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Immunological lung diseases
Hypersensitivity pneumonitis and sarcoidosis

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28.03.2019

Aims

- Understand the immunological mechanisms of hypersensitivity pneumonitis
- Understand the immunological alterations in sarcoidosis
- Understand that inflammation leads to fibrosis in some individuals

Overview

- Hypersensitivity pneumonitis
- Sarcoidosis
- Inflammation and fibrosis

Hypersensitivity pneumonitis

- acute, subacute or chronic lung disease
- Lymphocytic and granulomatous inflammation
- Affects peripheral airways, alveoli and surrounding interstitial tissue (alveolobronchiolitis)
- Lymphocytic alveolitis in BAL (CD4/CD8 ratio may be decreased)
- Non- IgE mediated allergic reaction

Quirce S et al. Occupational hypersensitivity pneumonitis: an EAACI position paper. Allerg 71 (2016) 765-779.

Hypersensitivity pneumonitis

- Induced by variety of organic materials or low-molecular weight agents
  - Bacteria
  - Fungi
  - animal proteins
  - plant proteins
  - low-molecular weight chemicals
  - metals

Quirce S et al. Occupational hypersensitivity pneumonitis: an EAACI position paper. Allerg 71 (2016) 765-779.

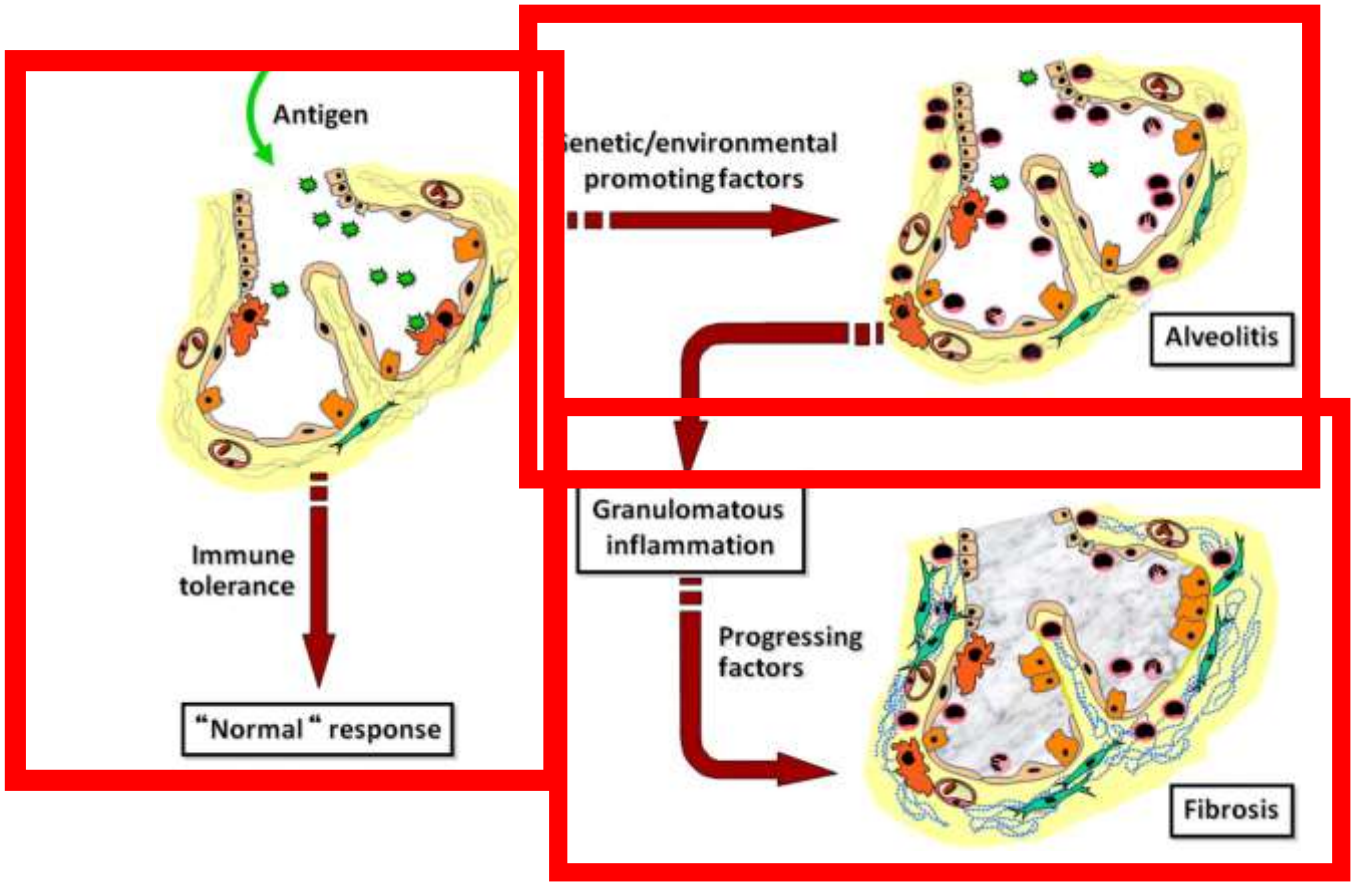
Etiological agents of HP

Disease	Antigen	Source
Fungal and bacterial		
Wood trimmer's lung	*Rhizopus* spp., *Mucor* spp.	Contaminated wood trimmings
Composter's lung	*T. vulgaris, Aspergillus*	Compost
Basement shower HP	*Epicoccum nigrum*	Mold on unventilated shower
Hot tub lung	*Mycobacterium avium complex*	Hot tub mists; mold on ceiling
Wine maker's lung	*Botrytis cinerea*	Mold on grapes
Woodsman's disease	*Penicillium* spp.	Oak and maple trees
Thatched roof lung	*Saccharomonospora viridis*	Dead grasses and leaves
Tobacco grower's lung	*Aspergillus* spp.	Tobacco plants
Potato riddler's lung	*Thermophilic actinomycetes*, *S. rectivirgula, T. vulgaris, Aspergillus* spp.	Moldy hay around potatoes
Summer-type pneumonitis	*Trichosporon cutaneum*	Contaminated old houses
Dry rot lung	*Merulius lacrymans*	Rotten wood
Stipatosis	*Aspergillus fumigatus; T. actinomycetes*	Esparto dust
Machine operator's lung	*Mycobacterium immunogenum; Pseudomonas fluorescens*	Aerosolized metalworking fluid
Residential provoked pneumonitis Amebae	*Aureobasidium pullulans*	Residential exposure
Humidifier lung	*Naegleria gruberi, Acanthamoeba polyphaga, Acanthamoeba castellani, Bacillus* sp., others	Contaminated water from home humidifier, ultrasonic misting fountains
Shower curtain disease	*Phoma violacea*	Moldy shower curtain
Animal proteins		
Pigeon breeder's or pigeon fancier's disease	Avian droppings, feathers, serum	Parakeets, budgerigars, pigeons, chickens, turkeys
Pituitary snuff taker's lung	Pituitary snuff	Bovine and porcine pituitary proteins
Fish meal worker's lung	Fish meal	Fish meal dust
Bat lung	Bat serum protein	Bat droppings
Furrier's lung	Animal fur dust	Animal pelts
Animal handler's lung; laboratory worker's lung	Rats, gerbils	Urine, serum, pelts, proteins
Insect proteins		
Miller's lung	*Sitophilus granarius* (i.e., wheat weevil)	Dust-contaminated grain
Lycoperdonosis	Puffball spores	Lycoperdon puffballs

Disease	Antigen	Source
Fungal and bacterial		
Farmer's lung	*Saccharopolyspora rectivirgula*	Moldy hay, grain, silage
Ventilation pneumonitis; humidifier lung; air conditioner lung	*Thermoactinomyces vulgaris, Thermoactinomyces sacchari, Thermoactinomyces candidus, Klebsiella oxytoca*	Contaminated forced-air systems; water reservoirs
Bagassosis	*T. vulgaris*	Moldy sugarcane (i.e., bagasse)
Mushroom worker's lung	*T. sacchari*	Moldy mushroom compost
Enoki mushroom worker's lung (Japan)	*Penicillium citrinum*	Moldy mushroom compost
Suberosis	*Thermoactinomyces viridis, Aspergillus fumigatus, Penicillium frequentans, Penicillium glabrum*	Moldy cork
Detergent lung; washing powder lung	*Bacillus subtilis* enzymes	Detergents (during processing or use)
Malt worker's lung	*Aspergillus fumigatus, Aspergillus clavatus*	Moldy barley
Sequoiosis	*Graphium, Pullularia, and Trichoderma* spp., *Aureobasidium pullulans*	Moldy wood dust
Maple bark stripper's lung	*Cryptostroma corticale*	Moldy maple bark
Cheese washer's lung	*Penicillium casei, A. clavatus*	Moldy cheese
Woodworker's lung	*Alternaria* spp., wood dust	Oak, cedar, and mahogany dust, pine and spruce pulp
Hardwood worker's lung	*Paecilomyces*	Kiln-dried wood
Paprika slicer's lung	*Mucor stolonifer*	Moldy paprika pods
Sauna taker's lung	*Aureobasidium* spp., other sources	Contaminated sauna water
Familial HP	*B. subtilis*	Contaminated wood dust in walls

Selman M et al. Hypersensitivity pneumonitis. Insights in diagnosis and pathobiology. Am J Respir Crit Care Med Vol. 186, Iss. 4 pp 314-324, Aug 15, 2012

Hypersensitivity pneumonitis: pathogenesis



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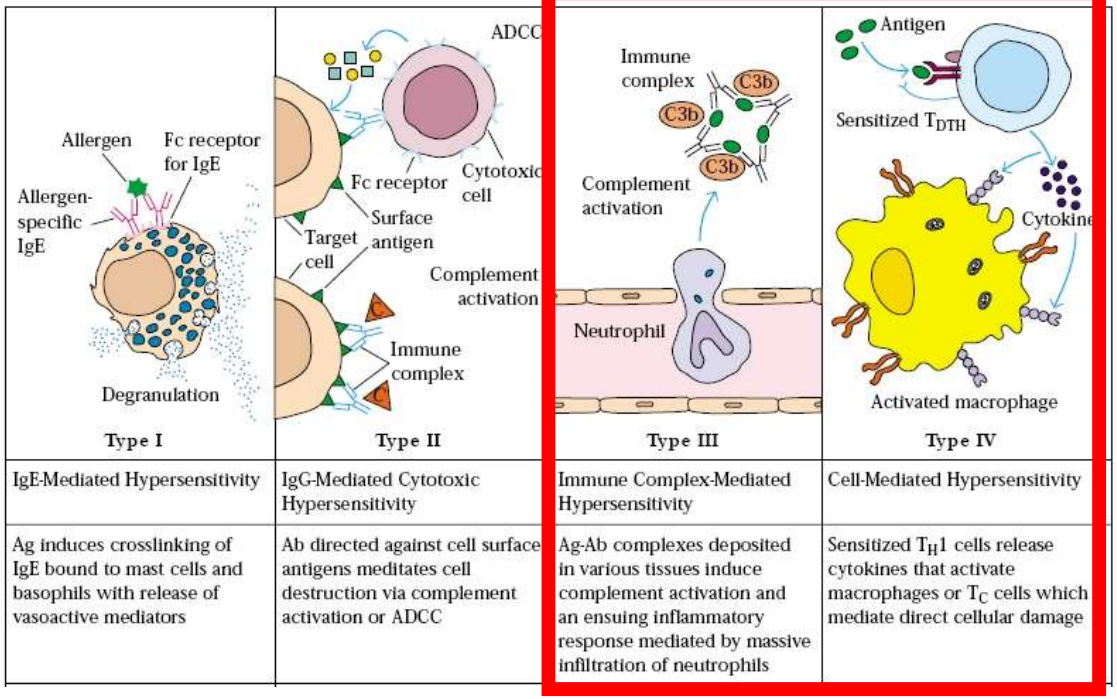
Hypersensitivity pneumonitis: pathogenesis



Type I	Type II	Type III	Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage

Mohr LC. Hypersensitivity pneumonitis. Curr Opin Pulm Med. 2004 Sep;10(5):401-11.

- Activated B-lymphocytes release IgG antibodies (contribute to disease or marker of exposure?)

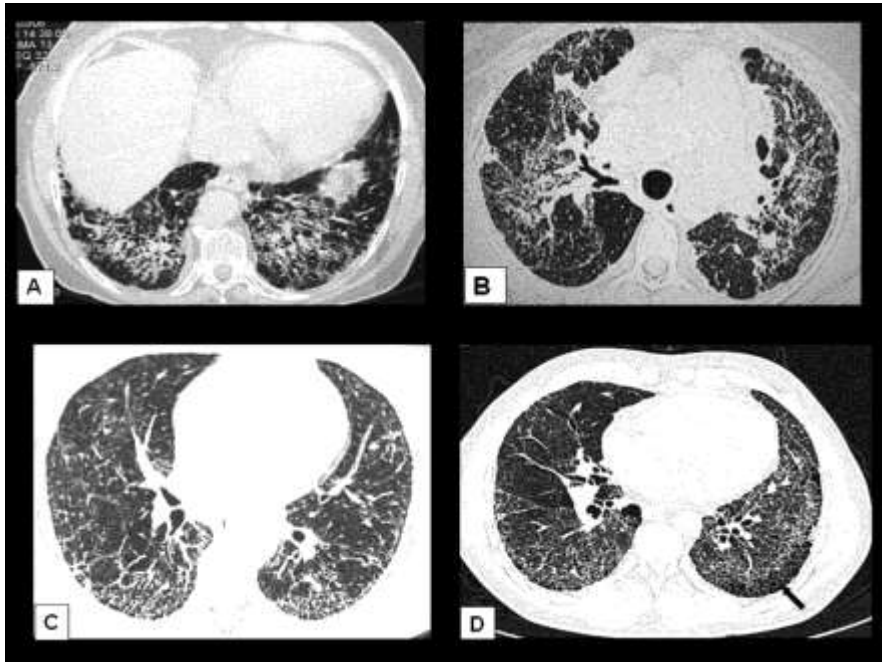
  Burell R et al. A critical review of the role of precipitins in HP. Eur Respir Dis 1981;62:332-343.

- increased IL-17 production with defective Treg-cell function

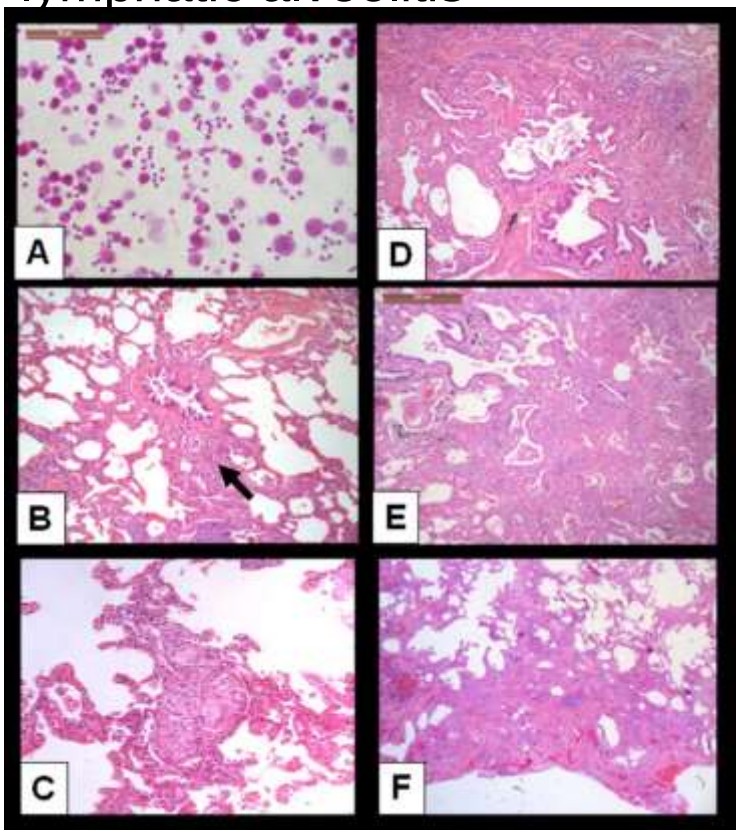
Girard M et al. Impaired function of regulatory T-cells in hypersensitivity pneumonitis. Eur Respir J. 2011 Mar;37(3):632-9.

Hypersensitivity pneumonitis - HP

- HRCT scan



- bronchiolocentric granulomatous lymphatic alveolitis



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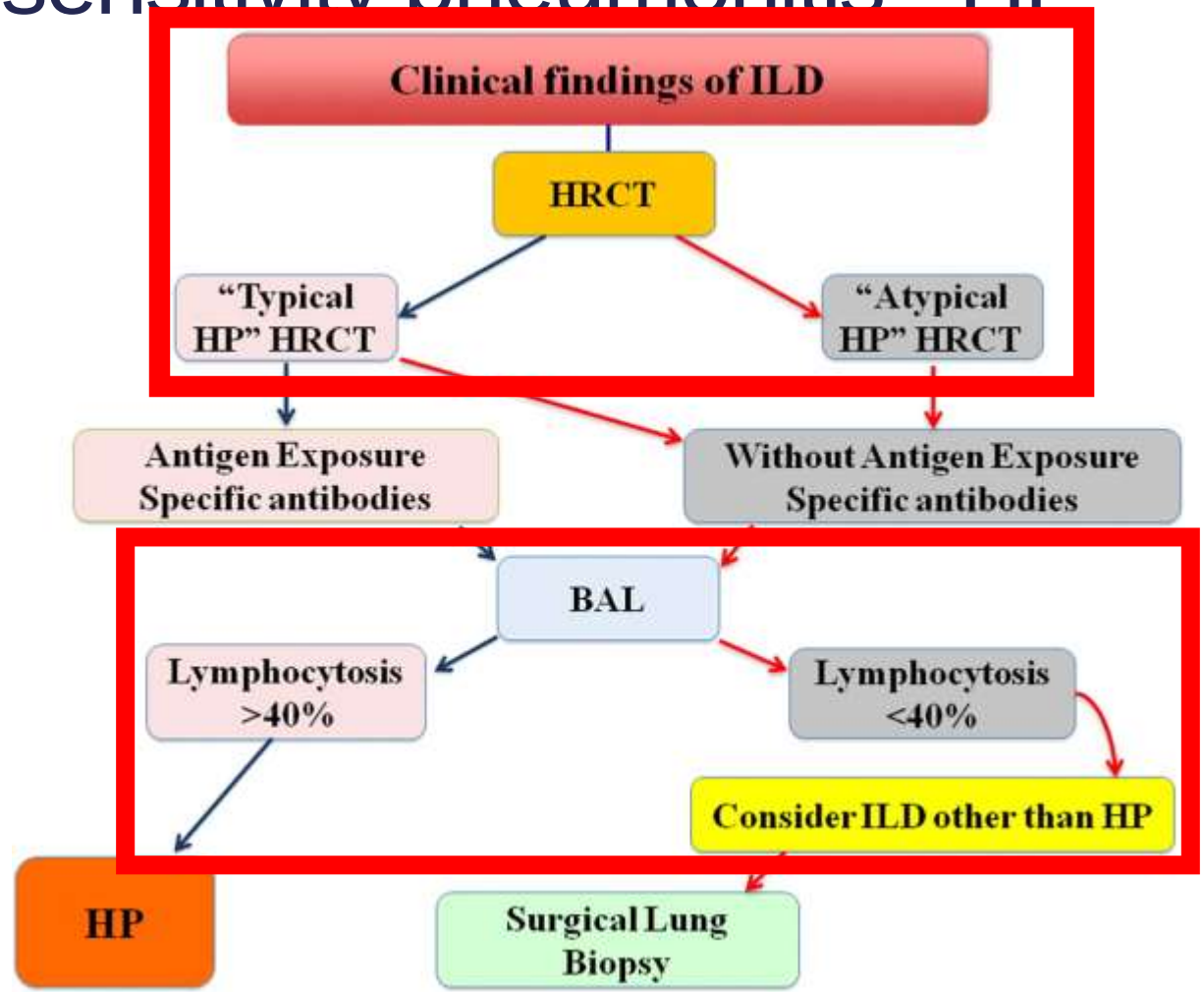
Hypersensitivity pneumonitis - HP



Selman M et al. Hypersensitivity pneumonitis. Insights in diagnosis and pathobiology. Am J Respir Crit Care Med Vol. 186, Iss. 4 pp 314-324, Aug 15, 2012

Diagnosis of acute/subacute occupational HP

Predictors of HP

1. Exposure to known offending antigen at workplace
2. Recurrent symptoms 4-8h after exposure
3. Positive specific IgG (precipitating) antibodies
4. Inspiratory crackles
5. HRCT pattern compatible with acute/subacute HP

Possible substitute for missing feature

1. Lymphocytosis in BAL
2. Signs of acute/subacute HP in lung pathology
3. Positive inhalation challenge test or improvement after avoidance

Quirce S et al. Occupational hypersensitivity pneumonitis: an EAACI position paper. Allergy 71 (2016) 765-779.

Chronic occupational HP Diagnosis

4 or more criteria

1. Exposure to known offending antigen at workplace
2. Positive specific IgG (precipitating) antibodies

Or

1. Lymphocytosis in BAL
2. Reduced DLCO and/or hypoxemia at rest or exercise
3. HRCT pattern compatible with chronic HP
4. Signs of chronic HP in lung pathology
5. Positive inhalation challenge test or improvement after avoidance

Quirce S et al. Occupational hypersensitivity pneumonitis: an EAACI position paper. Allergy 71 (2016) 765-779.

Hypersensitivity pneumonitis – HP: Identification of possible Antigens

Antigen exposure

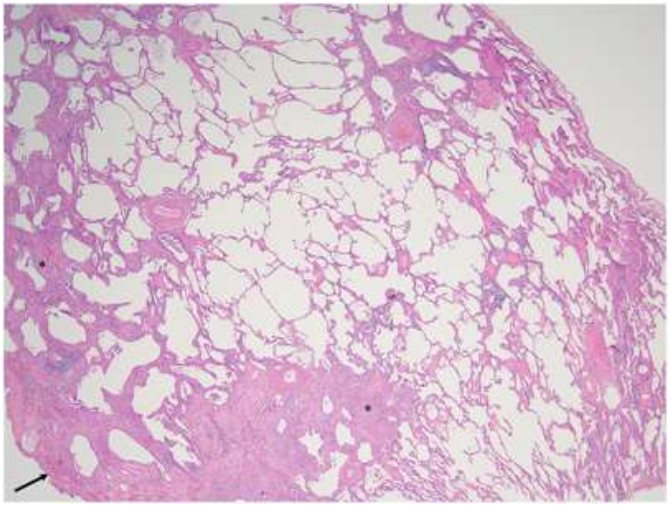
- Serological confirmation of exposure
  - Precipitines
  - Specific antibodies (IgG)

Fenoglio CM, Reboux G, Sudre B, et al. Diagnostic value of serum precipitins to mould antigens in active hypersensitivity pneumonitis. *Eur Respir J*. 2007;29(4):706–712.

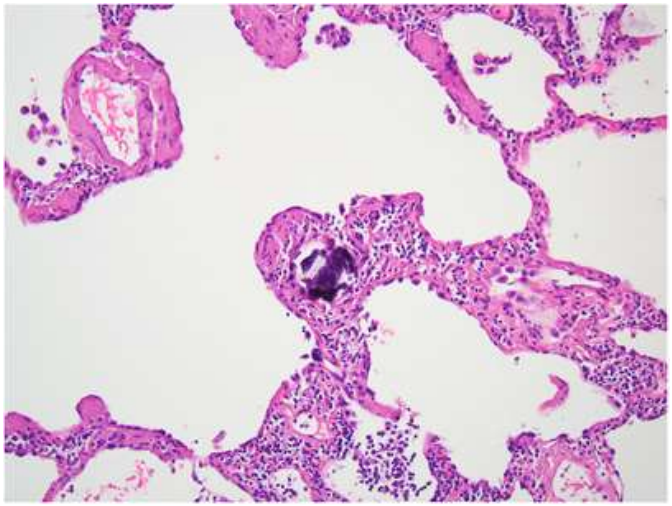
- Antigen challenge

Surgical lung biopsy in HP

- Airway-centered, variably cellular chronic interstitial pneumonia
- Lymphocyte-rich chronic bronchiolitis
- Poorly formed non-necrotizing granulomas



X20: UIP pattern



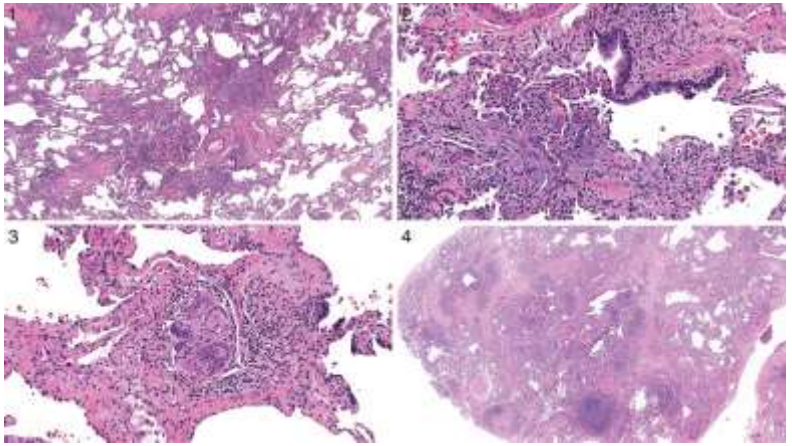
X200: peribronchiolar lymphocyte infiltrate with multinucleated giant cell

Myers J. Hypersensitivity pneumonia: the role of lung biopsy in diagnosis and management. Modern Pathology (2012) 25, S58-67.

Pathological criteria for HP

Classic Features of Hypersensitivity Pneumonitis	Additional Features or Clues	Correlate
Bronchiolocentric chronic interstitial pneumonia	Organizing pneumonia (may or may not be present)	Correlate histology with clinical and radiographic findings whenever possible
Chronic bronchiolitis	Airway-centered interstitial fibrosis	Incomplete or unknown clinical information: suggest a thorough clinical investigation
Peribronchiolar interstitial giant cells with or without vaguely formed nonnecrotizing granulomas (giant cells and granulomas can be in airspaces only)	Suspect when NSIP or UIP pattern is associated with interstitial giant cells or vaguely formed nonnecrotizing granulomas	

Abbreviations: NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.



Ross Miller, et al. (*2018*) Hypersensitivity Pneumonitis A Perspective From Members of the Pulmonary Pathology Society. Archives of Pathology & Laboratory Medicine: January 2018, Vol. 142, No. 1, pp. 120-126.

Multidisciplinary approach to HP

- Helpful as > 50% of patients with HP have no clear exposure
- Multidisciplinary discussion helps to distinguish HP from idiopathic ILD

Elicker BM et al. Multidisciplinary Approach to Hypersensitivity pneumonia. J Thorac Imaging 2015

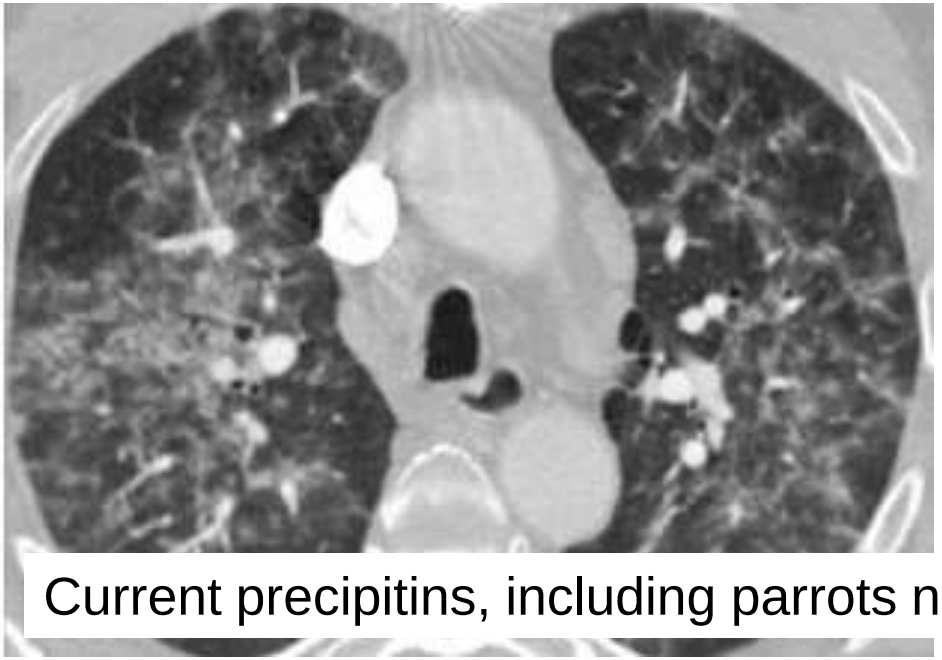
Identification of antigen is crucial

- Directly linked to mortality

Fernandez Perez Er et al. Identifying an inciting antigen is associated with improved survival in patients with chronic HP. Chest 2013 Nov;144(5):1644-51.

- Continued exposure can lead to chronic fibrosing forms

Bird fancier disease - Lovebirds



Current precipitins, including parrots negative.

Individual prepared precipitins positive!

TABLE 1 Serial pulmonary function test and arterial blood gas

Variable	Value		
	On admission	After 2 weeks	After 7 months
FVC L (% pred)	2.03 (55)	2.53 (69)	2.68 (74)
FEV_1 L (% pred)	1.56 (53)	2 (70)	1.95 (67)
FEV_1/FVC % (% pred)	77 (100)	79 (103)	73 (95)
TLC L (% pred)	4.25 (69)	4.62 (75)	4.87 (80)
RV/TLC % (% pred)	51 (138)	44 (119)	42 (114)
$D_{L,CO_{adj}}$ (% pred)	39	63	81
$K_{CO_{adj}}$ (% pred)	82	99	111
P_{O_2} mmHg#,¶	58	76	81
P_{CO_2} mmHg	36	36	36
P_{A-a,O_2} mmHg#,+	39	24	18
Sa,O_2 %#	90	94	96

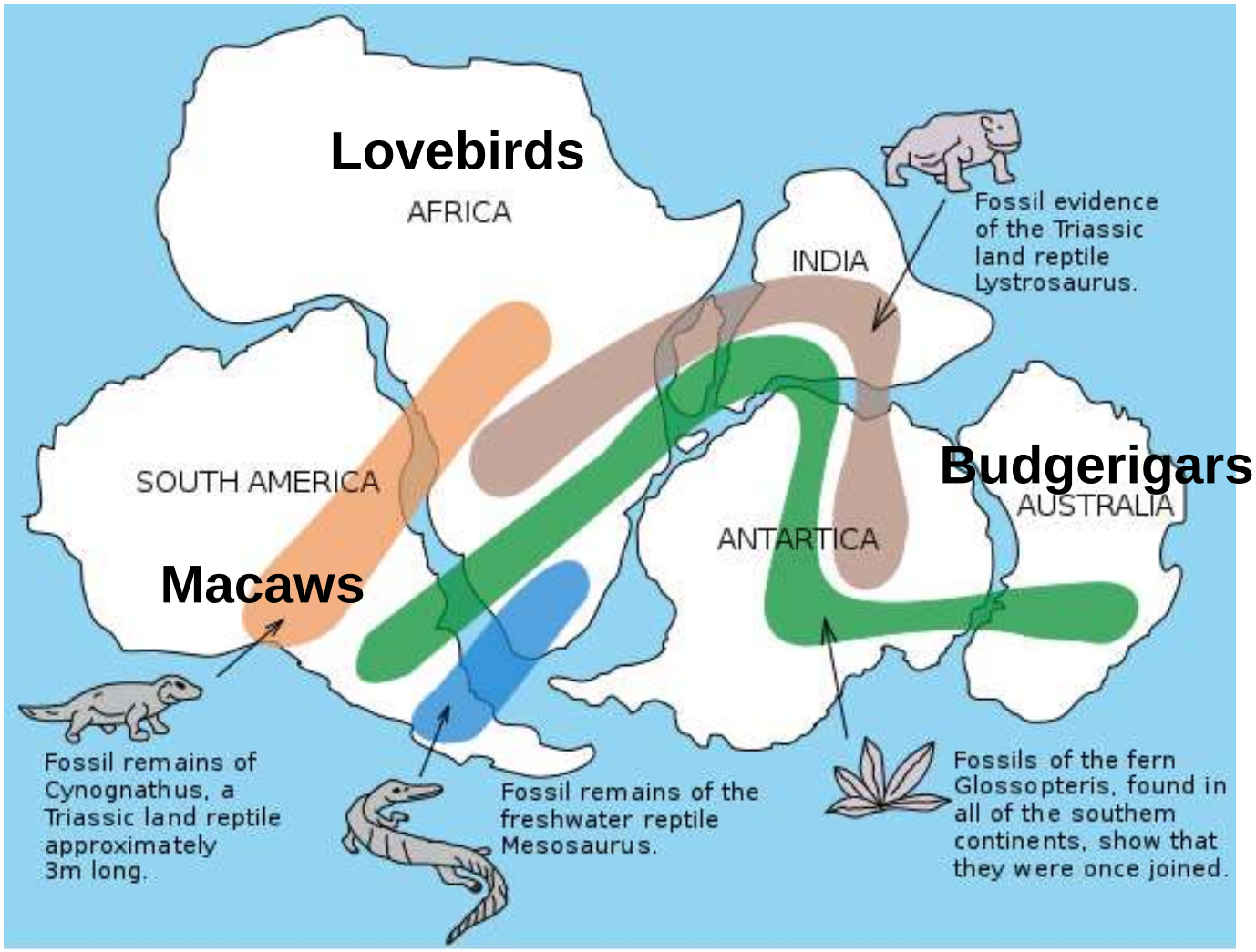
FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; $D_{L,CO_{adj}}$: diffusing ...g for carbon monoxide adjusted for haemoglobin; $K_{CO_{adj}}$: ...of the lung for carbon monoxide adjusted for haemoglobin; ...e of oxygen; P_{CO_2}: partial pressure of carbon dioxide; P_{A-a,O_2}: alveolar–arterial oxygen tension difference; Sa,O_2: arterial oxygen saturation. #: measured while the patient was breathing room air at 540 m above sea level; ¶: under normal limit at 540 m above sea level = 73, 75 and 75 mmHg on ...ission, after 2 weeks and after 7 months, respectively; +: upper normal limit ...mmHg.

Funke M, Fellrath JM. Hypersensitivity pneumonitis secondary to lovebrids: a new cause of bird fancier's disease. ERJ 2008;32:517-521

Diagnosis HP- example

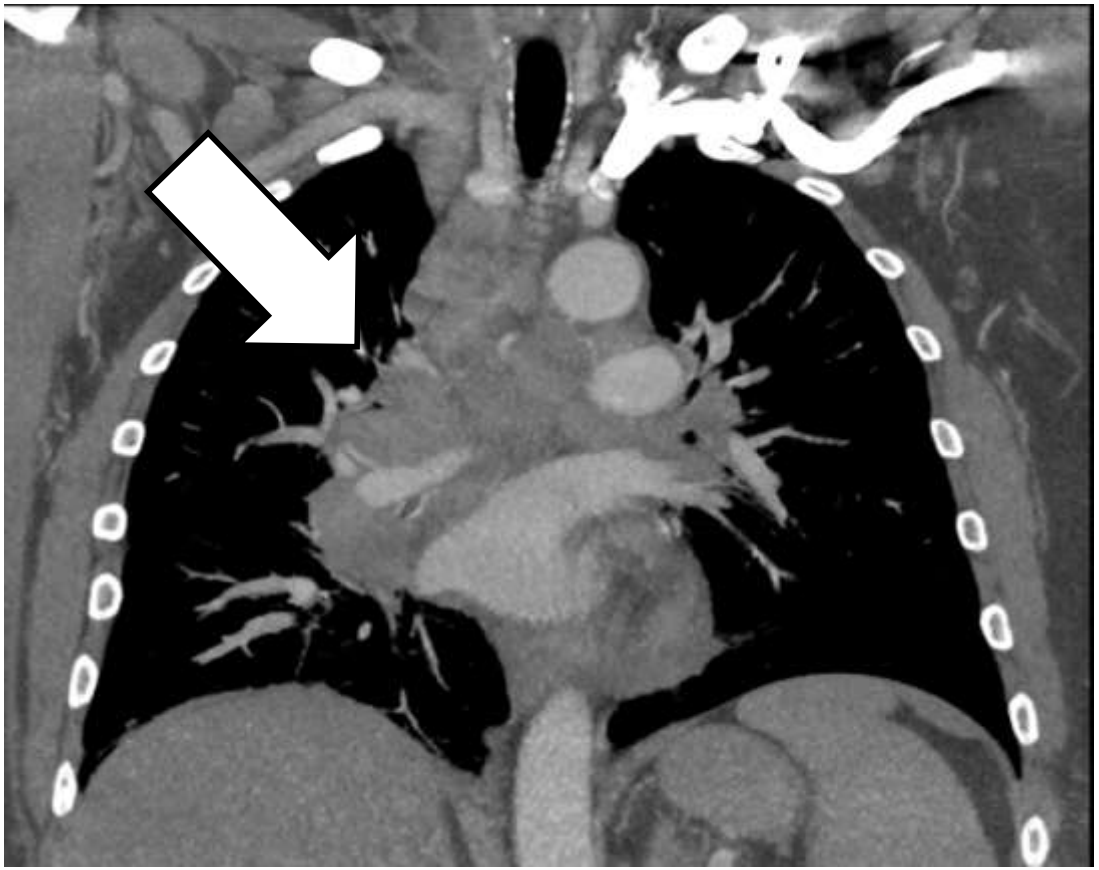
- Bird fancier disease
  - Most common HP
  - Lovebirds- parrots species (Psittacidae)
  - Psittacidae
    1. Lovebirds (genus agapornis)- Africa
    2. Budgerigars (genus Melopsittacus)- Oceania
    3. Macaws (genus ara)- Südamerika

Lovebirds fancier disease



Sarcoidosis: Patient 1965

- dyspnea (mMRC 2)

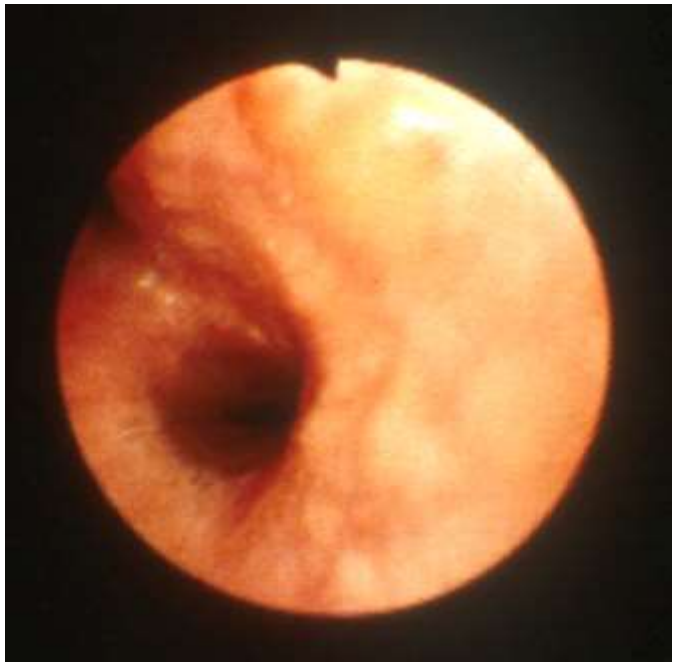


Sarcoidosis: Patient 1965

Bronchoscopy (before referal):

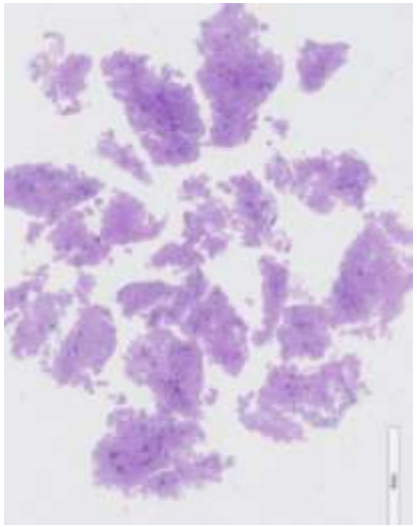
Cytology: no malignant cells, lymphocytic alveolitis

Mucosal biopsy:
no malignant cells,
no granuloma

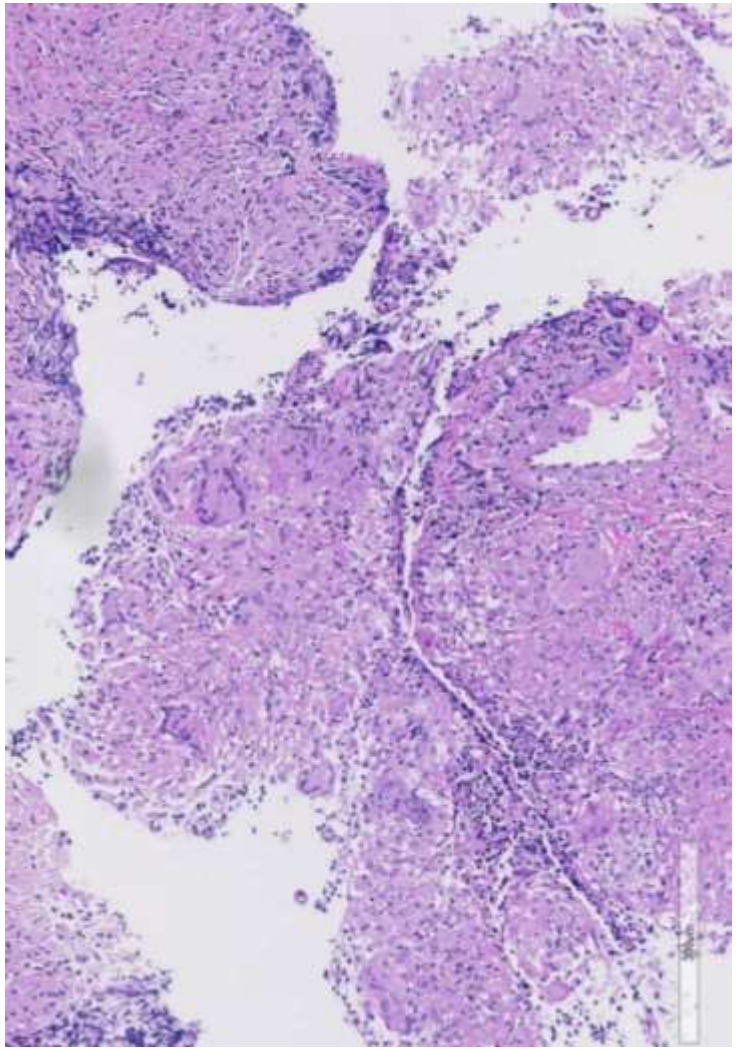


Sarcoidosis: Patient 1965

Mediastinoscopy (before referal)



- 2/4 LK non-necrotising lymphnodes
- no mycobacteria (Ziehl-Neelsen), negative fungus staining



Sarcoidosis: Patient 1965

- Heart Ultrasound: EF 35%

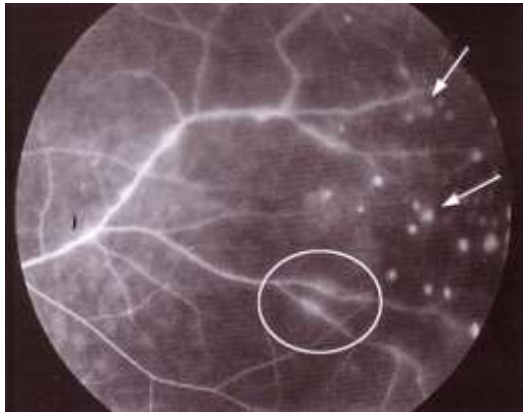
- Cardiac MRI:

compatible with cardiac sarcoidosis

Diagnosis: Sarcoidosis Stage I with cardiac involvement

Sarcoidosis: Clinical Symptomes

- Weight loss (20 %)
- Eye or skin involvement
- Acute form „Löfgren Syndrome“ (20 %)



- (fever, erythema nodosum, lymph nodes, arthralgia)

Sarcoidosis: Organs involved

Mediastinal lymphnodes	95-98%
Lung	>90%
Liver	50-80%
Spleen	40-80%
Eye	20-50%
Peripheral Lymphnodes	30%
Skin	25%
Nervous system	10%
Clinical heart involvement	5%

Sarcoidosis: Silzbach/Scadding Stages

BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 4 1961

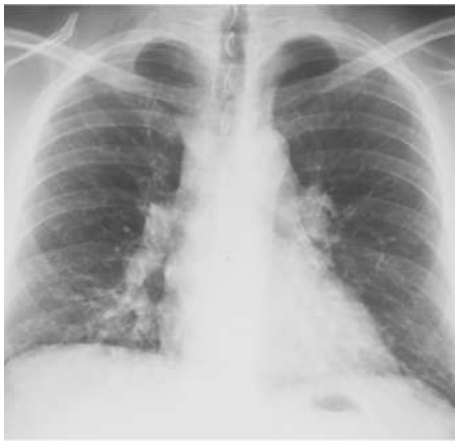
PROGNOSIS OF INTRATHORACIC SARCOIDOSIS IN ENGLAND

A REVIEW OF 136 CASES AFTER FIVE YEARS' OBSERVATION

BY

J. G. SCADDING, M.D., F.R.C.P.

Director of Studies, Institute of Diseases of the Chest, Brompton



I II III IV

Sarcoidosis: Diagnosis

- 90% diagnosis with BAL, TBB and EBUS

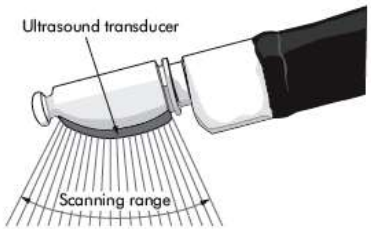
  Prasse A. Sarkoidose – was ist neu? Dtsch Med Wochenschr 2017;142:825-828.

- Lymphocytosis marked by elevated BALF CD4/CD8 ratio (>3.5) supports diagnosis

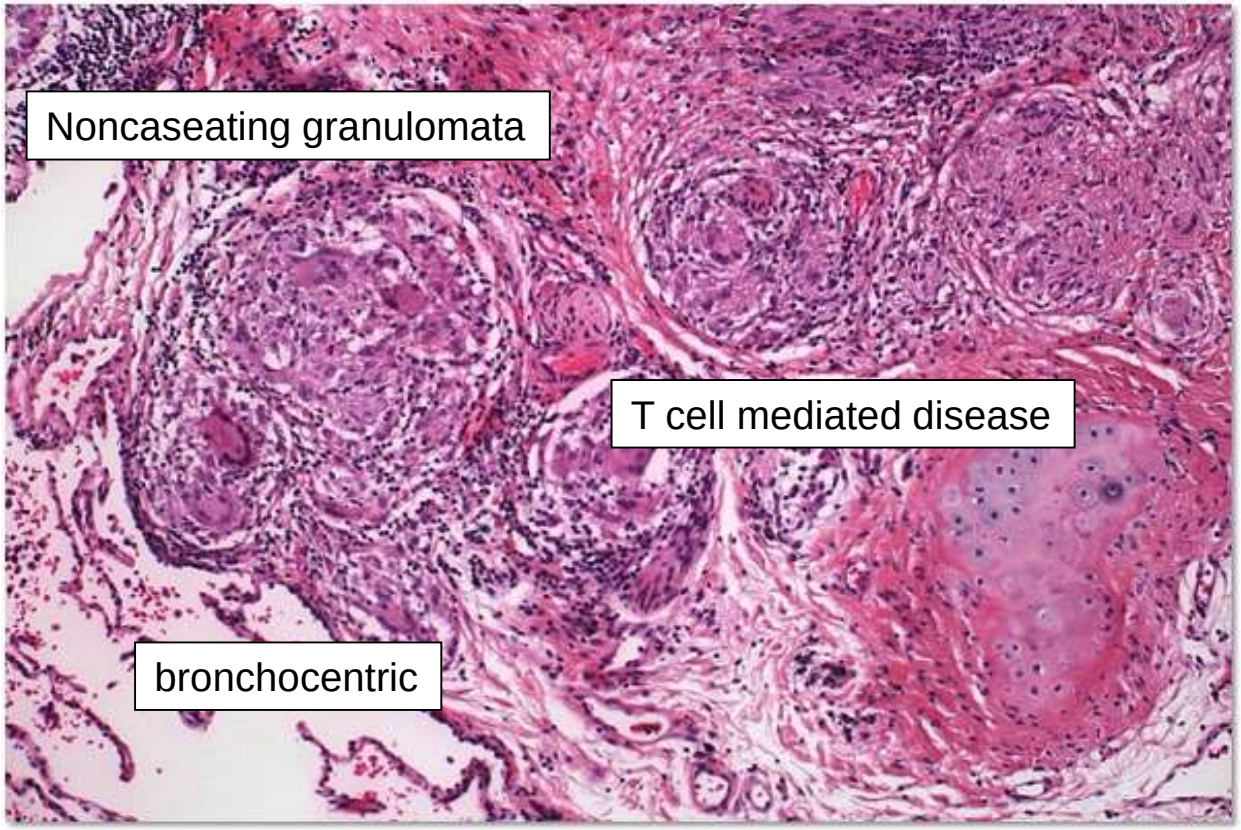
  D. Valeyre, A. et al. Sarcoidosis, Lancet 383 (2014) 1155e1167.

  U. Costabel, G.W. Hunninghake, ATS/ERS/WASOG statement on sarcoidosis. Eur. Respir. J. 14 (1999) 735e737.

- Bronchoscopy -EBUS

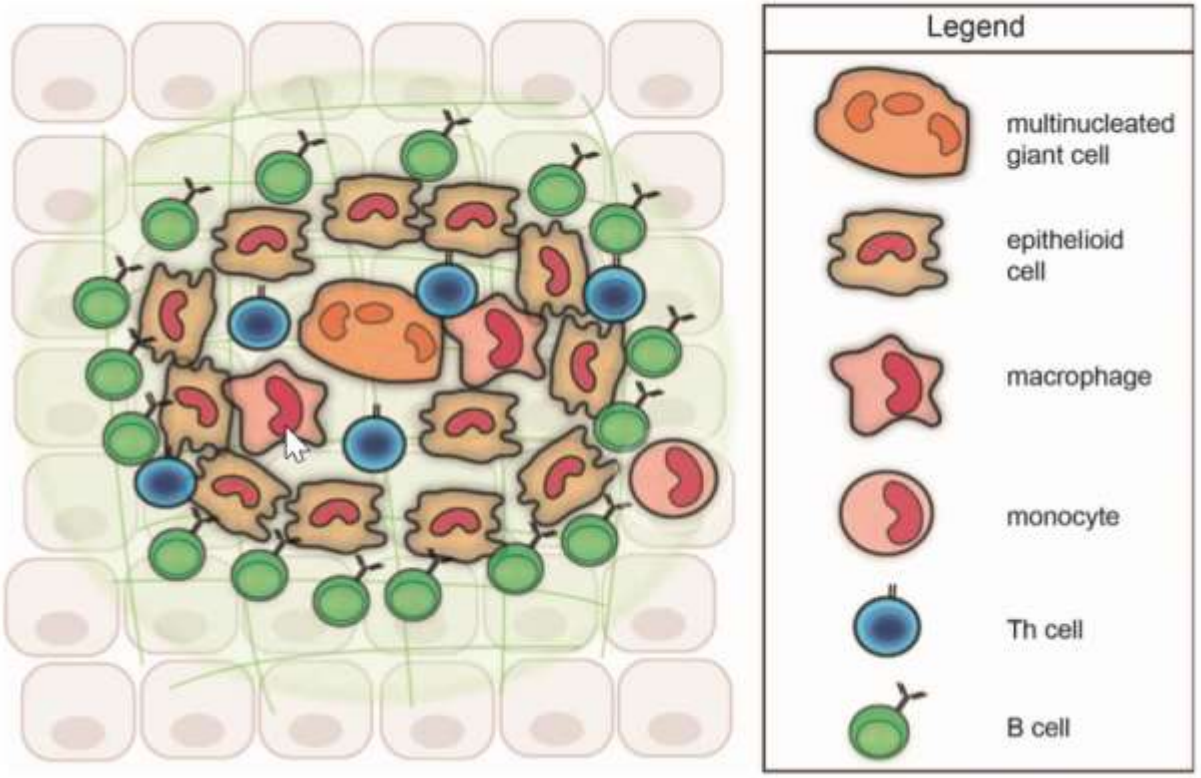


Sarcoidosis



Courtesy from Dr. Sabina Berezowska, Pathology Department University of Berne, Switzerland

Granuloma



Tmmermans WMC et al. Immunopathogenesis of granulomas in chronic autoinflammatory diseases. Clinical and translational Immunology (2016) 5, e118.

Sarcoidosis: Risk factors

- **Genetic predisposition**

  - HLA-DRB1*03
  - MHC2TA rs3087456
  - HLA-DRB1*12
  - HLA-DRB1*14
  - HLA-DRB1*15

  SNPs

  - CCR2 haplotype 2
  - BTNL2 rs3117099T
  - BTNL2 rs2076530A
  - NOTCH4
  - ANXA11 rs230C
  - XAF1
  - IL23R rs12069782
  - rs11209026A
  - TNF

Prasse A. Sarkoidose – was ist neu? Dtsch Med Wochenschr **2017**;142:825-828.

J. C. Schupp, B. C. Frye, G. Zissel, J. Müller-Quernheim. Neue pathogenetische Konzepte und frühe pharmakologische Studien bei der Sarkoidose. Pneumologie **2016**; 70(04): 231-240

Jelle R. Miedema et al. Th17-lineage cells in pulmonary sarcoidosis and Loefgren's syndrome: Friend or foe? Journal of Autoimmunity 87 (2018) 82-96.

Sarcoidosis: Risk factors

- **Infectious agents**
  - Mycobacteria (past infections?)
  - Propionibacteria
  - Fungals, others

Rotsinger JE et al. Molecular Analysis of Sarcoidosis Granulomas Reveals Antimicrobial Targets. AJRCCM Jan 25, 2016.

- **Self antigen**
  - vimentin
- **Environmental factors** - World trade center collapse

Izbicki G et al. World trade center sarcoid like granulomatous pulmonary disease in NYC Fire department rescue workers. Chest 2007; 131:1414.

Prasse A. Sarkoidose – was ist neu? Dtsch Med Wochenschr **2017**;142:825-828.

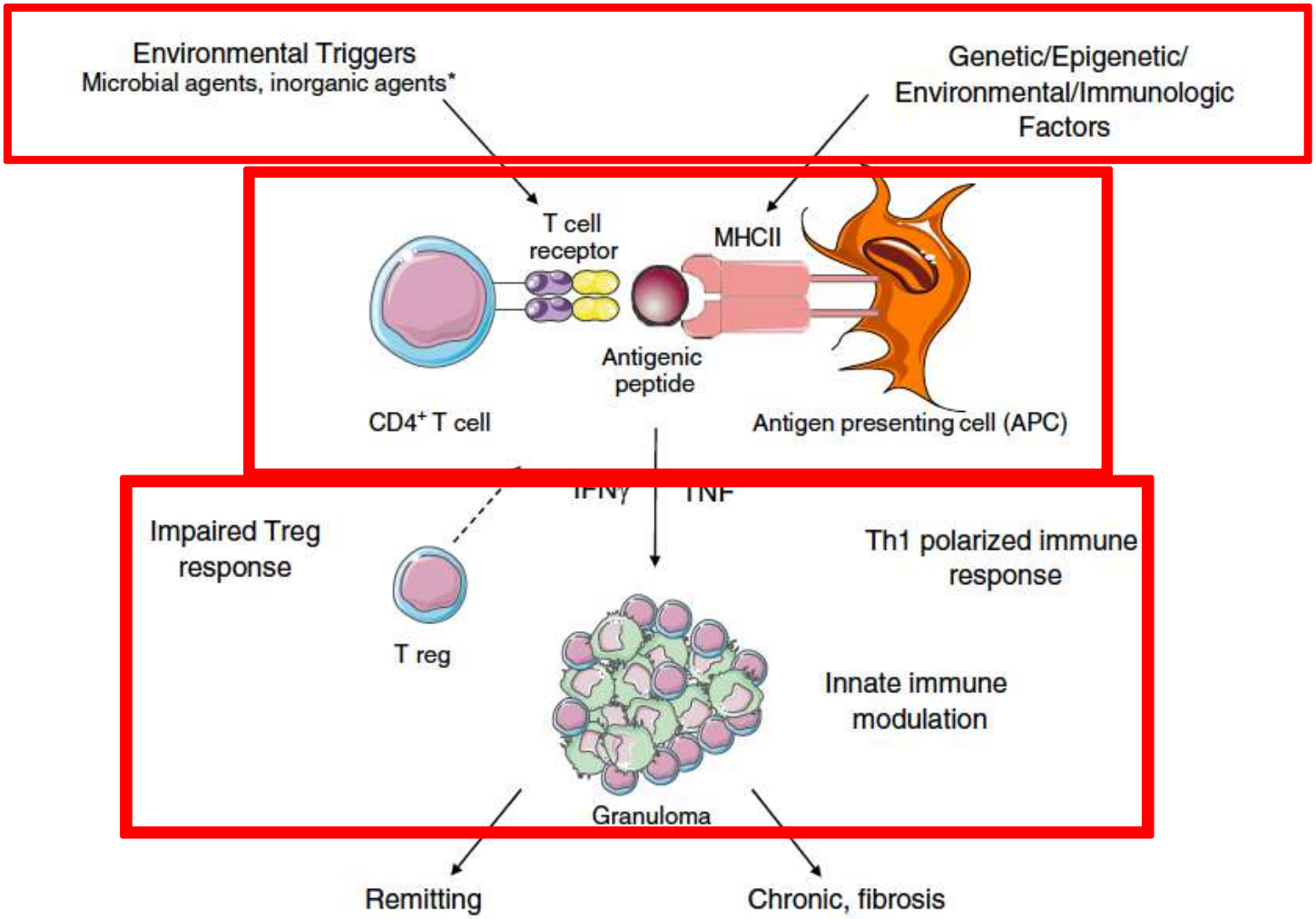
J. C. Schupp, B. C. Frye, G. Zissel, J. Müller-Quernheim. Neue pathogenetische Konzepte und frühe pharmakologische Studien bei der Sarkoidose. Pneumologie **2016**; 70(04): 231-240

Jelle R. Miedema et al. Th17-lineage cells in pulmonary sarcoidosis and Loefgren's syndrome: Friend or foe? Journal of Autoimmunity 87 (2018) 82-96.

Sarcoidosis: Immunological dysfunction

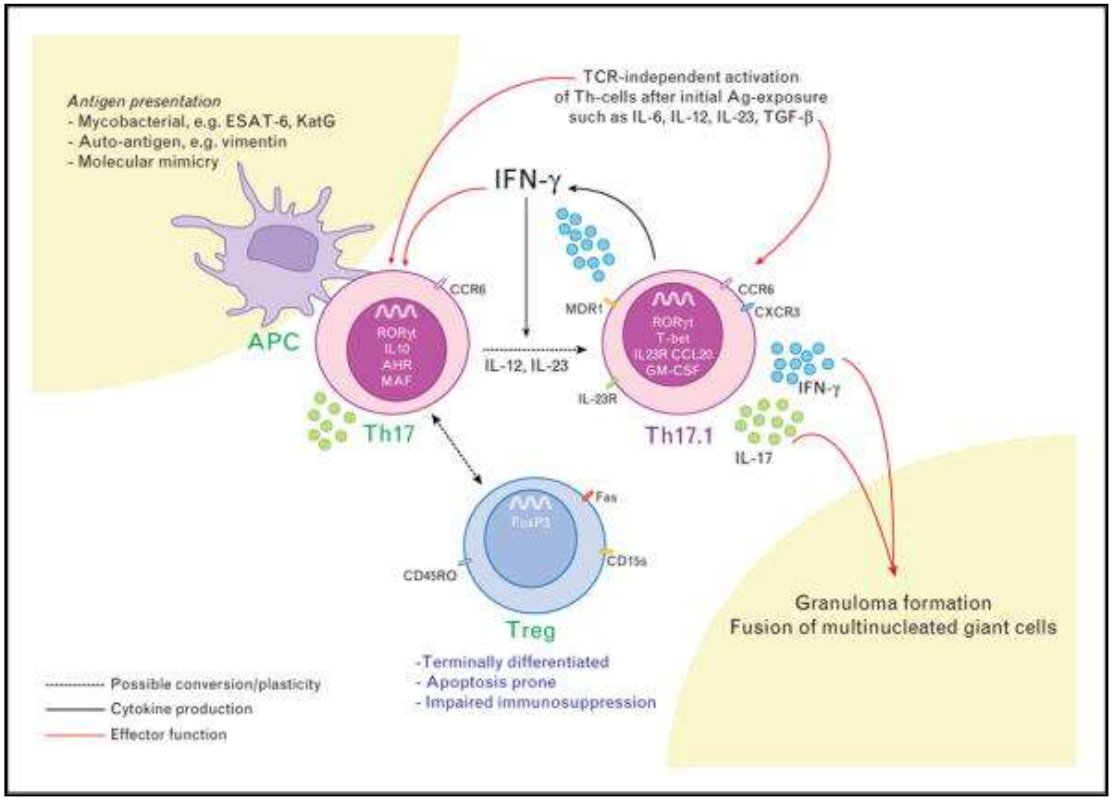
- CD4+ T cells, Th1 polarised disorder
- T cells dysfunction (Th1, Th17, Treg)
- exaggerated immune response to a specific antigen (Kveim)

Pathogenesis of sarcoidosis – historical view



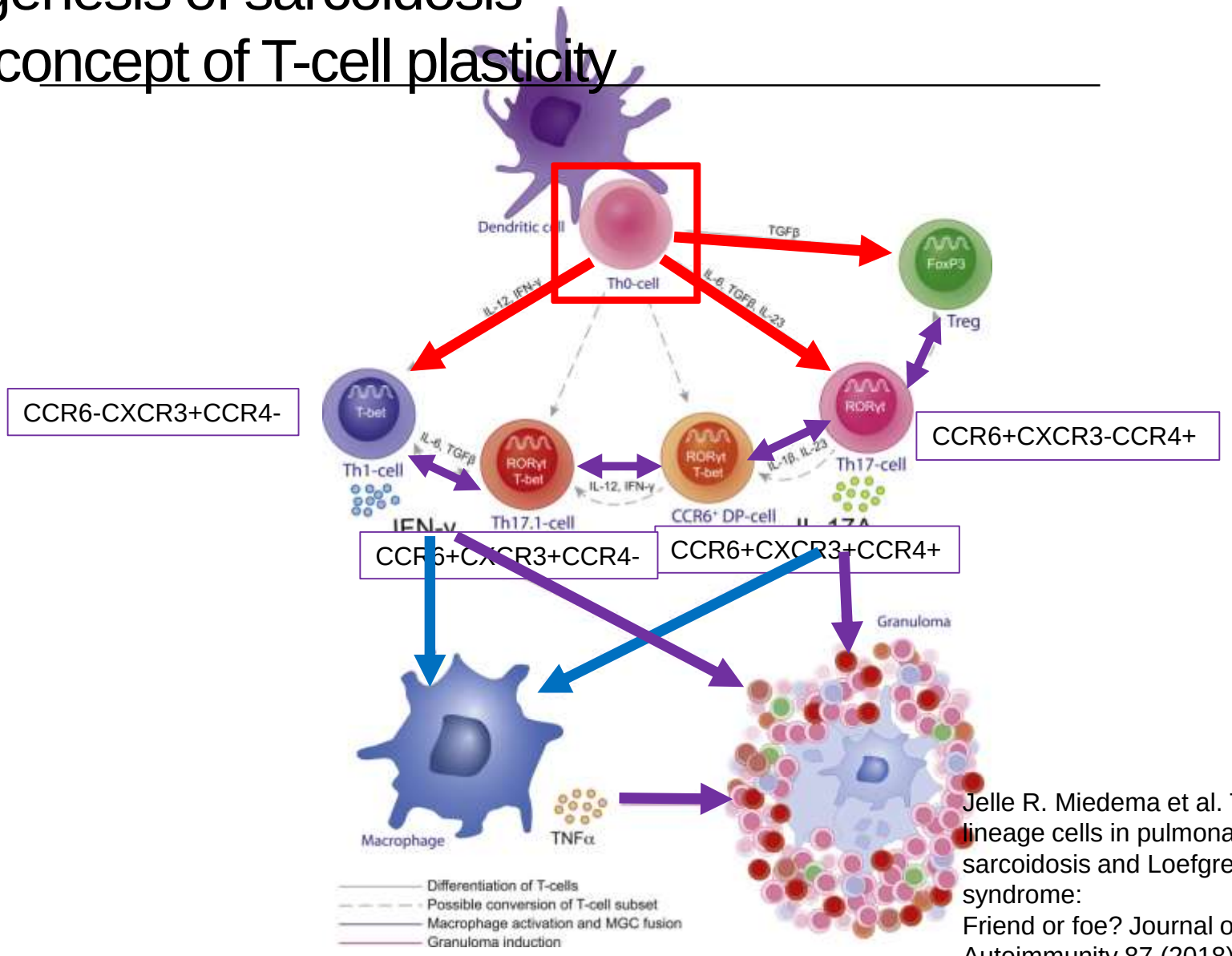
Moller DR, et al. Genetic, Immunologic, and Environmental Basis of Sarcoidosis. Ann Am Thorac Soc. 2017 Dec;14(Supplement_6):S429-S436.

Pathogenesis of sarcoidosis – new insights



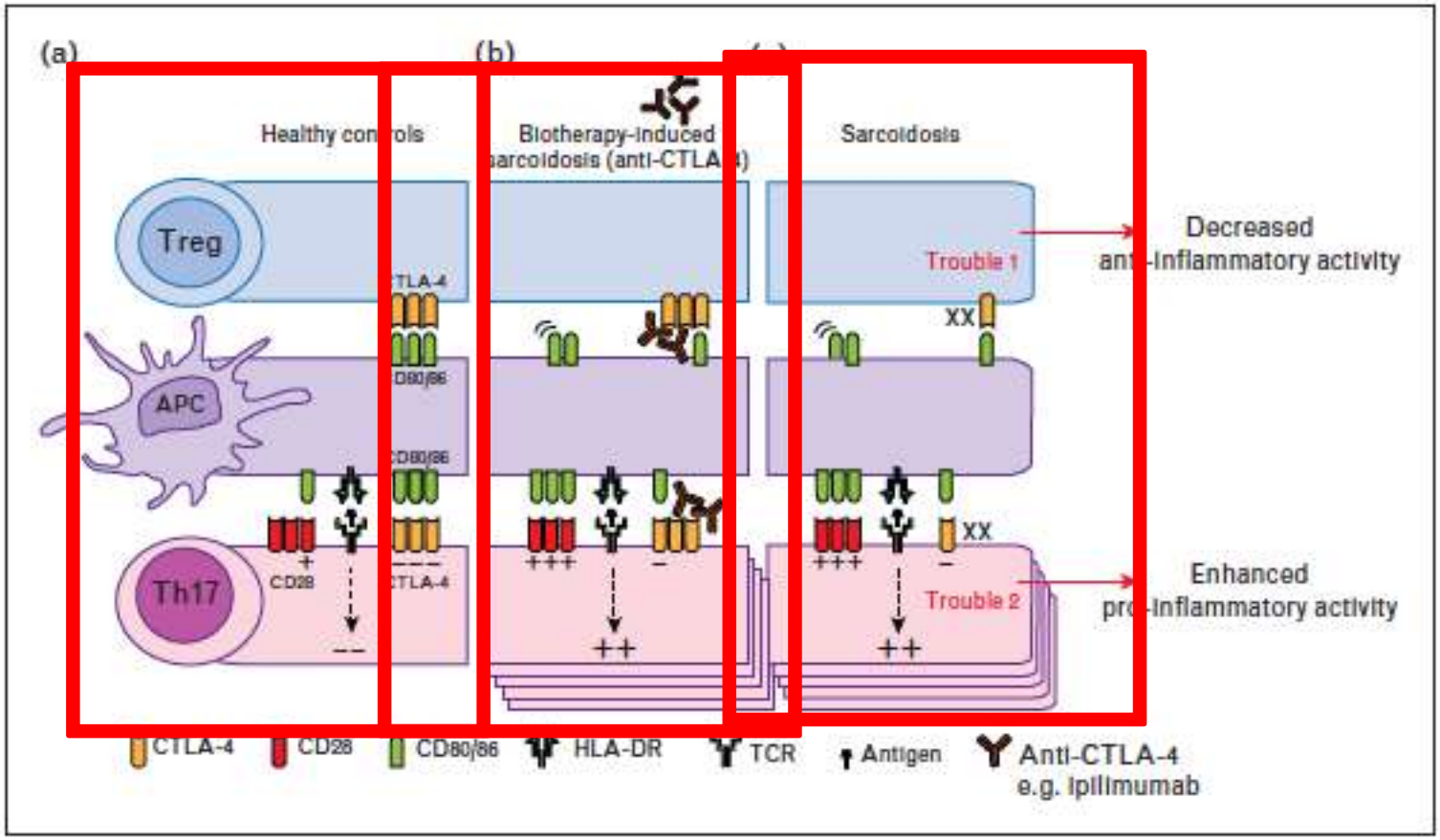
Broos, Caroline; Hendriks, Rudi; Kool, Mirjam. T-cell immunology in sarcoidosis: Disruption of a delicate balance between helper and regulatory T-cells. Current Opinion in Pulmonary Medicine. 22(5):476-483, September 2016.

Pathogenesis of sarcoidosis
- New concept of T-cell plasticity



Jelle R. Miedema et al. Th17-lineage cells in pulmonary sarcoidosis and Loefgren's syndrome:
Friend or foe? Journal of Autoimmunity 87 (2018) 82-96.

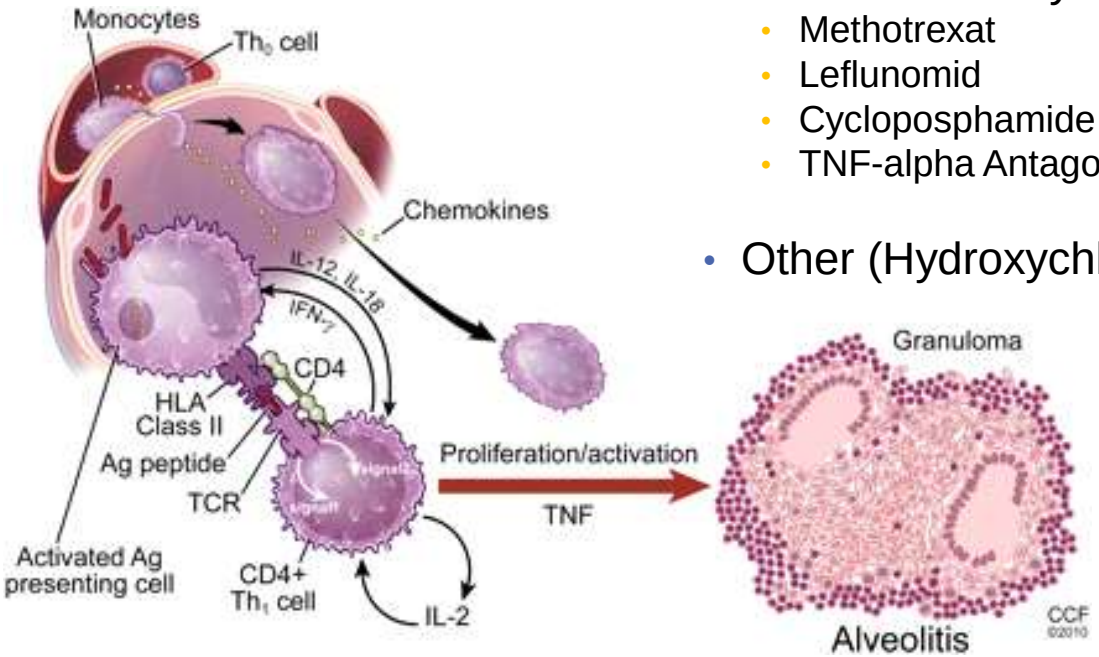
Pathogenesis of sarcoidosis - double trouble



Bross Ce et al. T-cell immunology in sarcoidosis: disruption of a delicate balance between helper and regulatory T-cells. Curr Opin Pulm Med. 2016 Sep;22(5):476-83.

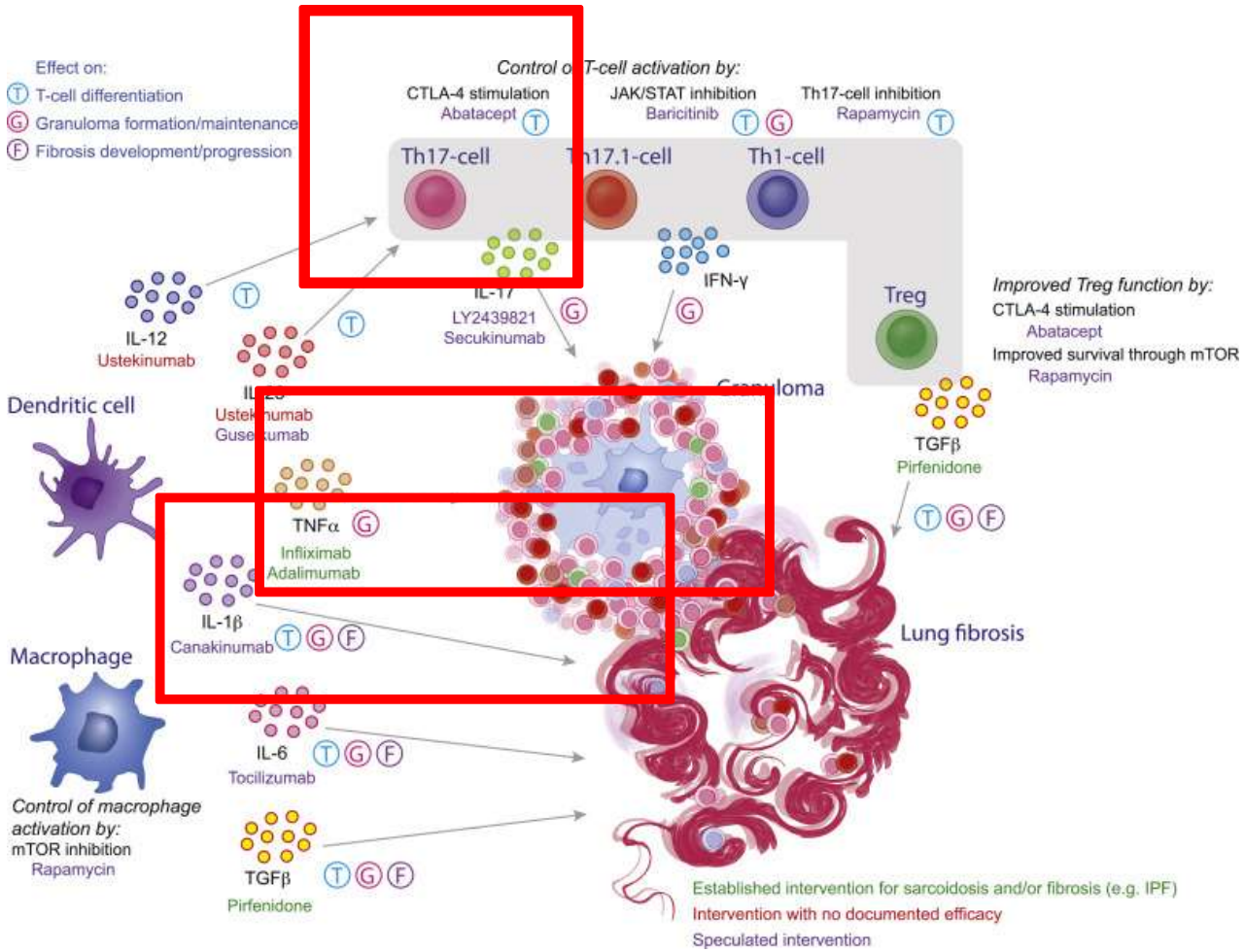
Treatment of sarcoidosis

- Immunsuppressive/cytotoxic
  - Prednison
  - Azathioprin
  - Mycophenolat mofetil
- Modulation of cytokines
  - Methotrexat
  - Leflunomid
  - Cycloposphamide
  - TNF-alpha Antagonists
- Other (Hydroxychloroquin)



Baughman RP et al. A Concise Review of Pulmonary Sarcoidosis AJRCCM 2011 Mar 1; 183(5): 573–581.

Treatment of sarcoidosis: New approaches



Jelle R. Miedema et al. Th17-lineage cells in pulmonary sarcoidosis and Loefgren's syndrome: Friend or foe? Journal of Autoimmunity 87 (2018) 82-96.

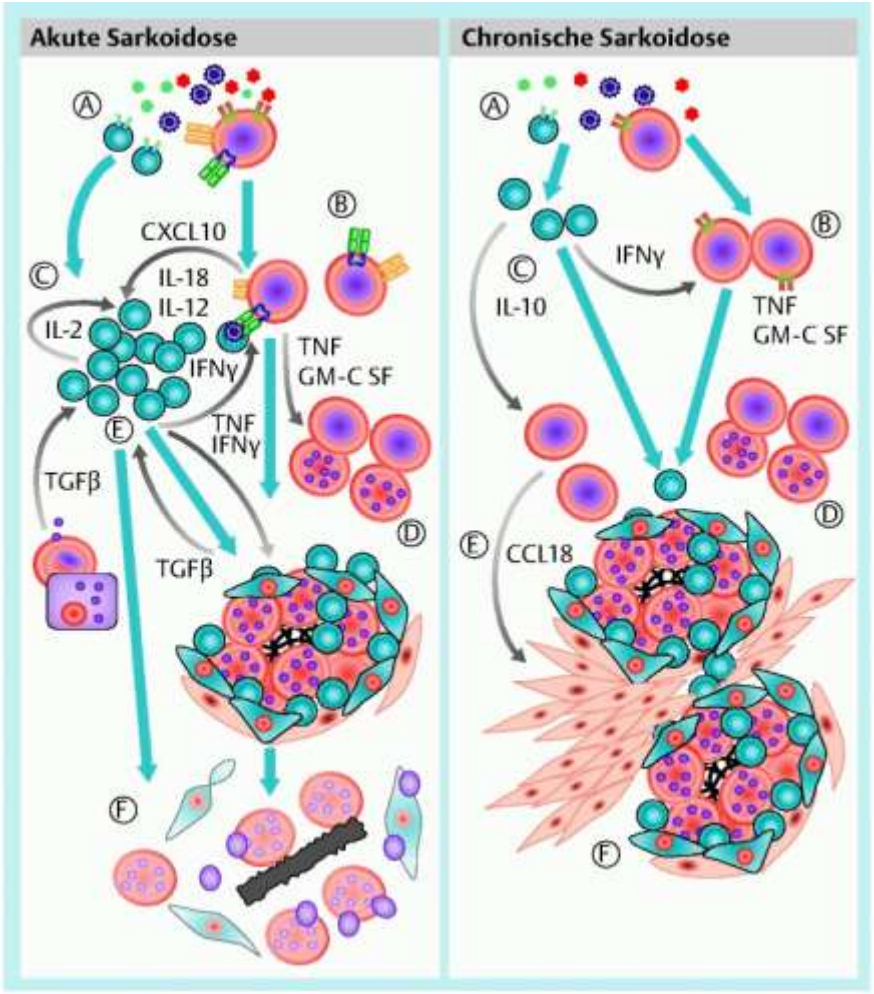
Sarcoidosis: Montitoring of Treatment Response

- Improved symptomes, functional improvement

- Inflammatory markers:
  - Soluble Interleukin-2-Receptor (sIL-2 or sCD25)
  - Neopterin
  - Angiotensin- Conversions Enzym (ACE)

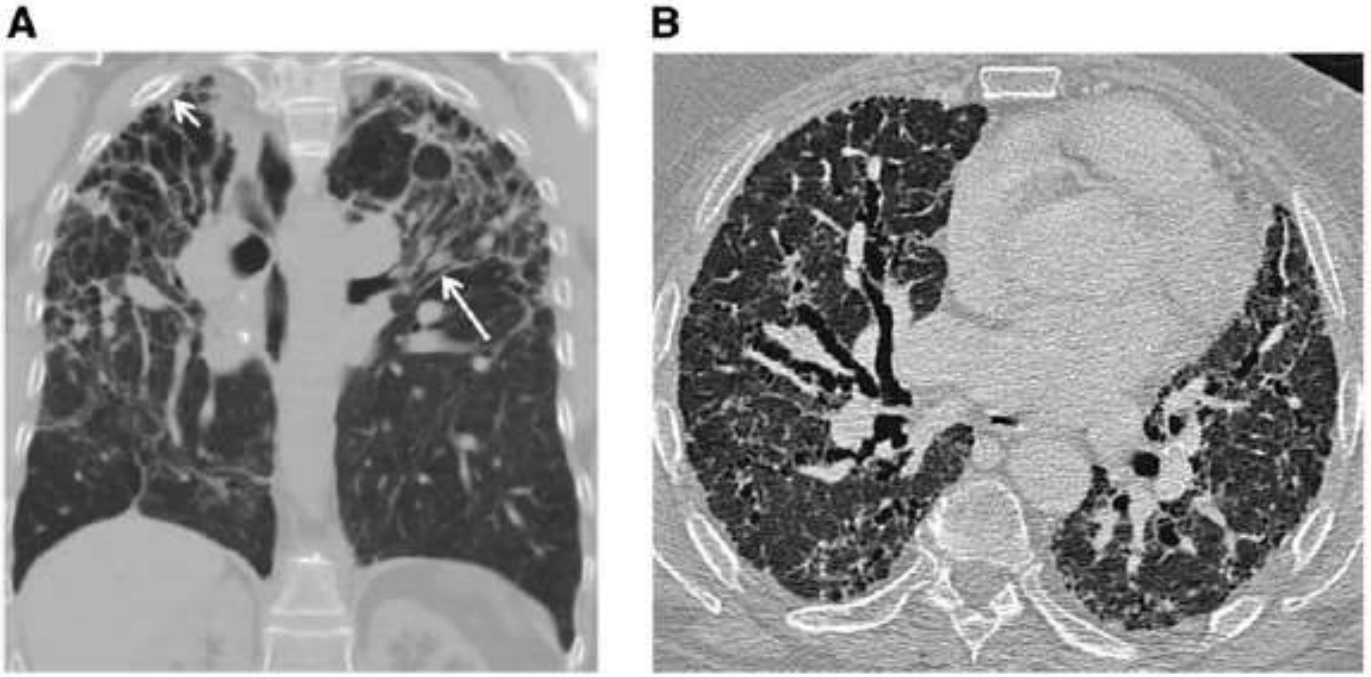
- Activity measurements (PET)

Acute vs chronic sarcoidosis



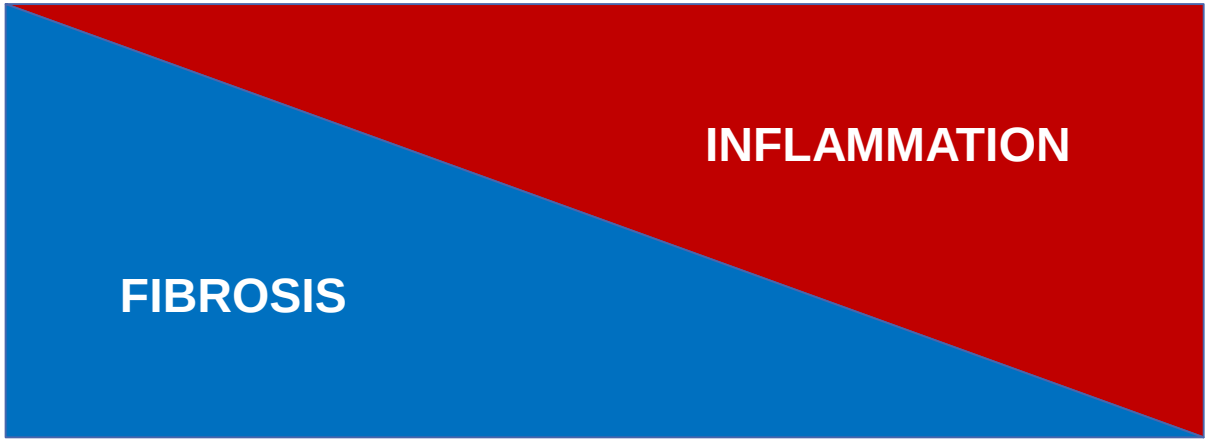
J. C. Schupp, B. C. Frye, G. Zissel, J. Müller-Quernheim. Neue pathogenetische Konzepte und frühe pharmakologische Studien bei der Sarkoidose. Pneumologie 2016; 70(04): 231-240

Sarcoidosis
- fibrotic pulmonary disease

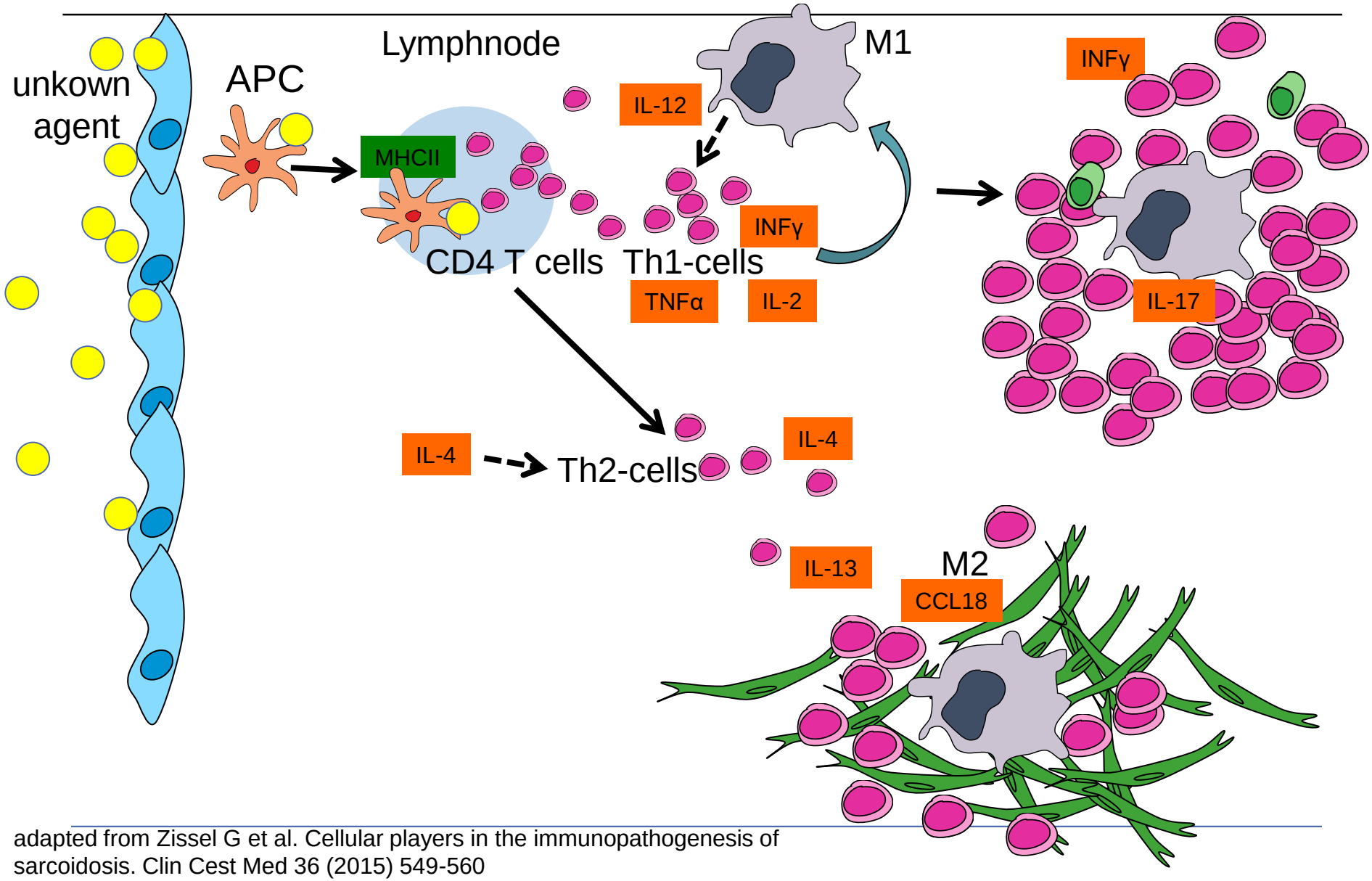


Patterson KC et al. Pulmonary Fibrosis in Sarcoidosis. Ann Am Thorac Soc Vol 10, No 4, pp 362-370.

CAUSES OF LUNG FIBROSIS

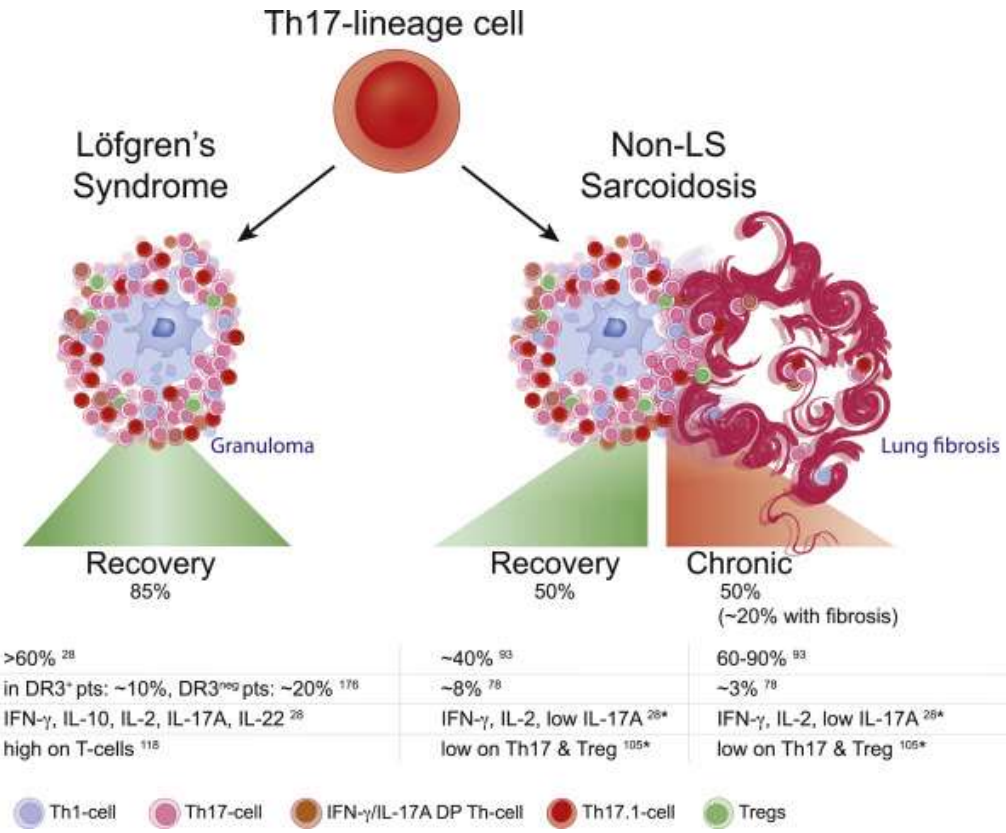


Pathomechanism of fibrotic sarcoidosis



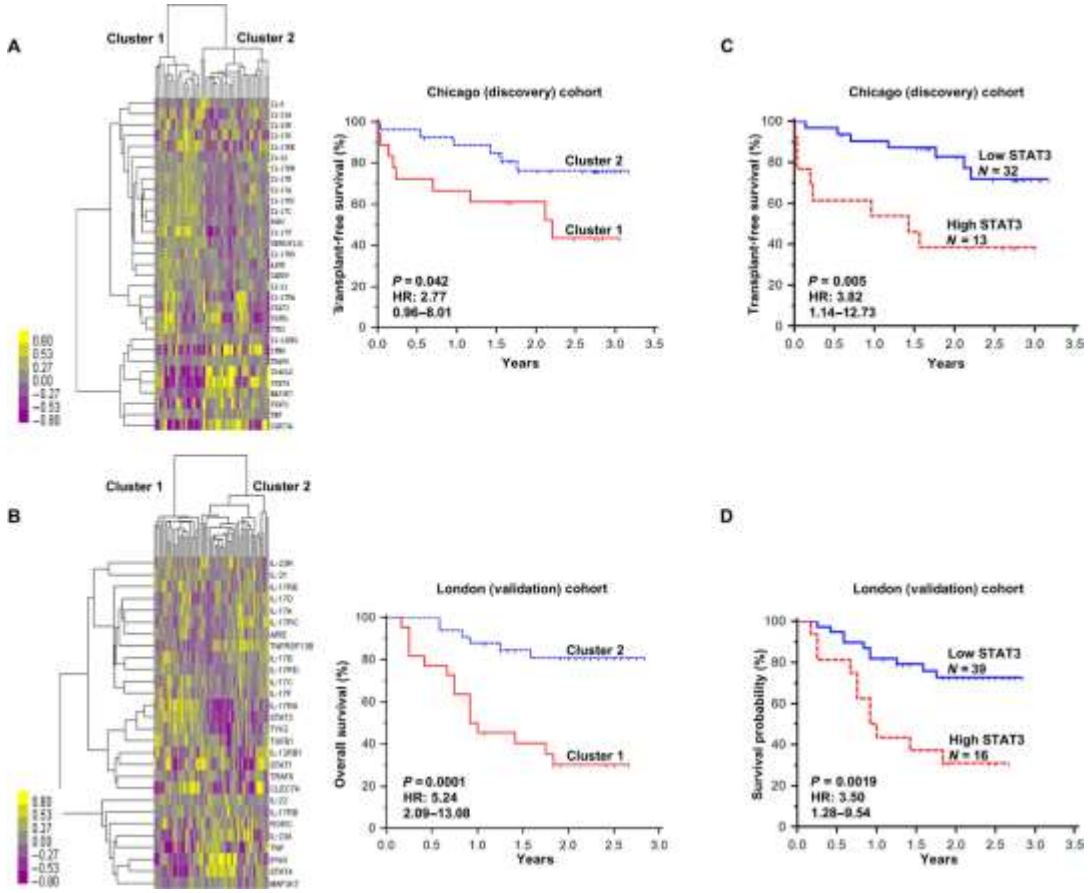
adapted from Zissel G et al. Cellular players in the immunopathogenesis of sarcoidosis. Clin Cest Med 36 (2015) 549-560

Pathomechanism of fibrotic sarcoidosis



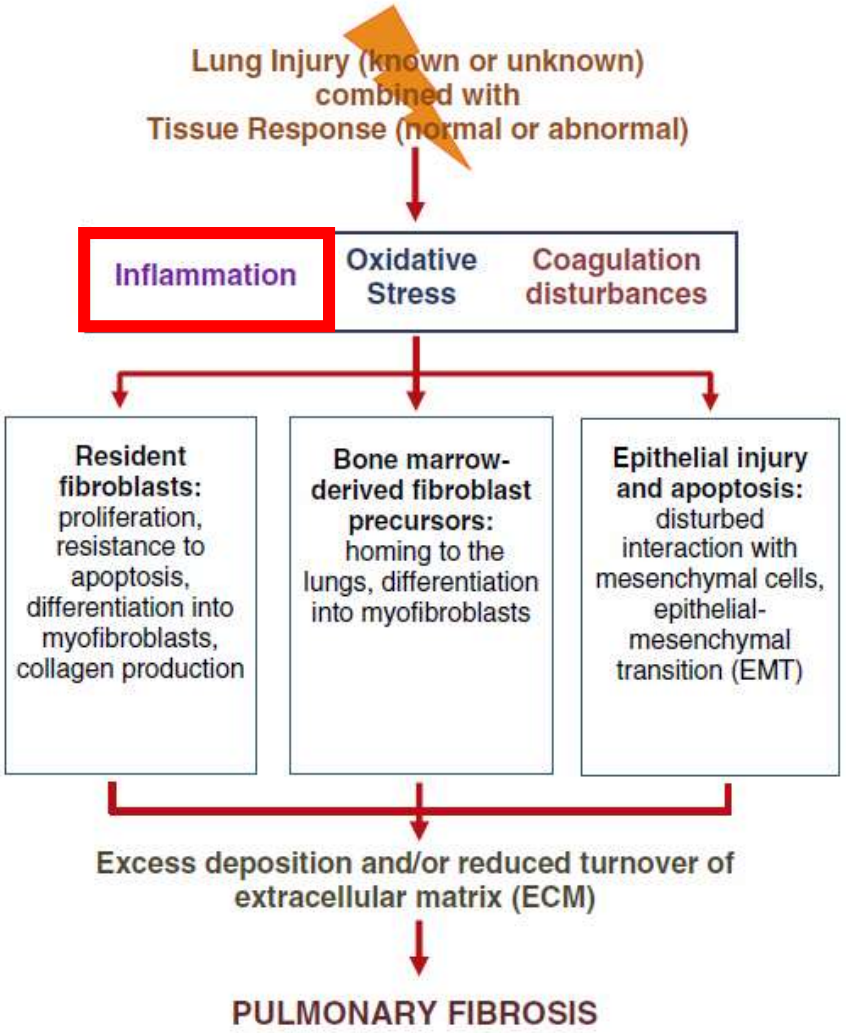
Jelle R. Miedema et al. Th17-lineage cells in pulmonary sarcoidosis and Loefgren's syndrome: Friend or foe? Journal of Autoimmunity 87 (2018) 82-96.

TH-17 in IPF



Celada LJ et al. PD-1 up-regulation on CD4+ T cells promotes pulmonary fibrosis through STAT3-mediated IL-17A and TGF-β1 production Sci Transl Med. 2018 September 26; 10(460).

PRO-FIBROTIC MECHANISMS



Todd NW et al. Molecular and cellular mechanisms of pulmonary Fibrosis. Fibrogenesis & Tissue Repair 2012, 5:11

Chronic forms of sarcoidosis- fibrotic forms

- Fibrotic lung disease is difficult to treat and most often irreversible

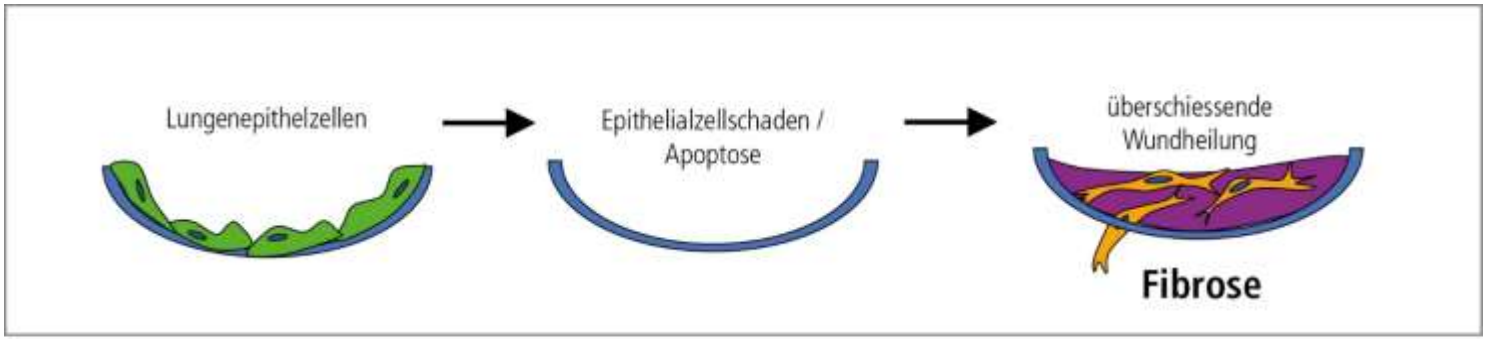


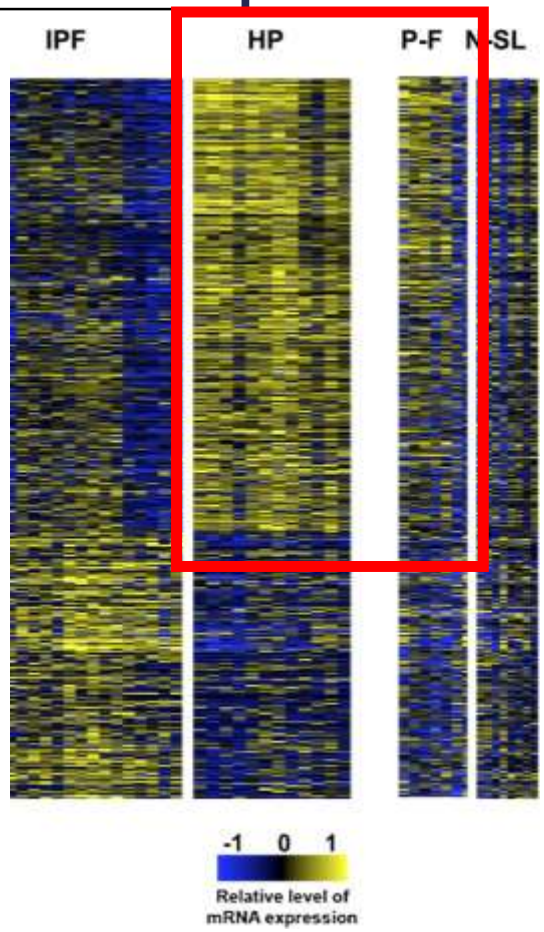
Abb. 2: Schematische Darstellung eines Alveolenbläschens. Nach initialem Epithelzellschaden kommt es zur überschiessenden Wundheilung mit Ansammlung von Fibroblasten und extrazellulärer Matrix, welche durch verschiedene Mediatoren stimuliert werden

Funke-Chambour M. Pathogenese bei idiopathischer Lungenfibrose und Sarkoidose Leading Opinions, **2016**

Fibrosis in HP and sarcoidosis
- Gene expression profiles of patients

Analysis of genes differentially expressed between:

- idiopathic pulmonary fibrosis (IPF)
- hypersensitivity pneumonitis (HP)
- Sarcoidosis (self-limiting: N-SL and fibrotic P-F)



Lockstone HE, Sanderson S, Kulakova N, Baban D, Leonard A, Kok WL, et al. Gene set analysis of lung samples provides insight into pathogenesis of progressive, fibrotic pulmonary sarcoidosis. Am J Respir Crit Care Med. 2010; 181(12):1367–75.

Key messages

- Hypersensitivity pneumonitis is a immune mediated disease upon antigen exposure
- Sarcoidosis is an exaggerated immune response with unclear agents
- Sarcoidosis has a defective Th17 and Treg response
- Hypersensitivity pneumonitis and sarcoidosis present with acute and chronic forms
- Chronic inflammation can lead to currently irreversible fibrosis

INSELSPITAL
Universitätsklinik für Pneumologie

Vielen Dank

Sprechstunde für interstitielle Lungenerkrankungen und Sarkoidose

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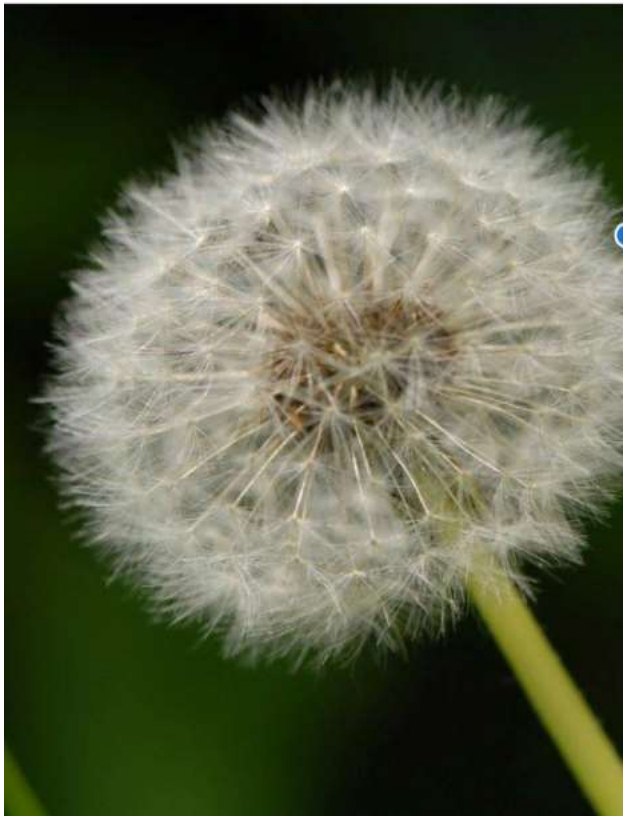

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