Immune-deficiencies

Immune deficiencies

- Primary
  - Hereditary
    - Can be categorized based on clinical presentation
      - Cell mediated (T cell)
      - Antibody mediated (B cell)
      - Non specific (phagocytes, NK cells)
      - Complement activation

Major clinical manifestations of immune disorders

Disorder	Associated Disease
Deficiency	
B cell deficiency – deficiency in Ab mediated immunity	Recurrent bacterial disease (otitis media, recurrent pneumonia)
T Lymphocyte deficiency – deficiency in cell mediated immunity	Increased susceptibility to viral, fungal,protozoal infection
T and B lymphocyte deficiency – combined deficiency of Ab- and cell-mediated immunity	Acute and chronic infections with viral, bacterial, fungal, and protozoal organisms
Phagocytic cell deficiency	Systemic infections with bacteria of usually low virulence, infections with pyogenic bacteria, impaired pus formation and would healing
NK cell deficiency	Viral infections, associated with several T cell disorders and X-linked lymphoproliferative syndromes
Complement component deficiency	Bacterial infections; autoimmunity

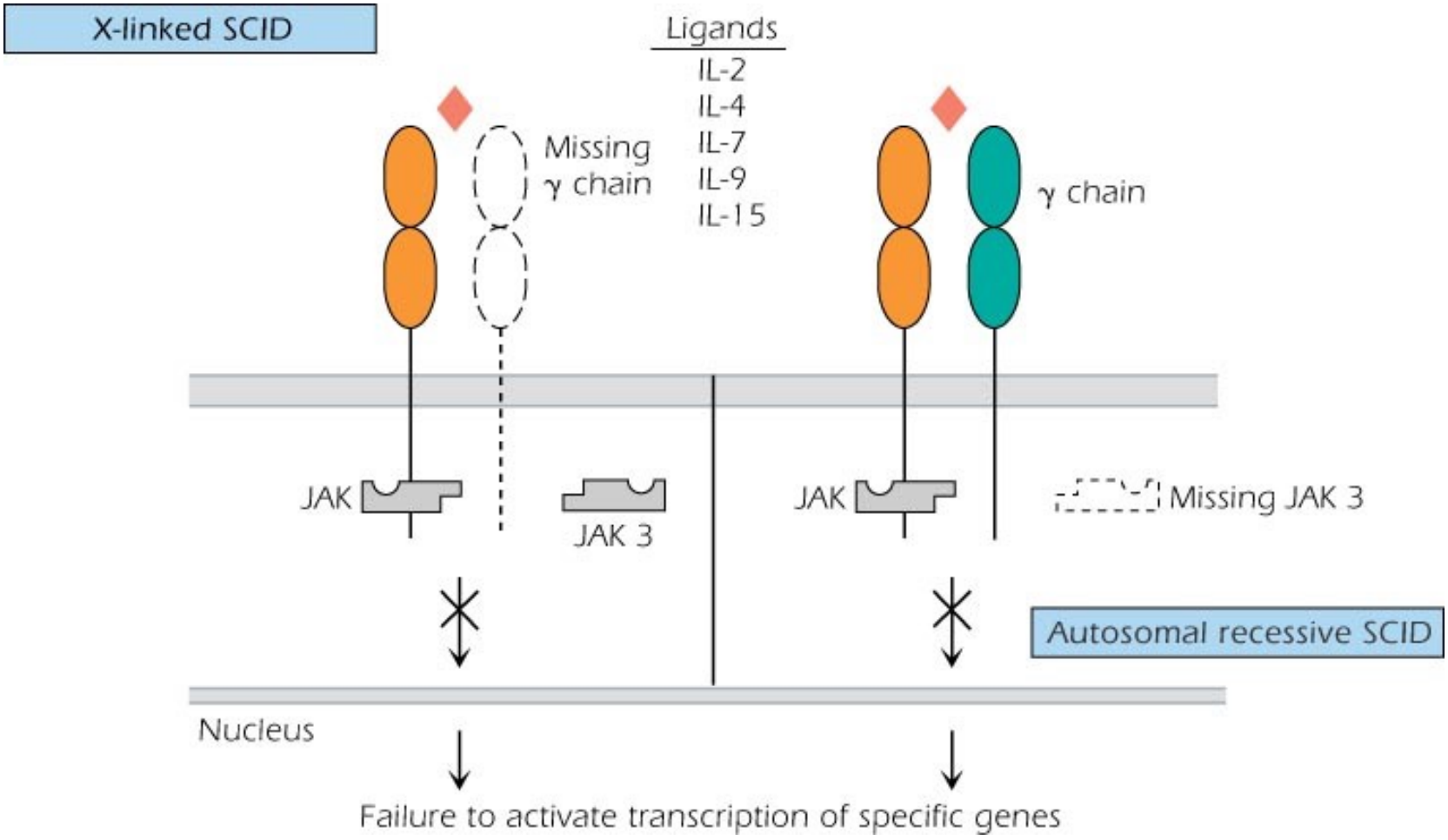
Severe Combined Immunodeficiency Disease (SCID)

- Life threatening infections soon after birth
- Lack of Thymic shadow
- Lack of CD3+, CD4+, CD8+ and lymphocyte response to antigens (also B-cell response)

Primary immunodeficiencies

- Severe Combined Immunodeficiency Disease
  - **T- B+**
    - X-linked SCID (40-50% of cases)
      - Lack γ chain (CD25) for common cytokine receptor
    - Autosomal recessive SCID
      - Mutation in gene that encodes JAK3 tyrosine kinase

X linked and autosomal recessive



“The Boy in the Bubble”

Primary immunodeficiency

- Severe Combined Immunodeficiency Disease
  - **T- B-**
    - Adenosine deaminase deficiency (20% of cases)
      - Missing housekeeping enzyme in purine salvage pathway, autosomal recessive, buildup of toxic wastes affects B and T cells
    - Purine nucleoside phosphorylase deficiency
      - Purine salvage pathway, toxic wastes affect neurologic system and T cells (these patients have autoimmunity?!)
    - Recombinase deficiency
      - RAG 1 and 2 required for the rearrangement of Ig genes and TCR. Cells are stuck in pre-B and pre-T stages. NK cell function OK

Primary Immunodeficiency

- Severe Combined Immunodeficiency Disease
  - **T+ B-**
    - Omenn syndrome
      - "leaky" SCID with partial RAG activity. Th2 imbalance and a tendency towards hyper IgE syndrome
  - **T+ B+**
    - Bare lymphocyte syndrome
      - Failure to express HLA molecules
    - ZAP-70 mutation
      - Unable to signal through TCR and BCR

Management of SCID patients

- Bone marrow/ placental stem cell transplant
- IV Ig if necessary
- Supportive care
- Avoid live viral vaccines!
- Gene therapy, if possible

Future research directions….

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Why Gene Therapy Caused Leukemia In Some 'Boy In The Bubble Syndrome' Patients

ScienceDaily (Aug. 10, 2008) — Severe combined immunodeficiency (SCID), sometimes called 'Boy in the bubble syndrome', is a genetic disorder in which the patient lacks most types of immune cell. Almost 10 years ago, two independent groups (one in London, United Kingdom, and one in Paris, France) used gene therapy to treat a few infants with the most common form of SCID, SCID-X1, which is caused by mutations in the IL2RG gene.

See also:

Health & Medicine
- Gene Therapy
- Leukemia
- Genes
- Personalized Medicine
- Diseases and Conditions
- Human Biology

Reference
- Vector (biology)
- Tumor suppressor gene
- Introduction to genetics
- Gene therapy

Although most infants showed dramatic improvement following gene therapy, 4 of the 9 infants that were successfully treated in Paris developed leukemia between 3 and 6 years after the treatment. The groups in London and Paris had used very similar gene therapy approaches and until now it was not clear why leukemia was detected only in some of the infants treated in Paris. However, Adrian Thrasher and colleagues, at the Institute for Child Health, London, now report that 1 of the infants successfully treated in London also developed a form of leukemia known as T cell acute lymphoblastic leukemia (T-ALL).

In the study, Thrasher and colleagues go on to show why that infant developed leukemia. During gene therapy, the correct form of the IL2RG gene and the vector that carried this into the cells integrated into part of the genome that contained a gene known as LMO2

Related Stories

New Genetic Cause Of Boy In The Bubble Syndrome (Dec. 18, 2008) — Severe combined immunodeficiency (SCID) is an inherited disease sometimes known as "boy in the bubble syndrome," because the patient lacks one or more

Other immunodeficiencies of T cells and cell -mediated immunity

Other immunodeficiencies of T cells and cell -mediated immunity

- Patients are susceptible to viral, fungal, and protozoal infections
- Often exhibit selective defects in Ab production
- Can be difficult to distinguish from SCID patients

T cell deficiencies with normal peripheral T cell numbers

- Functional, rather than numerical defect in T cell population
- Susceptible to opportunistic infections, high incidence of autoimmune disease
- Autosomal recessive
  - Deficient expression in:
    - ZAP-70 tyrosine kinase (phenotype includes CD8 deficiency and SCID-like symptoms
    - CD3ε
    - CD3γ

Autoimmune LymphoProliferative Syndrome (ALPS)

- Systemic autoimmune disease, susceptible only to chronic viral infections
- Increased CD4-/CD8- T cells, can develop B cell lymphomas
- Most patients have a mutation in gene encoding for *Fas* (CD95)

B cell or Ig-associated Immunodeficiency

- May be associated with defective B cell development (absence of all Ig subclasses) or deficiency in subclass or class of Ig
- Patients suffer from recurrent or chronic infections

Brunton's agammaglobulinemia

- X-linked infantile agmmaglobulinemia
- 1:100,000
- Noticed in infants at 5-6 months of age
- Serious and repeated bacterial infections
- Defect in BTK gene
  - Pre-B cells cannot develop into mature B cells
- Treatment consists of Ivlg injections, but chronic lung disease is a problem

Phagocytic dysfunctions

- Affect the innate and acquired response to pathogens
- Dysfunction in:
  - Action required to phagocytize
  - Migration and adhesion of phagocytic cells

Leukocyte adhesion deficiency (LAD)

- Autosomal recessive
- Group of disorders in which the leukocyte interaction with vascular endothelium is disrupted
  - β subunit of integrins
  - Selectin ligands
- Consequences:
  - Recurrent soft tissue bacterial infection
  - Increased blood WBC counts
  - No pus formation or effective wound healing

Chronic Granulomatous Disease

- X-linked, autosomal recessive
- Skin, lymph node, lung infections
- High WBC in blood
- Phagocytes unable to complete respiratory burst
- Treatments include antibiotics, antifungals, IFNγ

Complement Abnormalities

- Deficiencies inherited in autosomal fashion, heterozygotes have 50% of given complement protein
- Complement is required for:
  - Opsonization and killing of bacteria
  - Chemotaxis
  - B cell activation
  - Elimination of Ag-Ab complexes

INCIDENCE OF COMPLEMENT DEFICIENCIES IN NORMAL POPULATION

POPULATION	SWISS	BRITISH	JAPANESE
N° OF SUBJECTS EXAMINATED	40,000	2,000	145,640
N° OF SUBJECTS WITH C DEFICIENCY	14	1	154
DEFECTIVE COMPONENT	C2, C4	C6 + C7	C5(2), C6(4), C7(6), C8(4), C9 (138)
REFERENCE	Hessing et al, 1964	Lachman et al, 1978	Fukumori et al 1989; Inai et al 1989

THE INHERITED DEFICIENCIES OF C COMPONENTS AND REGULATORS ARE RARE IN THE GENERAL POPULATION

The estimated frequency is 0.03%
(3 per 10,000)

MBL DEFICIENCY IS COMMON IN THE GENERAL POPULATION

Estimated frequency is 5-10%
(Asymptomatic)

Early complement protein deficiencies

- C1, C2, C4 or C3 deficiency
- Pyogenic infections

- Autoimmunity – SLE very common

Late complement protein deficiencies

- C5 - C9
- Prevents formation of membrane attack complex

- Gram negative bacterial infections

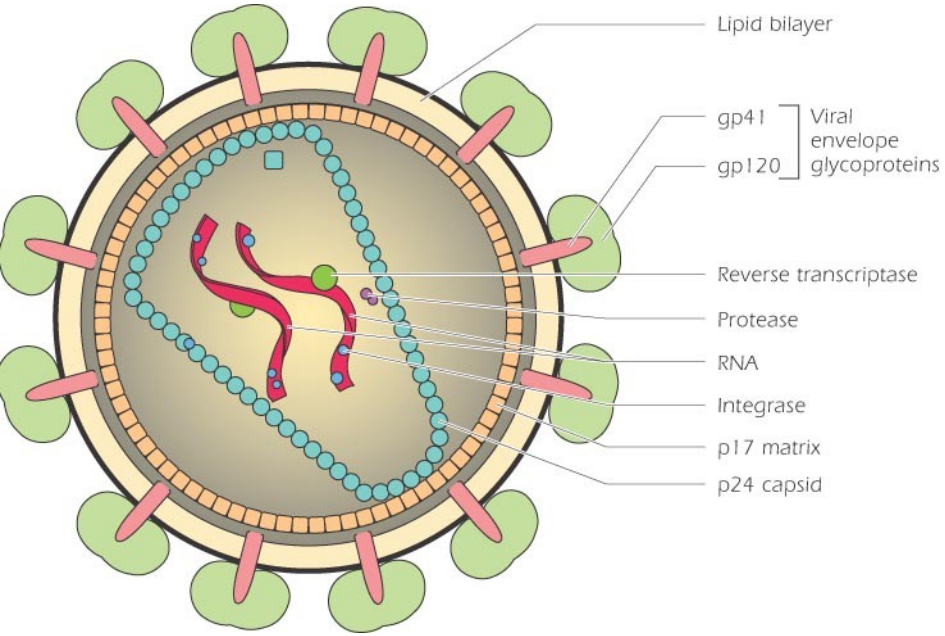
Immune deficiencies

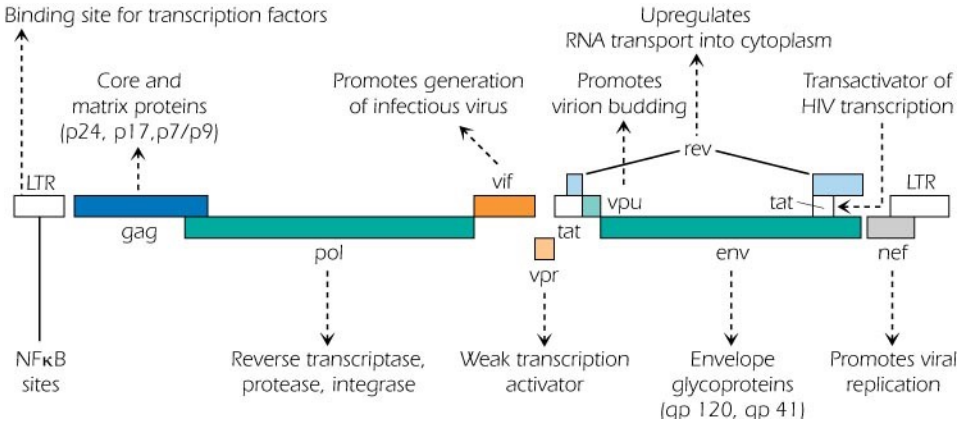
- Primary
  - Hereditary
    - Can be categorized based on clinical presentation
      - Cell mediated (T cell)
      - Antibody mediated (B cell)
      - Non specific (phagocytes, NK cells)
      - Complement activation
- **Secondary**
  - Immune deficiency is the result of another disease

Acquired Immunodeficiencies

- Secondary immune deficiencies that are the consequences of other diseases
  - Viral Infection

HIV


Lipid bilayer
gp41
gp120
Viral envelope glycoproteins
Reverse transcriptase
Protease
RNA
Integrase
p17 matrix
p24 capsid


Binding site for transcription factors
Upregulates RNA transport into cytoplasm
Core and matrix proteins (p24, p17,p7/p9)
Promotes generation of infectious virus
Promotes virion budding
Transactivator of HIV transcription
rev
LTR
vif
vpu
tat
LTR
gag
tat
pol
vpr
env
nef
NFκB sites
Reverse transcriptase, protease, integrase
Weak transcription activator
Envelope glycoproteins (gp 120, gp 41)
Promotes viral replication

Immuno-pathogenesis of HIV-Infection

- HIV infects and ultimately destroys CD4+ , CCR5+ or CXCR4+ T cells, monocytes, & dendritic cells.
- Primary HIV Infection: A vigorous immune response to HIV controls the primary infection (clonal Cytotoxic T cells, suppressive chemokines, poorly neutralizing antibody)

Immuno-pathogenesis of HIV-Infection (continued)

- Chronic Asymptomatic Phase: Viral trapping & replication in lymphoid tissues, **high rate turnover of virus and CD4 T** cells, **loss of CD4 functional help** to CTL and antibody responses, **destruction of lymph tissue**, **viral mutation** and escape from recognition, **exhaustion or viral inhibition of CD4 T cell renewal**.

Immunopathogenesis of HIV-Infection (continued)

- Overt AIDS: CD4 count declines, viral load increases, opportunistic infections.

Acquired Immunodeficiencies

- Secondary immune deficiencies that are the consequences of other diseases
  - Viral Infections
  - Chemotherapeutic agents

IMMUNODEFICIENCY CAUSED BY DRUGS

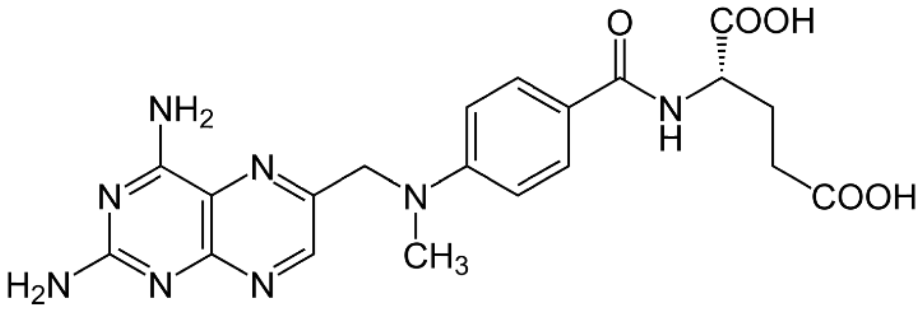
CORTICOSTEROIDS

- Inhibit cytokine synthesis

- Cause changes in circulating leukocytes
- Depletion of CD4 cells
- Monocytopenia
- Decreased in circulating eosinophils and basophils
- Inhibition of T cell activation and B cell maturation

IMMUNODEFICIENCY CAUSED BY DRUGS

METHOTREXATE

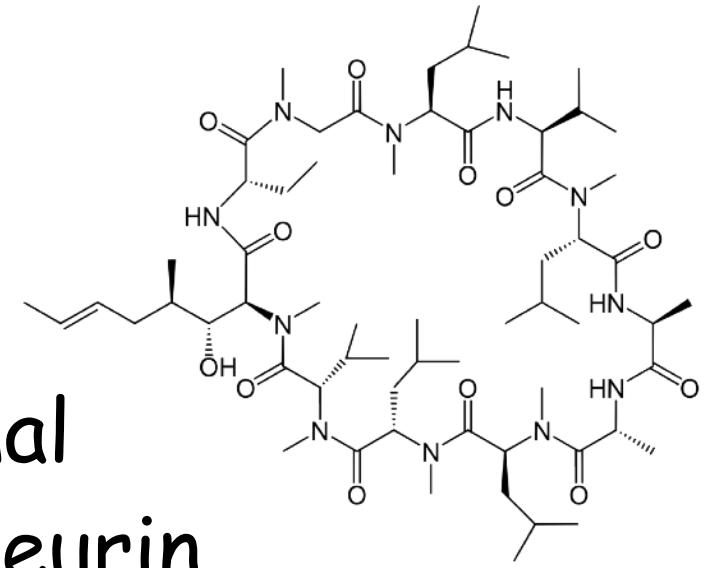


- Structural analogue of folic acid
- Blocks folic acid dependent-synthetic pathways essential for DNA synthesis

- Prolonged use for treatment reduces immunoglobulin synthesis

IMMUNODEFICIENCY CAUSED BY DRUGS

CYCOLOSPORIN



- Inhibit IL 2 dependent signal transduction blocking calcineurin

- Have severe effects on T cell signaling and functions

Acquired Immunodeficiencies

- Secondary immune deficiencies that are the consequences of other diseases
  - Viral Infections
  - Chemotherapeutic agents
  - Malnutrition
  - Untreated autoimmunity
  - Overwhelming bacterial infection

Take Home Message

- Immunodeficiency may be congenital or acquired
- It can involve any component of the immune system such as cells, antibodies, complement etc.
- Most common presentation of immunodeficiency is recurrent infections that may be fatal due to delay in diagnosis and lack of appropriate therapy

Animal models in Immunology

- Immunedeficency studies (genetic, acquired, temporary o induced) and its consequences

Infective diseases

Autoimmune diseases

Cancer

Nude mice

Topi Nudi: mutazione autosomica recessiva del locus nu sul cromosama 11.

Porta ad aplasia timica (detti topi atimici), perdita di pelo (topi nudi).

Mancanza di cellule T attive ma presenza di normali cellule B, NK, macrofagi, granulociti e complemento.

SCID mice

SCID: Severe combined immunodeficiency

Topi SCID: Ceppo di topi derivante dai C57/Bl privi totalmente di linfociti B e T per blocco precoce della maturazione linfocitaria dai precursori midollari. Tali topi presentano una mutazione a carico di un componente di un enzima (protein kinasi DNA-dipendente) necessario per la riparazione delle rotture del DNA a doppia elica. Il deficit enzimatico comporta alterazioni nelle giunzioni dei segmenti genici del TCR e delle Ig nel corso della ricombinazione dei geni dei recettori antigenici; ne consegue impossibilità di proseguire la maturazione da parte dei linfociti T e B per la mancata espressione di TCR e BCR.
Rimane "immutata" l'immunità innata.

NOD mice

NOD: Diabetici non obesi. Topi mostrano una suscettibilità allo sviluppo della forma spontanea autoimmune di diabete mellito insulino-dipendente (IDDM).

Topi NOD: Topi NOD possiedono polimorfismi nel locus Idd3 che è collegato a IL-2. IL-2 promuove o l'immunità o la tolleranza in un modo dipendente dalla concentrazione, agendo sulle cellule helper T, cellule NK e CTL. Basse quantità di IL-2 sono necessari per promuovere la sopravvivenza dei Treg nei topi. Perdita di IL-2 può quindi contribuire allo sviluppo di autoimmunità nei topi NOD.

Incrociati per ottenere topi NOD-SCID

NSG mice

NSG: NOD SCID Gamma

Topi NSG:

The NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice, commonly known as NOD SCID Gamma (NSG), are severely immunocompromised, featuring absence of mature T or B cells, lack of functional NK cells and deficiency in cytokine signaling. The strain combines the features of the NOD/ShiLtJ background, the severe combined immune deficiency mutation (scid, which is caused by a spontaneous mutation in the Prkdc gene), and IL2 receptor gamma chain deficiency. Defect in C5 was also described.

As a result, engraftment of human hematopo
blood mononuclear cells in the NSG mice is
mouse strain.

Applications of immune-deficient mice

1. human tissue implantation

Identification of Synovium-Specific Homing Peptides by In Vivo Phage Display Selection

Lewis Lee,[1] Christopher Buckley,[2] Mark C. Blades,[1] Gabriel Panayi,[1] Andrew J. T. George,[3] and Costantino Pitzalis[1]

Objective. **To identify homing peptides specific for human synovium that could be used as targeting devices for delivering therapeutic/diagnostic agents to human joints.**

Methods. **Human synovium and skin were transplanted into SCID mice. A disulfide-constrained 7–amino acid peptide phage display library was injected intravenously into the animals and synovial homing phage recovered from synovial grafts. Following 3–4 cycles of enrichment, DNA sequencing of homing phage clones allowed the identification of specific peptides that were synthesized by a-fluorenylmethyloxycarbonyl chemistry and used in competitive in vivo assays and immunohistochemistry analyses.**

Results. **We isolated synovial homing phages displaying specific peptides that distinctively bound to synovial but not skin or mouse microvascular endothelium (MVE). They retained their tissue homing specificity in vivo, independently from the phage component, the original pathology of the transplanted tissue, and the degree of human/murine graft vascularization. One such peptide (CKSTHDRLC) maintained synovial homing specificity both when presented by the phage and as a free synthetic peptide. The synthetic peptide also competed with and inhibited in vivo the binding of the parent phage to the cognate synovial MVE ligand.**

Conclusion. **This is the first report describing peptides with homing properties specific for human synovial MVE. This was demonstrated using a novel approach targeting human tissues, transplanted into SCID mice, directly by in vivo phage display selection. The identification of such peptides opens the possibility of using these sequences to construct joint-specific drug delivery systems that may have considerable impact in the treatment of arthritic conditions.**

The microvascular endothelium (MVE) plays a major role in the pathogenesis of rheumatoid arthritis (RA), making it an important therapeutic target. RA is a condition characterized by a proliferative synovitis that is responsible for cartilage and bone damage leading to progressive joint destruction (1,2). Florid sprouting of new blood vessels (neoangiogenesis) is typically seen in the early phases of RA synovitis, suggesting that it is a critical element in this condition (3). In the established chronic phase of the disease, the MVE is also important, since it functions as a conduit for the continuous influx of inflammatory cells from the bloodstream into the

Applications of immune-deficient mice

2. implantation of non-murine cells in mice

- transplantation of human hematopoietic stem cells
- human cancer models in mice