

GK1172
Basics in Medicine and Pharmacology

Rheumatoid Arthritis Clinical Appearance, Treatment and Status of Current Research

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Rheumatoid Arthritis

- One of the most common inflammatory disease (0.8% WHO)
- Prevalence 500-1000/100000 inhabitants (500.000 patients in Germany)
- Female / Male = 3:1 (onset often after pregnancy)
- Age of onset 20-45 years, up to now: life-long disease
- Joint damage and systemic inflammation results in average of 5-to 10-year decrease in life expectancy
- cause strong socio-economic consequences (disease costs 15.000 € per patient per year (without anti-TNF))
- at diagnosis already irreversible bone erosions

courtesy Dr. med. Andrea Himsel, Med. Klinik II.

Clinical features



Osteoporosis
Bone erosion
ankylosis



- symmetrical swelling of joints
- tenderness
- luxation
- loss of function

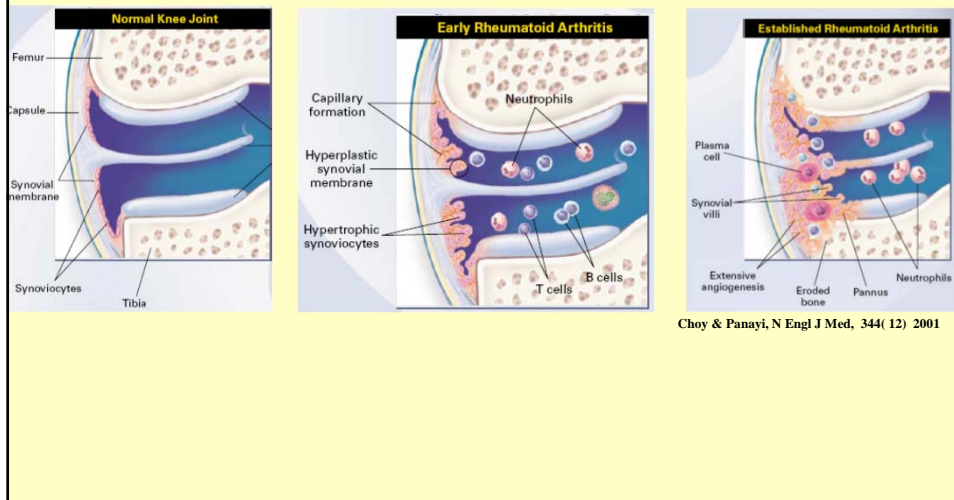
courtesy Dr. med. Andrea Himsel, Med. Klinik II.

Synovialitis



courtesy Dr. med. Andrea Himsel, Med. Klinik II.

Joint Tissue: Destructive Rheumatoid Arthritis



Rheumatoid Arthritis

joint destruction



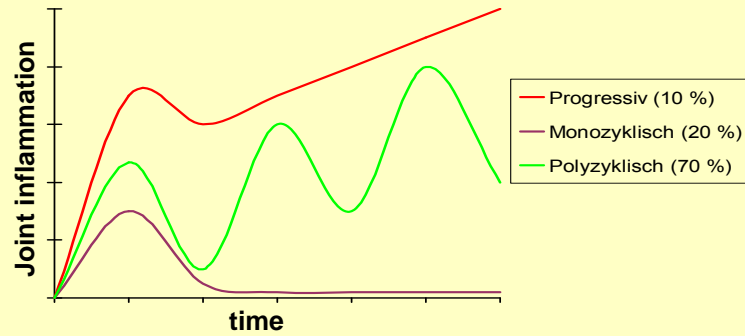
- Most characteristic feature of RA
- Based on hyperplastic synovial membrane
- Bone / joint destruction „silent“ progress independent of acute inflammation phases
- caused by enzymes (metalloproteinases) as well as Cytokines (TNF- α , IL-1)

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Rheumatoid Arthritis

disease course

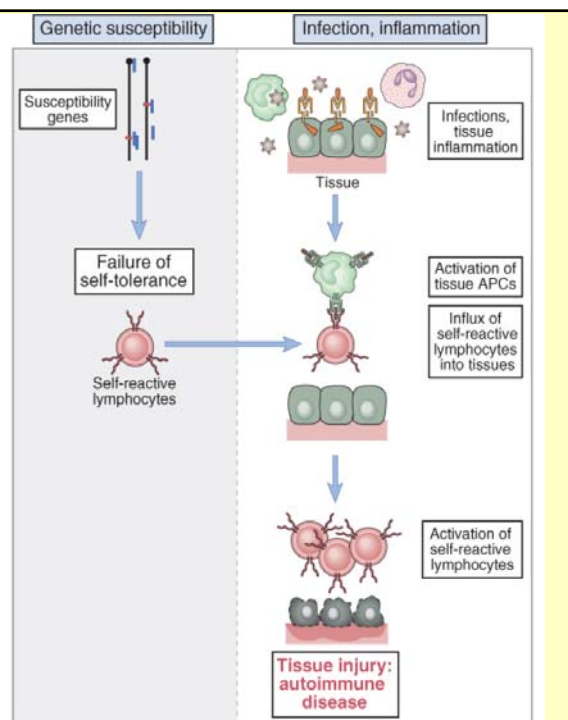
- Variable course (monocyclic, recurrent, progressive)



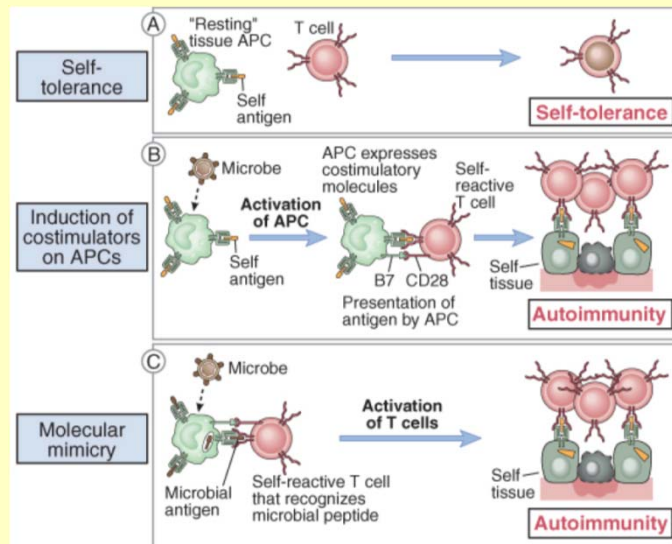
- Joint destruction accumulating = residual functional defects increasing over time
- Increased cardiovascular events, lymphoma, decreased life expectancy

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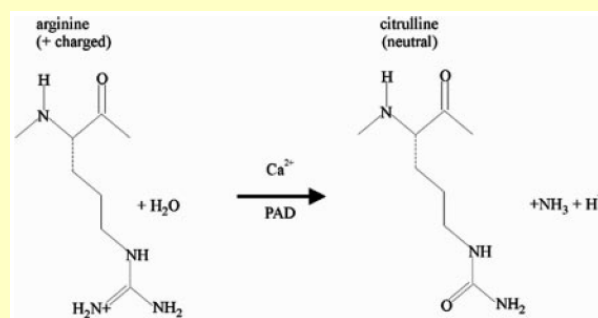
From defective genes to inflammation



Breaking of Self-tolerance and Molecular Mimicry

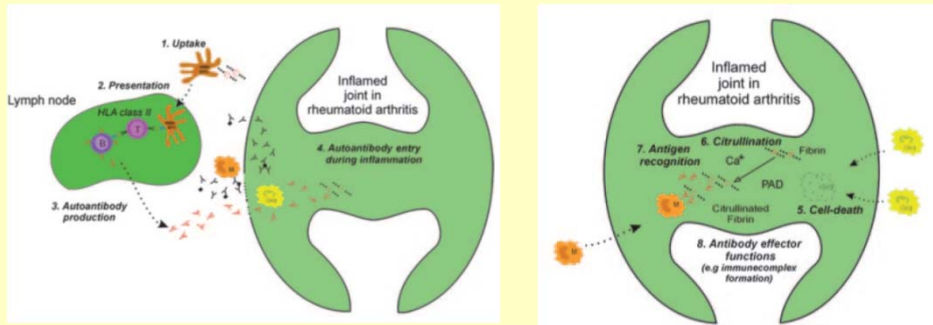


development of autoreactivity



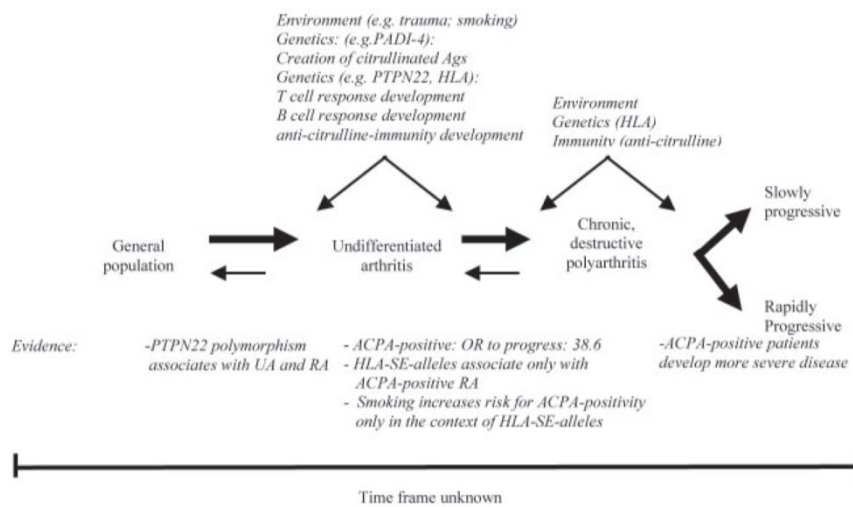
Enzymatic conversion of arginine to citrulline is catalyzed by PAD enzymes. Five mammalian peptidylarginine deiminases (PADs), PAD1–4 and PAD6, are known

Development of an anti-citrullinated protein autoimmunity in RA



- associated with HLA-DR genetics
- only with HLA-DR enhancement by smoking
- antibodies to citrullinated proteins found up to 9 years before onset of RA !!

Multiple Hit Model for RA



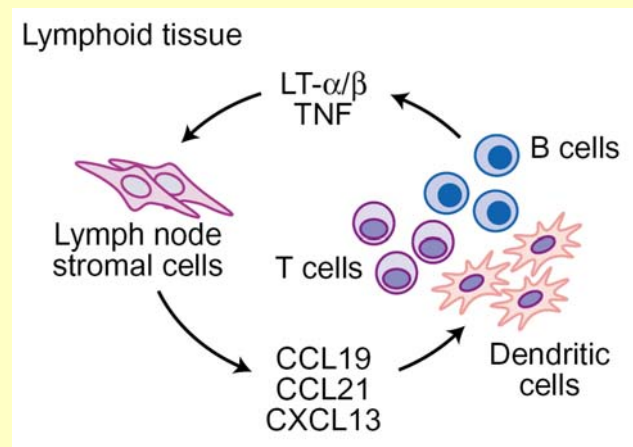
Concepts of Chronic Inflammation

Why does inflammation persist: a dominant role for the stromal microenvironment?

Michael R. Douglas, Karen E. Morrison, Michael Salmon and Christopher D. Buckley

Inflammatory responses occur within tissue microenvironments, with functional contributions from both haematopoietic (lymphocytic) cells and stromal cells (including macrophages and fibroblasts). These environments are complex – a compound of many different cell types at different stages of activation and differentiation. Traditional models of inflammatory disease highlight the role of antigen-specific lymphocyte responses and attempt to identify causative agents. However, recent studies have indicated the importance of tissue microenvironments and the innate immune response in perpetuating the inflammatory process. The prominent role of stromal cells in the generation and maintenance of these environments has begun to challenge the primacy of the lymphocyte in regulating chronic inflammatory processes. Sensible enquiries into factors regulating the persistence of inflammatory disease necessitate an understanding of the mechanisms regulating tissue homeostasis

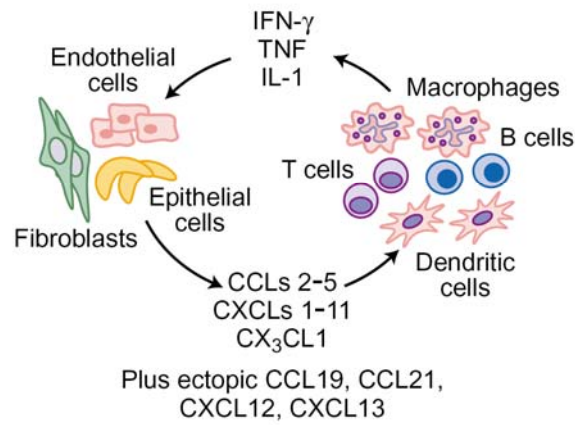
Chemokines and cytokines define the cellular composition of lymphatic organs (normal)



Modified from CD Buckley. Why does inflammation persist? expert reviews in molecular medicine 2002

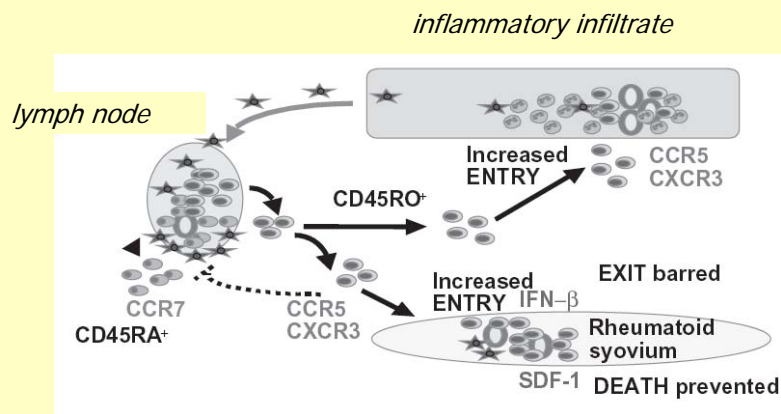
Chemokines and cytokines also define the cellular composition of pathological lymph nodes

b Chronic inflammation



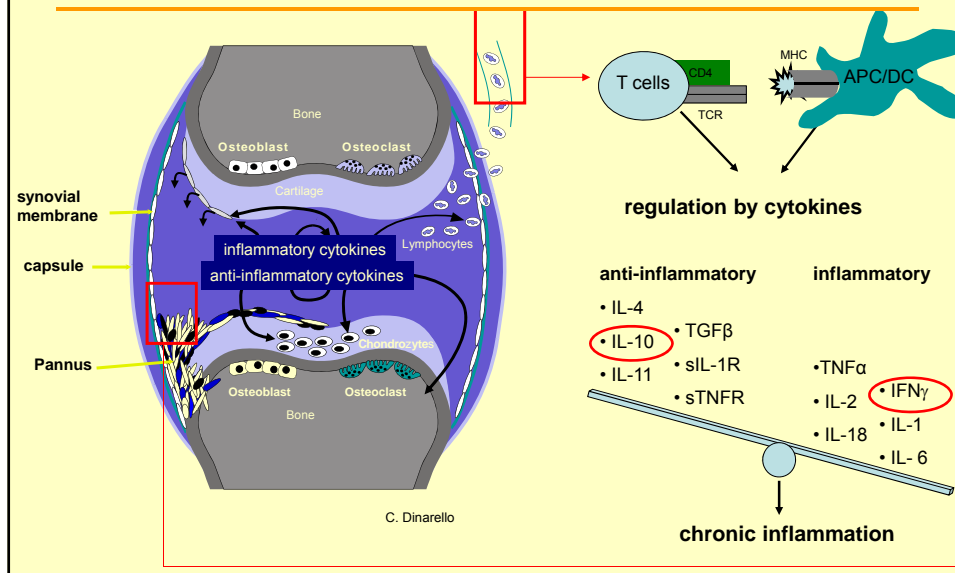
Modified from CD Buckley. Why does inflammation persist? expert reviews in molecular medicine 2002

Why leukocytes accumulate in synovial tissue...



RA: tertiary lymph follicle

Rheumatoid Arthritis: immunological activity in three compartments



Regulatory T cells in Rheumatoid Arthritis

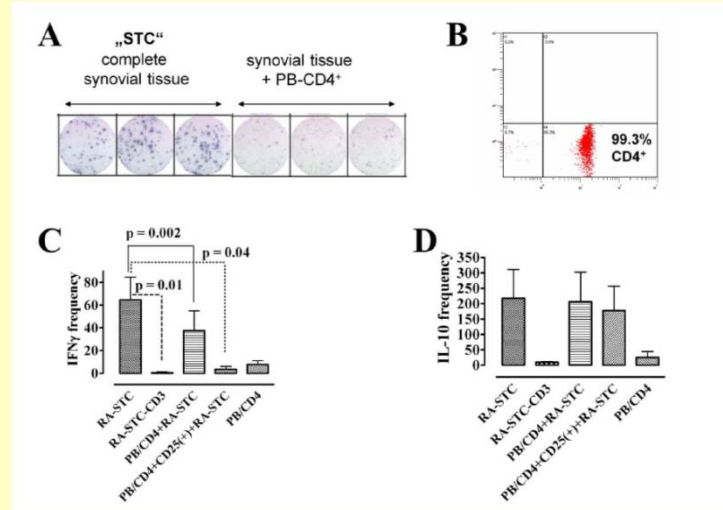
Behrens F, Himsel A, ...Radeke HH. *Annals of the Rheumatic Diseases*, 66:1151-1156, 2007

- controversy exists regarding to the frequency of Treg cells in the peripheral circulation of patients with RA
- elevated numbers of Treg cells are present in the synovial fluid of patients with RA as compared with the peripheral circulation
- However, little known about regulatory T cells in situ, i.e. in the synovial tissue

courtesy Dr. med. Andrea Himsel, Med. Klinik II.

High Th1 inflammatory activity in synovial tissue (ST) and inhibition by autologous Tregs

Behrens F, Himsel A, ...Radeke HH. *Annals of the Rheumatic Diseases*, 66:1151-1156, 2007



Tregs in RA

Behrens F, Himsel A, ...Radeke HH. *Annals of the Rheumatic Diseases*, 66:1151-1156, 2007

- If Treg are present in principle and are able to reduce immune responses

Why don't they suppress arthritis?

Possible Reasons:

- can't invade into the synovial membrane ?
- impaired function ?

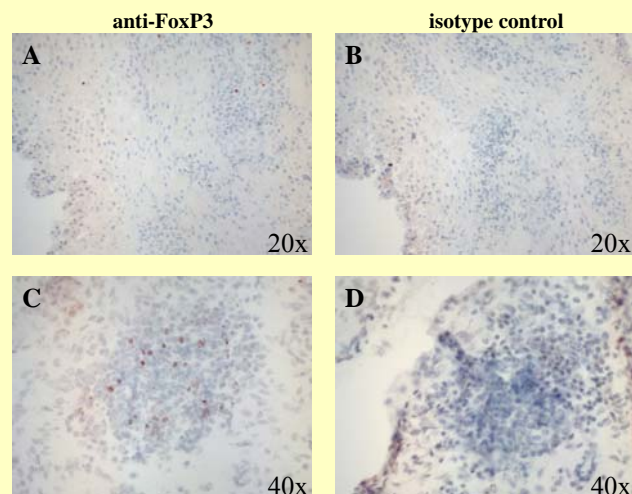
Initial questions

Behrens F, Himsel A, ...Radeke HH. *Annals of the Rheumatic Diseases*, 66:1151-1156, 2007

- Can we identify specific markers for Treg (Foxp3) vs. Th1-lymphocytes (T-bet) at transcription level in the target organ of RA - synovial tissue- in situ (ex vivo) ?
- how is the distribution of Foxp3 and T-bet between the different compartments of RA-joint ?

FoxP3-positive Tregs in synovial tissue

Behrens F, Himsel A, ...Radeke HH. *Annals of the Rheumatic Diseases*, 66:1151-1156, 2007



How can we normalize the patient samples from different tissues?

Behrens F, Himsel A, ...Radeke HH. *Annals of the Rheumatic Diseases*, 66:1151-1156, 2007

1.

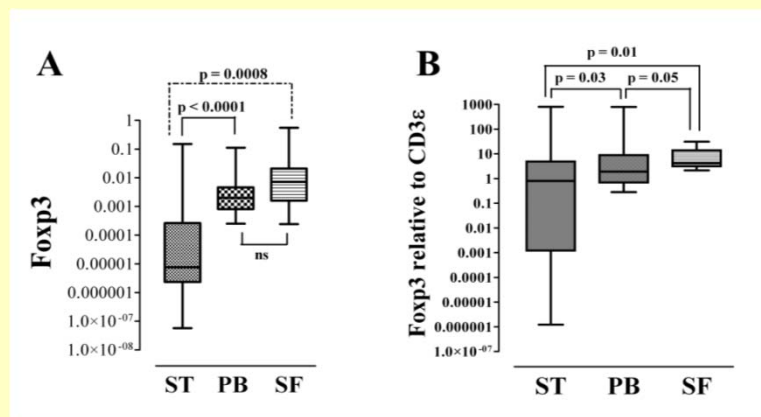
18S rRNA is the **most** stable housekeeping gene (compared to GAPDH and β -actin) for normalization of mRNA expression levels in human T lymphocytes (A. Bas et al.; *Scandinavian Journal of Immunology* 59, 566–573)

2.

CD3 ϵ is constitutively expressed in T lymphocytes and a single-mutation in the CD3 ϵ change cause immunodeficiency (SCID) (G. de Saint Basile et al.; *J Clin Invest.* 114,1512-1517)

relative lack of Tregs in synovial tissue

Behrens F, Himsel A, ...Radeke HH. *Annals of the Rheumatic Diseases*, 66:1151-1156, 2007



The ins and outs of Ly in RA: cell sorting is a pathomechanism...

Behrens F, Himsel A, ...Radeke HH. *Annals of the Rheumatic Diseases*, 66:1151-1156, 2007

T-bet mRNA:

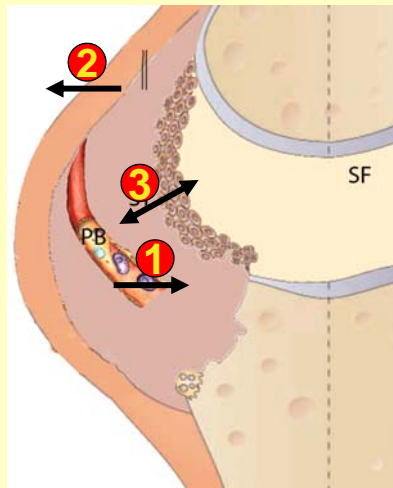
ST > PB > SF

FoxP3/T-bet mRNA

ST << PB < SF

disease activity correlates with:

DAS 28 \triangleq T-bet/FoxP3 in ST



Rheumatoid Arthritis

Therapy – „DMARDs“ **NON Biologics!**

- Different types of drugs and pharmacological mechanisms
- Mostly introduced empirically
 - ✓ Methotrexate
 - ✓ Leflunomide
 - ✓ Cyclosporine
 - ✓ Sulfasalazine
 - ✓ Azathioprin
 - ✓ Cyclophosphamide
 - ✓ D-Penicillamine
- More selective inhibition of immune processes by Cyclosporin und Leflunomid
 - ✓ T cell proliferation

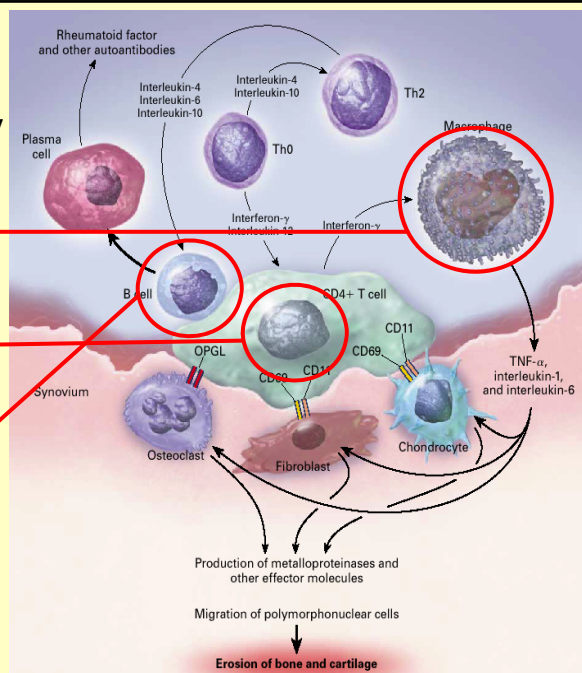
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Pathogenesis of RA and immune therapy

1. Autoinflammation
anti-„monokine“ biologics

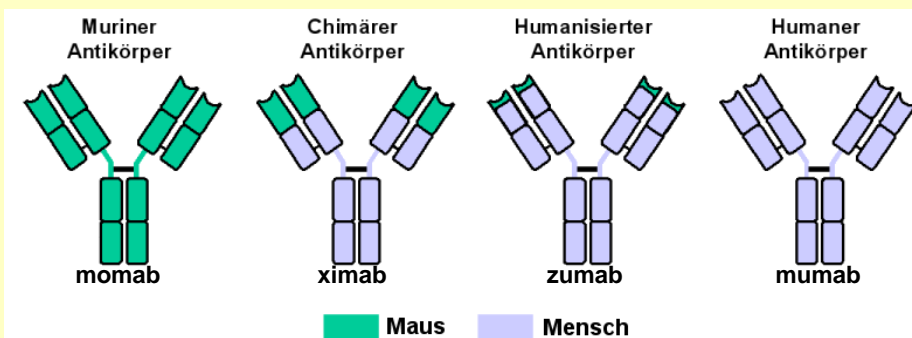
2. T cell autoimmunity
T cell or Treg biologics

3. B cell autoimmunity
B cell depleting biologics



Choy & Panayi, *NEJM* 2001;344:907-16.

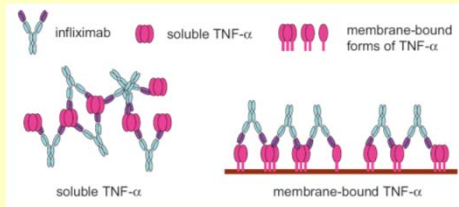
Rheumatoid Arthritis „Biologics“



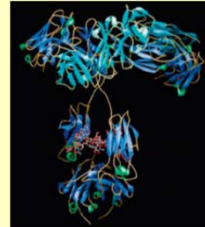
Fusion protein: Receptor & IgG-Fc: -cept

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Therapeutic success and serious side effects of the **TNF-alpha** blockade with Etanercept, Infliximab, and Adalimumab



Infliximab



Adalimumab

Serious Adverse Events:

- reactivation of latent tuberculosis
- increased risk of lymphoma
- anti-nuclear antibodies (SLE)
- demyelinating disease (MS)
- infection rate increased



Rheumatoid Arthritis

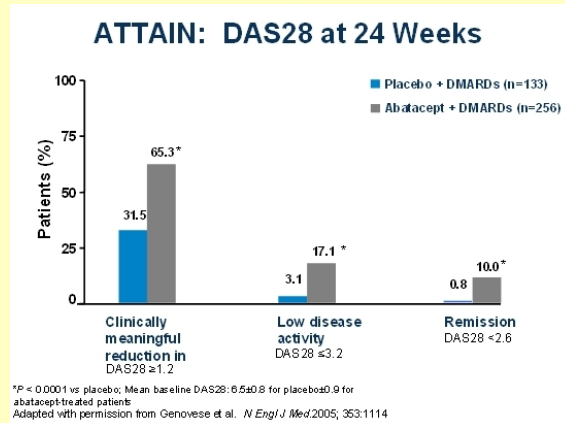
causal pathogenesis; Treg failure

CTLA4: Regulator of regulatory T cells... see above

- **Abatacept (fusion protein CTLA4-IgGFc)**
 - ✓ Abatacept; 10 mg/ kg KG, i.v., day 1, 15, 29, then every 28 days
- **Start of therapeutic effect late in comparison to anti-TNF- α therapy**
- **Active also if anti-TNF- α fails**
- **Radiologic progression is reduced**
- **anti-CD25-Ab not applicable due to serious side effects**

RA – Therapy with Biologics

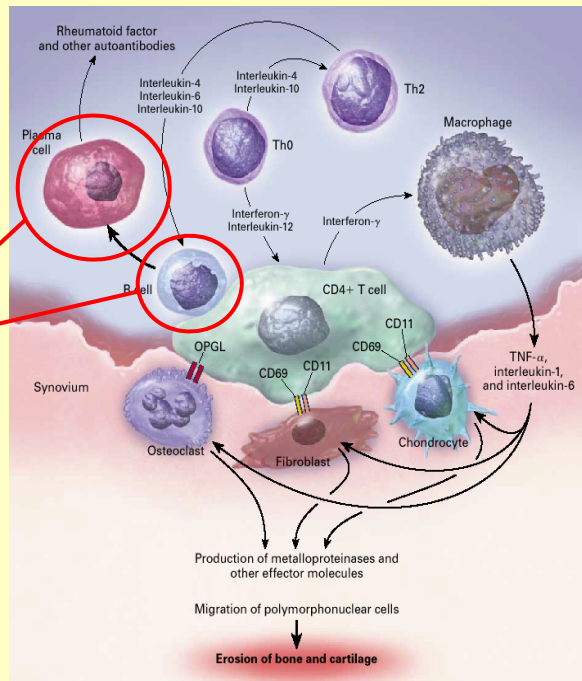
- Abatacept (fusion protein CTLA4-IgGfC)
 - Abatacept, 10 mg/ kg KG, iv., day 1, 15, 29, thereafter every 28 days



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Pathogenesis of RA

- B cell hyperactivity

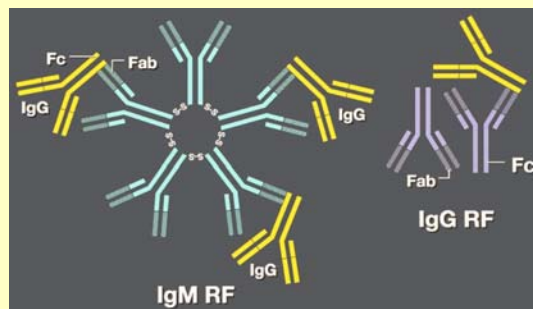


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Rheumatoid Arthritis

autoantibodies

- Rheumatic factor
 - ✓ IgM-Ab against IgG-Fc (less often IgG-RF, IgA-RF)
 - ✓ In RA ca. 70% positive (initially low), specificity low
 - ✓ No specific deposition in joint
 - ✓ No direct relationship between RF and disease activity
 - ✓ Is found also during other diseases (infection, cancer, hepatitis)
 - ✓ Also in healthy elder persons (> 60 years ca. 20-30%)



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Rheumatoid Arthritis

causal pathogenesis; B cells

Case Report

Remission of inflammatory arthropathy in association with anti-CD20 therapy for non-Hodgkin's lymphoma

A. Protheroe, J. C. W. Edwards¹, A. Simmons, K. Maclennan and P. Selby

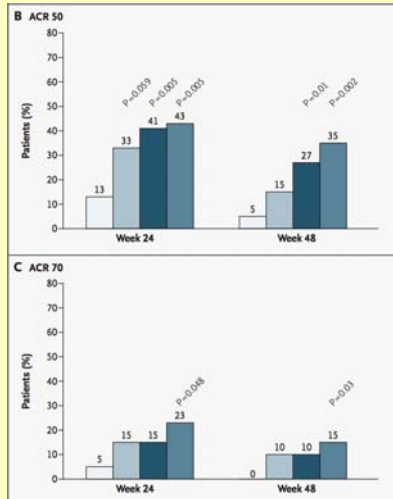
ICRF Cancer Medicine Research Unit, St James' University Hospital, Leeds and ¹Centre for Rheumatology, University College London, UK

Protheroe et al., *Rheumatology* 1999;38:1150-2.

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Rheumatoid Arthritis

causal pathogenesis; B cells

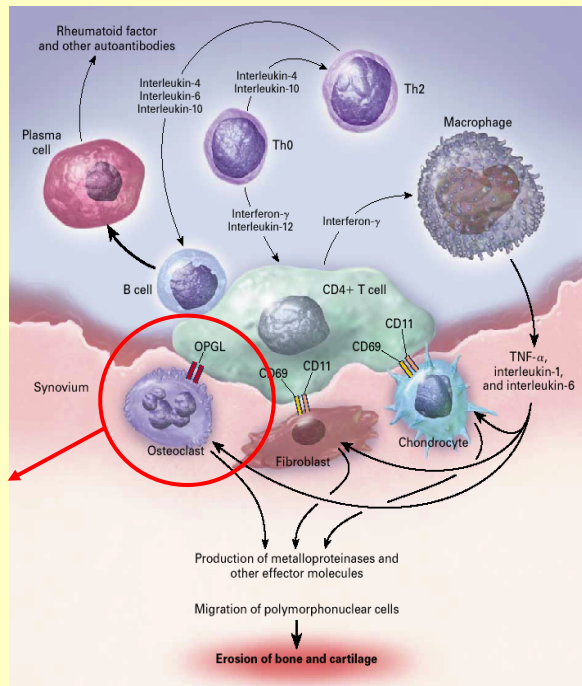


■ Mtx & Rituximab
 □ Mtx & Placebo

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Pathogenesis of RA

• Activation of osteoclasts

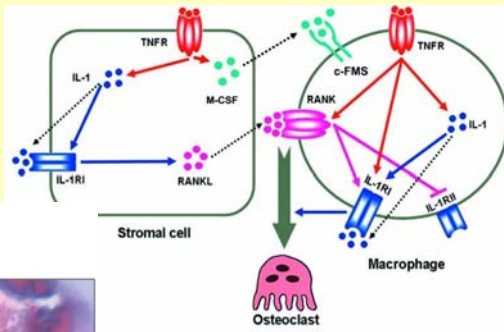


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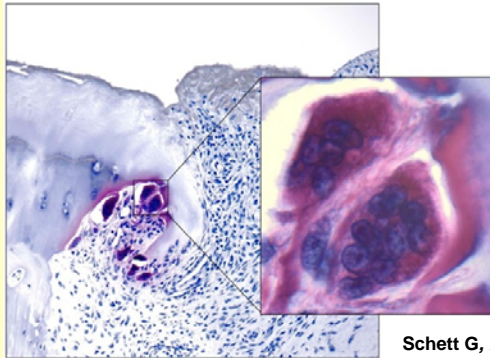
Rheumatoid Arthritis

causal pathogenesis; destruction

blocking destruction of joint chondroid and bone



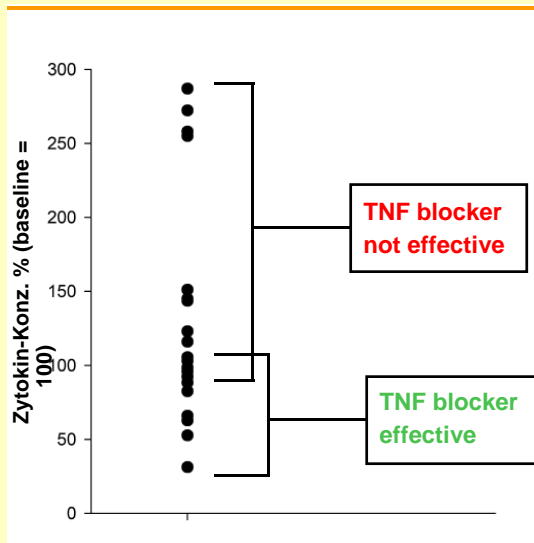
Teitelbaum SL, *Arthr Res Therapy* 2006;8:201.



Schett G, *Arthritis Res Ther* 2007;9 (Suppl 1):S2.

Rheumatoid Arthritis

therapy – future outlook



- Define markers for specific RA subtype

Goal:

- individually optimised therapy for each patient and activity state

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Discussion – new targets – possible GK1172 projects

- New targets? **IL-6** (IL-6R Ab), **IL-12**, IL-15, **IL-17** IL-18, **IL-21**, **IL-23**, B lymphocytes (**CD20/Rituximab**), collagenases, co-stimulatory (**CTLA4-Ig** (Abatacept, binding CD80/86), PD-1) and adhesion molecules (**VLA-4**, **LFA-1** alpha subunit CD11a (Efalizumab, CD2 – a LFA-3/Ig fusion protein binding to **CD2 (Alefacept)**) and chemokines (CCR2-, CXCR3 antagonists), TLRs (TLR3, etc.)
- Dr. Cornelia Richter is working on a completely new target - **ncf1** (Rikard Holmdahl, Lund – Karolinska): a NADPH-oxidase component p47phox whose genetic defect „paradoxically“ leads to enhanced frequency of CIA in rats and mice. Classically it is deduced that a lack of NADPH oxidase components might improve inflammatory conditions (see therapeutic concepts involving the toxicity of oxygen radicals), however in this case the opposite is happening OR NOT...?!
- Clinical Trials running: IL-15Ab, IL-18RA, CTLA4-Ig, CD11a, IL12p40AB ... etc. pp.

Summary

- Rheumatoid Arthritis is a multifactorial autoimmune and chronic inflammatory disease with high prevalence, social and individual costs and reduced life expectancy
- genetic and environmental mechanisms of Th1, Th17, B cell autoimmunity, but also „autoinflammation“ can be detected
- Mechanisms of **Chronicity** include
 - deterioration of local synoviocytes „autonomic pannus tumor“,
 - chemokine-induced tertiary lymph nodes (DC) and/or a
 - pathological distribution of regulatory T cell activity
- modern „**biologics**“ for the first time may deserve the label DMARDs: „**disease modifying anti-rheumatic drugs**“
- Future therapies may be based on markers and an individual therapeutic cocktail (see case history seminar)