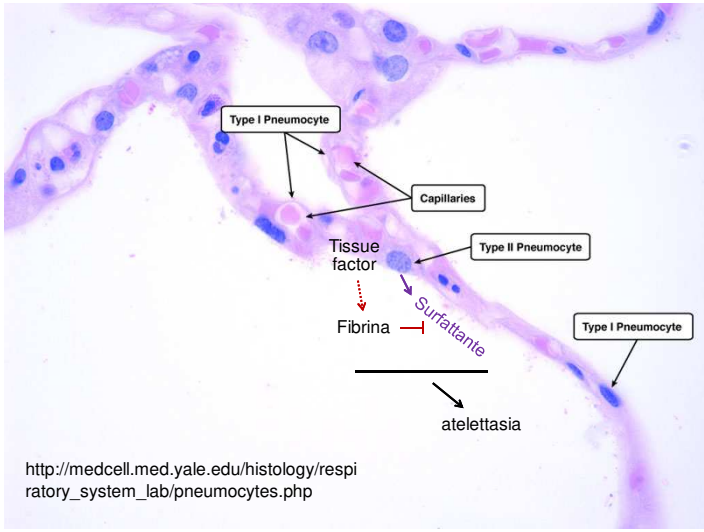


FIGURE 2. Tissue factor (TF)-dependent activation of the coagulation cascade in pulmonary fibrosis. a) TF immunoreactivity (arrows) associated with the epithelium overlying fibrotic foci in idiopathic pulmonary fibrosis.



http://medcell.med.yale.edu/histology/respiratory_system_lab/pneumocytes.php

Cell
Volume 64, Issue 6, 22 March 1991, Pages 1057-1068
Article

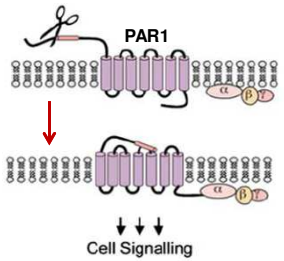
Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation

Thien-Khai H. Vu *, David T. Hung *, [1, 2], Virginia I. Wheaton *, Shaun R. Coughlin *,

We isolated a cDNA encoding a functional human thrombin receptor by direct expression cloning in Xenopus oocytes. mRNA encoding this receptor was detected in human platelets and vascular endothelial cells. The deduced amino acid sequence revealed a new member of the seven transmembrane domain receptor family with a large amino-terminal extracellular extension containing a remarkable feature. A putative thrombin cleavage site (LDPR/S) resembling the activation cleavage site in the zymogen protein C (LDPR/I) was noted 41 amino acids carboxyl to the receptor's start methionine. A peptide mimicking the new amino terminus created by cleavage at R41 was a potent agonist for both thrombin receptor activation and platelet activation. "Uncleavable" mutant thrombin receptors failed to respond to thrombin but were responsive to the new amino-terminal peptide. These data reveal a novel signaling mechanism in which thrombin cleaves its receptor's amino-terminal extension to create a new receptor amino terminus that functions as a tethered ligand and activates the receptor.

PAR = Proteinase Activated Receptors (1,2,3,4)

Trombina (Tripsina, MMP-1)



Procoagulant signalling following lung injury
RC Chambers

Table 2 Pro-inflammatory mediators released following PAR_1 activation

Cytokine/ chemokine	*Cell type*	*Reference*
IL-1β	Monocytes/macrophages	Naldini *et al.* (1998, 2002)
IL-2	T lymphocytes	Mari *et al.* (1994)
IL-6	Fibroblasts, epithelial cells, monocytes/macrophages, mast cells, smooth muscle cells	Sower *et al.* (1995), Cirino *et al.* (1996), Kranzhofer *et al.* (1996) and Naldini *et al.* (1998)
IL-8	Fibroblasts, epithelial cells, monocytes/macrophages	Ueno *et al.* (1996), Suk and Cha (1999), Ludwicka-Bradley *et al.* (2000) and Asokananthan *et al.* (2002)
PGE_2	Epithelial cells	Asokananthan *et al.* (2002)
CCL2/ MCP-1	Fibroblasts, endothelial cells, monocytes/ macrophages	Riewald *et al.* (2002), Bachli *et al.* (2003) and Colognato *et al.* (2003)
TNF-α	Monocytes/macrophages	Naldini *et al.* (1998)

Table lists the major cytokines/chemokines released by cell types present in the lung.
Abbreviations: CCL2, chemokine (C–C motif) ligand 2; IL, interleukin; MCP-1, monocyte chemotactic protein 1; TNFα, tumour necrosis factor-alpha.

TABLE 2 Major functional roles of proteinase-activated receptor-1 during tissue repair

Haemostasis
- Promotion of platelet aggregation and regulation of vascular tone

Endothelial barrier function
- Low thrombin concentration: protective
- High thrombin concentration: highly disruptive

Pro-inflammatory responses
- Production of IL-1, -2, -6 and -8
- Production of chemokines (*e.g.* CCL2)
- Promotion of adhesion molecule expression

Mitogenic responses
- Promotes fibroblast, endothelial cell and smooth muscle cell mitogenesis *via* the release of secondary mediators and upregulation of their signalling receptors (*e.g.* PDGF and PDGFαR)

Fibrogenic responses
- Promotion of myofibroblast differentiation and ECM production
- Activation of TGF-β
- Induction of CTGF

IL: interleukin; CCL2: CC-motif chemokine ligand 2; PDGF: platelet-derived growth factor; PDGFαR: PDGFα receptor; ECM: extracellular matrix; TGF: transforming growth factor; CTGF: connective tissue growth factor.

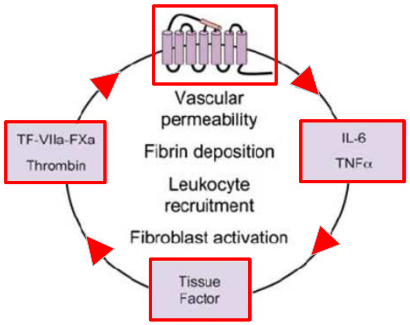
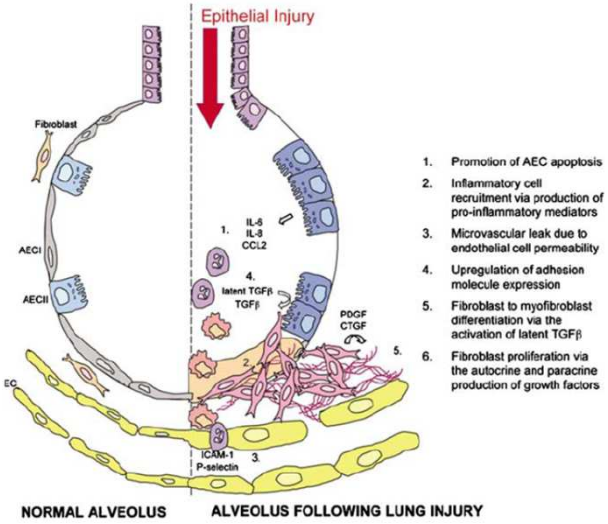


Figure 3 Proteinase-activated receptors (PARs) perpetuate the interplay between coagulation and inflammation. Activation of PARs leads to the induction of potent pro-inflammatory mediators, which are capable of inducing tissue factor expression. Tissue factor initiates the activation of the extrinsic coagulation pathway resulting in activation of PARs. The functional consequences in the injured lung include microvascular permeability, fibrin deposition, leukocyte recruitment and fibroblast activation.



Pathogenesis, current treatments and future directions for idiopathic pulmonary fibrosis☆

Hillary Loomis-King[1], Kevin R Flaherty[1] and Bethany B Moore[1,2]

Interstitial pulmonary fibrosis (IPF) is the result of an aberrant wound healing process

The initial/repetitive injury occurs to the lung epithelium, likely to type I alveolar epithelial cells (AECs). Under homeostatic conditions, type I AECs are believed to keep pulmonary structural mesenchymal cells in check through the secretion of various mediators and cell–cell contact.

When type I AECs are injured or lost, it is thought that type II AECs undergo hyperplastic proliferation to cover the exposed basement membranes. If this process is inefficient, alveoli can collapse and consolidate.

In normal repair, the hyperplastic type II AECs will undergo regulated apoptosis. The remaining cells will spread and undergo a differentiation process to become type I AEC. Under pathologic conditions and in the presence of TGFβ, fibroblasts accumulate in these areas of damage and differentiate into α-smooth muscle actin (SMA)-expressing myofibroblasts that secrete collagen and other ECM proteins.

Pathologic examination reveals the diagnostic lesions known as 'fibroblastic foci' (dense collections of myofibroblasts and scar tissue).

The AECs adjacent to these fibroblastic foci often remain hyperplastic and abnormal rather than undergoing appropriate repair.

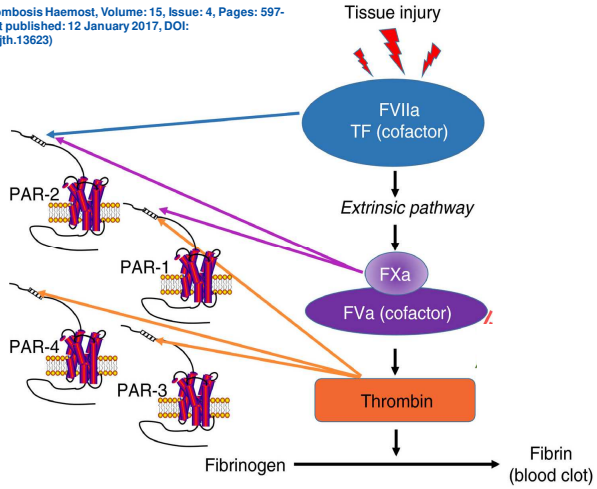
Current Opinion in Pharmacology 2013, **13**:377–385

The disease is progressive, and often results in respiratory insufficiency within 3–5 years post-diagnosis.

Variable natural history:

- Some patients experience a relatively gradual decline in lung function.
- Some experience stable disease over extended periods of time.
- **Others have acute deteriorations with rapid worsening and disease progression.**

J of Thrombosis Haemost, Volume: 15, Issue: 4, Pages: 597-607, First published: 12 January 2017, DOI: (10.1111/jth.13623)



PAR1

Application of antagonists of protease-activated receptors (PARs) in different fibrotic or inflammatory disorders

Antagonists	Organs/tissue	Models	Key results
SCH79797	Heart [85]	Ischemia–reperfusion injury	Limited left ventricular dilation and improved left ventricular systolic function of the reperfused myocardium
	Kidney [86]	Ischemia–reperfusion injury	Significantly attenuated kidney damage histologically
	Intestine [87]	Ischemia–reperfusion injury	Intestinal myeloperoxidase expression and adhesion molecule expression were significantly decreased
	Brain [89]	Surgically induced brain injury	Reduced secondary brain injury by decreasing both brain edema and apoptosis
SCH602539	Intestine [87]	Chronic intestinal radiation fibrosis	Markedly reduced early intestinal radiation injury, but had no effect on the level of delayed intestinal radiation fibrosis
P1pal-12S	Lung [25,92]	Cecal ligation and puncture-induced sepsis	Early administration significantly increased survival rate
		Bleomycin-induced fibrosis	Reduced pulmonary fibrosis significantly; treatment starting after the onset of fibrosis was also effective
SCH530348	Lung [90]	Intranasal inoculation of *Sterptococcus pneumoniae*-induced pneumonia	Significantly decreased pulmonary levels of proinflammatory cytokines and chemokines, and attenuated alveolar leakage
RWJ-56110	Liver [91]	Bile duct ligation-induced fibrosis	Reduced liver type I collagen mRNA and protein expression, as well as hepatic and urinary excretion of hydroxyproline

PAR2

Application of antagonists of protease-activated receptors (PARs) in different fibrotic or inflammatory disorders

Antagonists	Organs/tissue	Models	Key results
NDGA	Skin [97]	Oxazolone-induced atopic dermatitis	Rebuilt the skin barrier and increased transepidermal water loss recovery
GB88	Joint [93]	Collagen-induced arthritis	Reduced pathologic and histopathologic changes (i.e. edema, macrophage invasion, mast cell degranulation, etc.)
	Colon [94]	PAR-2 agonist or 2,4,6-trinitrobenzenesulfonic acid-induced colitis	Reduced mortality and pathology (including colon obstruction, ulceration, wall thickness, and myeloperoxidase release)
ENMD-1068	Joint [95]	Intra-articular carrageenan/kaolin injection-induced joint swelling	Dose-dependently attenuated joint inflammation
FSLLRY-amide	Lung [98]	Hypoxia-induced pulmonary hypertension	Reversed established pulmonary hypertension in hypoxia-exposed mice
P2pal-18S	Pancreas [96]	Retrograde intraductal bile acid infusion-induced biliary pancreatitis	Reduced the severity of biliary pancreatitis
	Lung [99]	Bleomycin-induced fibrosis	Reduced pulmonary fibrosis significantly; treatment starting after the onset of fibrosis was also effective
PZ-235	Liver [100]	Carbon tetrachloride-induced fibrosis	Suppressed liver fibrosis significantly

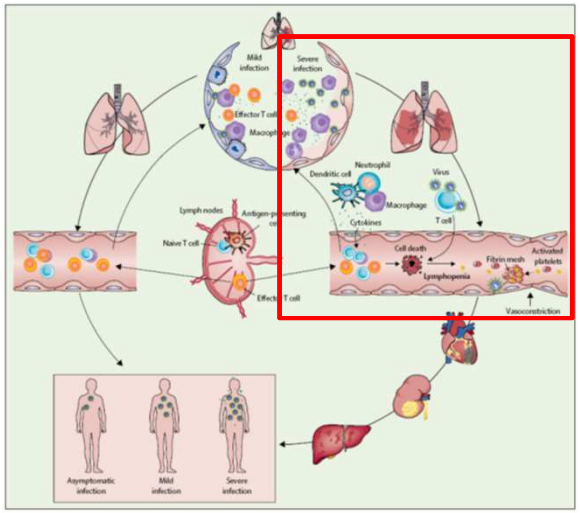
Hypothesis

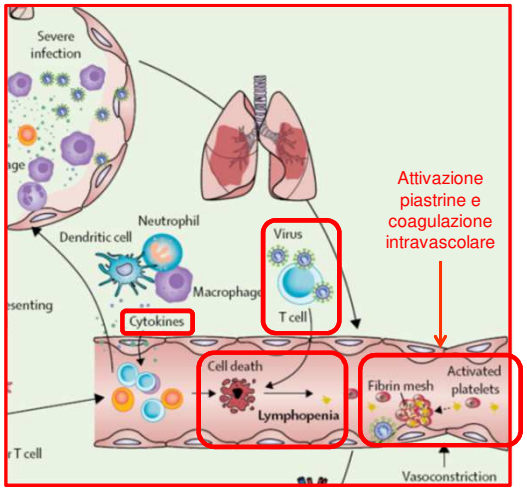
Lancet 2020; 395: 1517–20

SARS-CoV-2 and viral sepsis: observations and hypotheses

Hui Li, Liang Liu, Dingyu Zhang, Jiuyang Xu, Huaping Dai, Nan Tang, Xiao Su, Bin Cao

Since the outbreak of coronavirus disease 2019 (COVID-19), clinicians have tried every effort to understand the disease, and a brief portrait of its clinical features have been identified. In clinical practice, we noticed that many severe or critically ill COVID-19 patients developed typical clinical manifestations of shock, including cold extremities and weak peripheral pulses, even in the absence of overt hypotension. Understanding the mechanism of viral sepsis in COVID-19 is warranted for exploring better clinical care for these patients. With evidence collected from autopsy studies on COVID-19 and basic science research on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and SARS-CoV, we have put forward several hypotheses about SARS-CoV-2 pathogenesis after multiple rounds of discussion among basic science researchers, pathologists, and clinicians working on COVID-19. We hypothesise that a process called viral sepsis is crucial to the disease mechanism of COVID-19. Although these ideas might be proven imperfect or even wrong later, we believe they can provide inputs and guide directions for basic research at this moment.





Article 268 | Nature | Vol 585 | 10 September 2020

Respiratory disease in rhesus macaques inoculated with SARS-CoV-2

https://doi.org/10.1038/s41586-020-2324-7
Received: 22 March 2020
Accepted: 1 May 2020
Published online: 12 May 2020

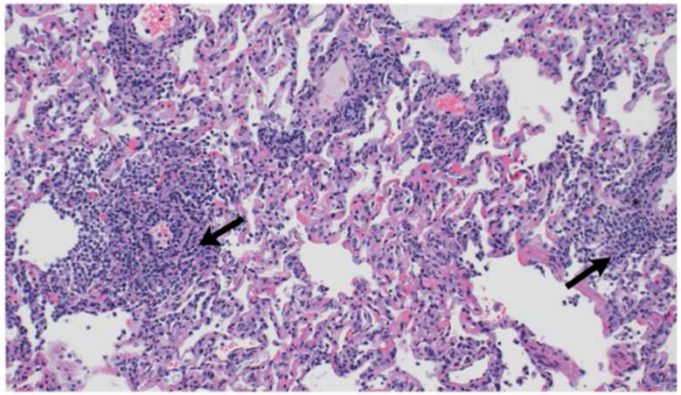
Vincent J. Munster[1], Friederike Feldmann[2], Brandi N. Williamson[1], Neeltje van Doremalen[1], Lizzette Pérez-Pérez[1], Jonathan Schulz[1], Kimberly Meade-White[1], Atsushi Okumura[1], Julie Callison[1], Beniah Brumbaugh[2], Victoria A. Avanzato[1], Rebecca Rosenke[2], Patrick W. Hanley[2], Greg Saturday[2], Dana Scott[2], Elizabeth R. Fischer[3] & Emmie de Wit[1]✉

Here we show that SARS-CoV-2 causes a respiratory disease in rhesus macaques that lasts between 8 and 16 days. Pulmonary infiltrates, which are a hallmark of COVID-19 in humans, were visible in lung radiographs. We detected high viral loads in swabs from the nose and throat of all of the macaques, as well as in bronchoalveolar lavages; in one macaque, we observed prolonged rectal shedding. Together, the rhesus macaque recapitulates the moderate disease that has been observed in the majority of human cases of COVID-19. The establishment of the rhesus macaque as a model of COVID-19 will increase our understanding of the pathogenesis of this disease, and aid in the development and testing of medical countermeasures.

Fig. 3 | Pathological changes in rhesus macaques infected with SARS-CoV-2.

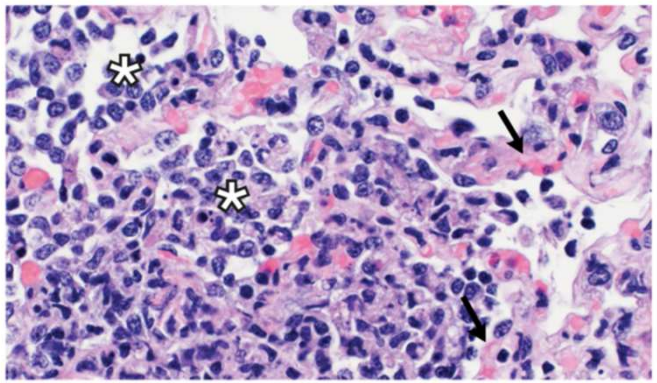
at 3 dpi

e 100x



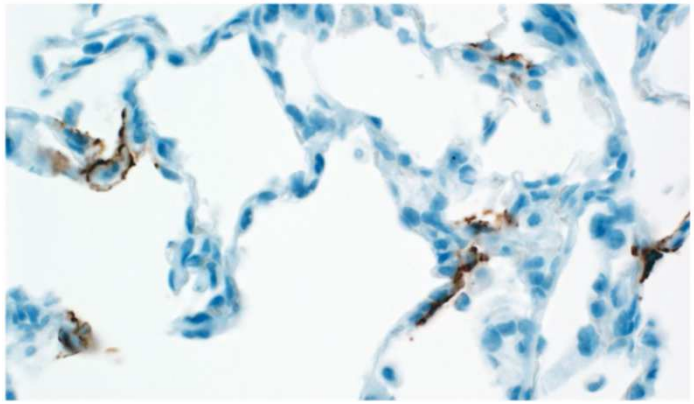
e, Pulmonary vessels surrounded by moderate numbers of lymphocytes, and fewer macrophages (arrows).

f 400x



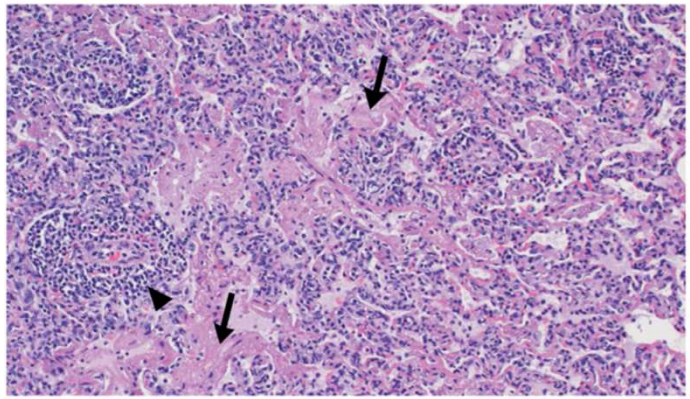
f, Alveoli filled with small-to-moderate numbers of macrophages and neutrophils (asterisks). The adjacent alveolar interstitium (arrows) is thickened by oedema, fibrin, neutrophils, lymphocytes and macrophages.

g 400x



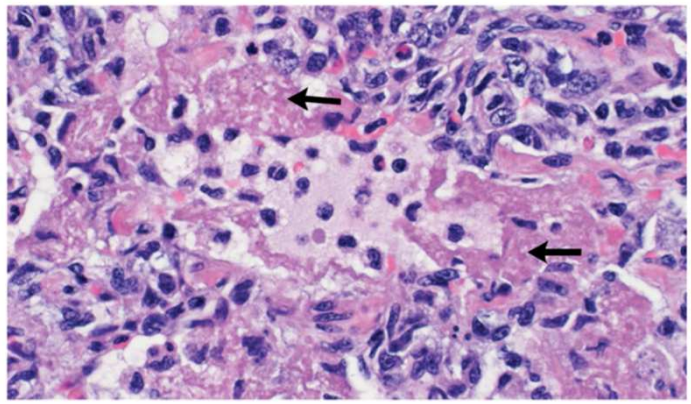
g, SARS-CoV-2 antigen detected by immunohistochemistry in type-I pneumocytes.

h 100x



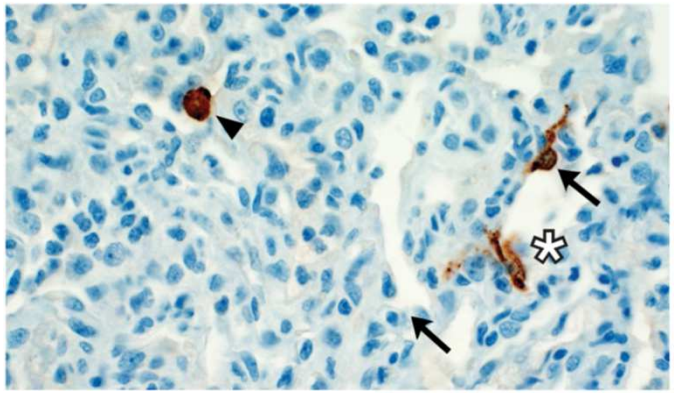
h, Pulmonary vessels bounded by lymphocytes (arrowhead) and hyaline membranes (arrows) line the alveolar spaces.

i 400x



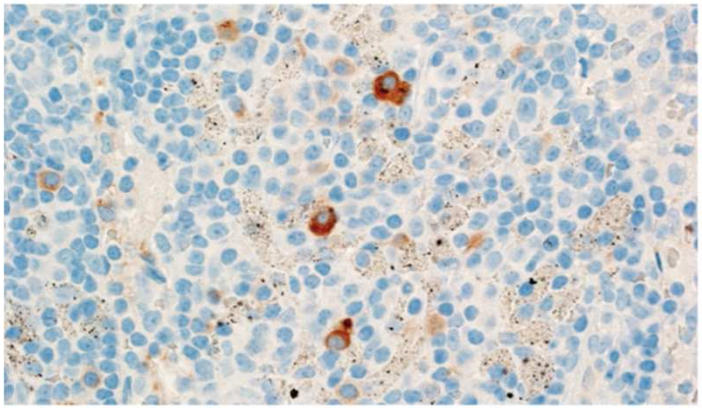
i, Hyaline membranes line the alveoli (arrows)

j



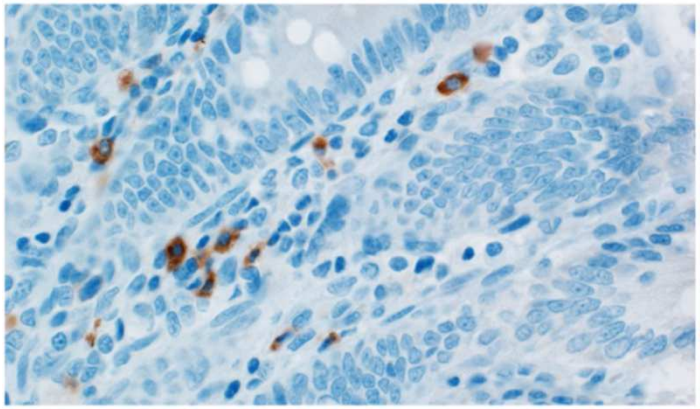
j, SARS-CoV-2 antigen detected by immunohistochemistry in type-I pneumocytes (asterisk) and type-II pneumocytes (arrow), as well as in alveolar macrophages (arrowheads)

k



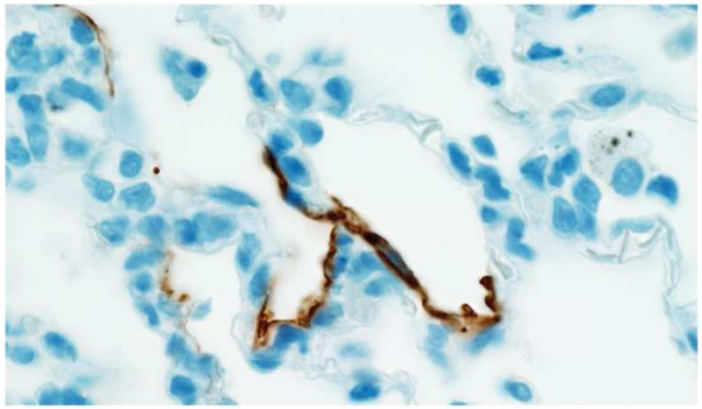
k, SARS-CoV-2 antigen detected by immunohistochemistry in macrophages in a mediastinal lymph node.

l 400x



l, SARS-CoV-2 antigen detected by immunohistochemistry in macrophages and lymphocytes in the lamina propria of the caecum.

m 1,000x



m, SARS-CoV-2 detected by immunohistochemistry in type-I pneumocytes.

Received 18 February 2020; revised 20 February 2020; accepted 20 February 2020

SPECIAL REPORT

Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer

CASE 1: The first case was an 84-year-old female patient who was admitted for treatment evaluation of a tumor measuring 1.5 cm in the right middle lobe of the lung. The tumor was discovered on chest computed tomography scan at an outside hospital. She had a past medical history of hypertension for 30 years, as well as type 2 diabetes. Despite comprehensive treatment, assisted oxygenation, and other supportive care, the patient's condition deteriorated, and she died. Subsequent clinical information confirmed that she was exposed to another patient in the same room who was subsequently found to be infected with the 2019 novel coronavirus.

CASE 2: The second case was a 73-year-old male patient who presented for elective surgery for lung cancer, which presented as a small mass in the right lower lobe of the lung. He had a past medical history of hypertension for 20 years, which had been adequately managed. Nine days after lung surgery, he developed a fever with dry cough, chest tightness, and muscle pain. A nucleic acid test for COVID-19 came back as positive. He gradually recovered and was discharged after 20 days of treatment in the infectious disease unit.

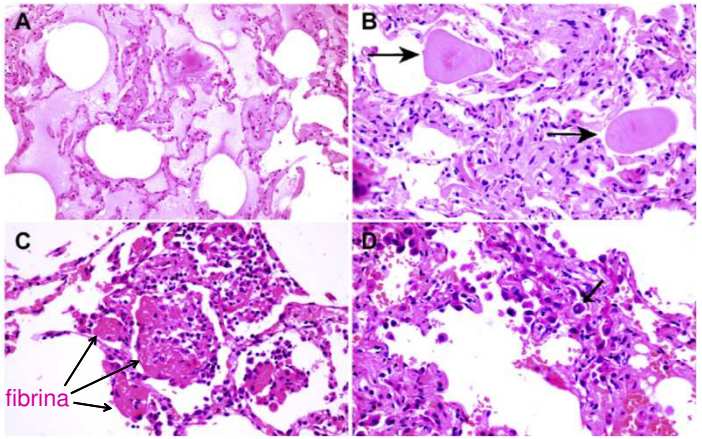


Figure 2. Histologic changes from case 1. (**A**) Proteinaceous exudates in alveolar spaces, with granules; (**B**) scattered large protein globules (arrows); (**C**) intra-alveolar fibrin with early organization, mononuclear inflammatory cells, and multinucleated giant cells; (**D**) hyperplastic pneumocytes, some with suspected viral inclusions (arrow).

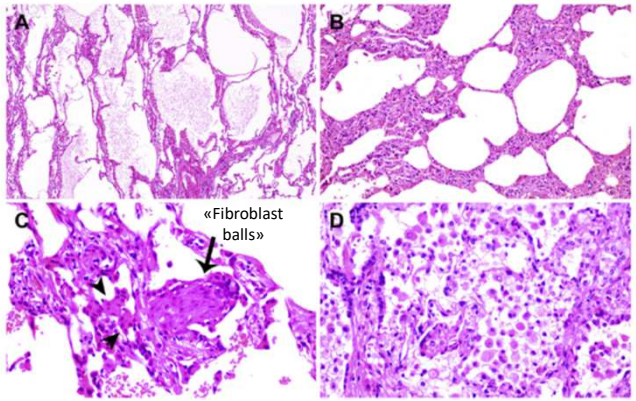
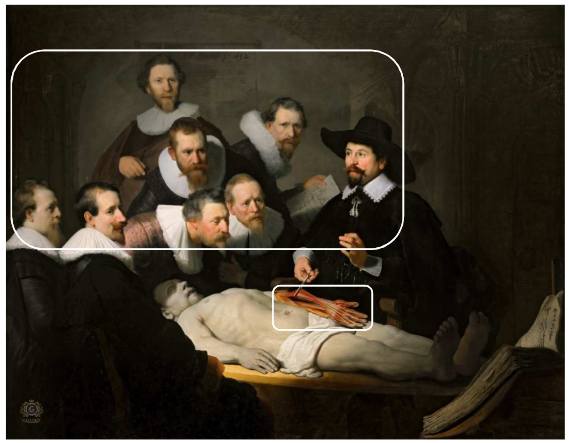


Figure 3. Histologic changes of coronavirus disease 2019 pneumonia in case 2. (A) Evident proteinaceous and fibrin exudate; (B) diffuse expansion of alveolar walls and septa owing to fibroblastic proliferations and type II pneumocyte hyperplasia, consistent with early diffuse alveolar damage pattern; (C) plugs of proliferating fibroblasts or "fibroblast balls" in the interstitium (arrow); (D) abundant macrophages infiltrating airspaces and type II pneumocyte hyperplasia.



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