Biological Agents in Psoriasis

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Introduction

Indications for systemic therapy :

1. > 5% BSA
2. Vulnerable areas (PP)
3. Pustular, erythrodermic and guttate
4. Unresponsive to topical and causing physical, social and emotional impairment
5. + Psoriatic arthritis

Introduction

Traditional systemic therapies :

Methotrexate, cyclosporine, Retinoids

Problems :

- Inconvenience
- Toxicity – organ damage
- 40%-frustrated with current therapies due to lack of control of their psoriasis

Introduction

Need for systemic therapy :

- For all ages
- Safe with continous long term treatment
- Not contraindicated in females child bearing age
- Fewer organ toxicities

Introduction

Recent advances in the field of immunology has led to massive change in the understanding of certain diseases like psoriasis

T cell (lymphocyte) disease rather than just thought to be a disorder of keratinization

This has led to development of newer therapeutic options (**biologicals)** which target these T cell mediated immunological process of psoriasis at various stages

Biologicals

Protein drugs produced in living organisms “or” products derived from living materials & used for the treatment, prevention and cure of diseases in humans

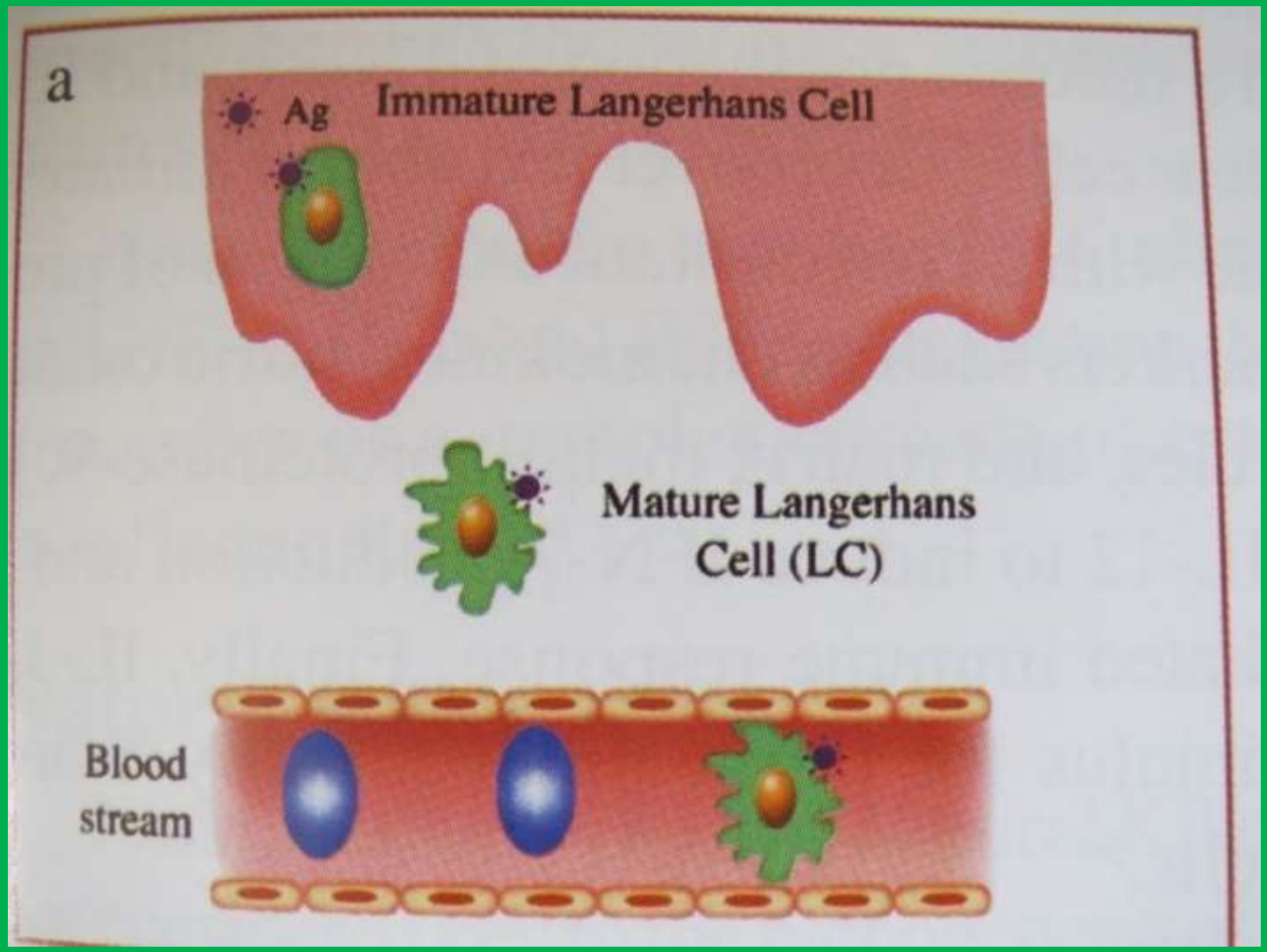
Umab- monoclonal antibodies

Ximab- chimeric (murine variable) monoclonals

Zumab -humanized monoclonals

Cept- receptor antibody fusion protein

APC maturation & migration



Pathogenesis: T cell activation

Ag ? -----APC-----maturation and migration to Lymph nodes-----interaction with naive T cells and their activation

2 signals simultaneously

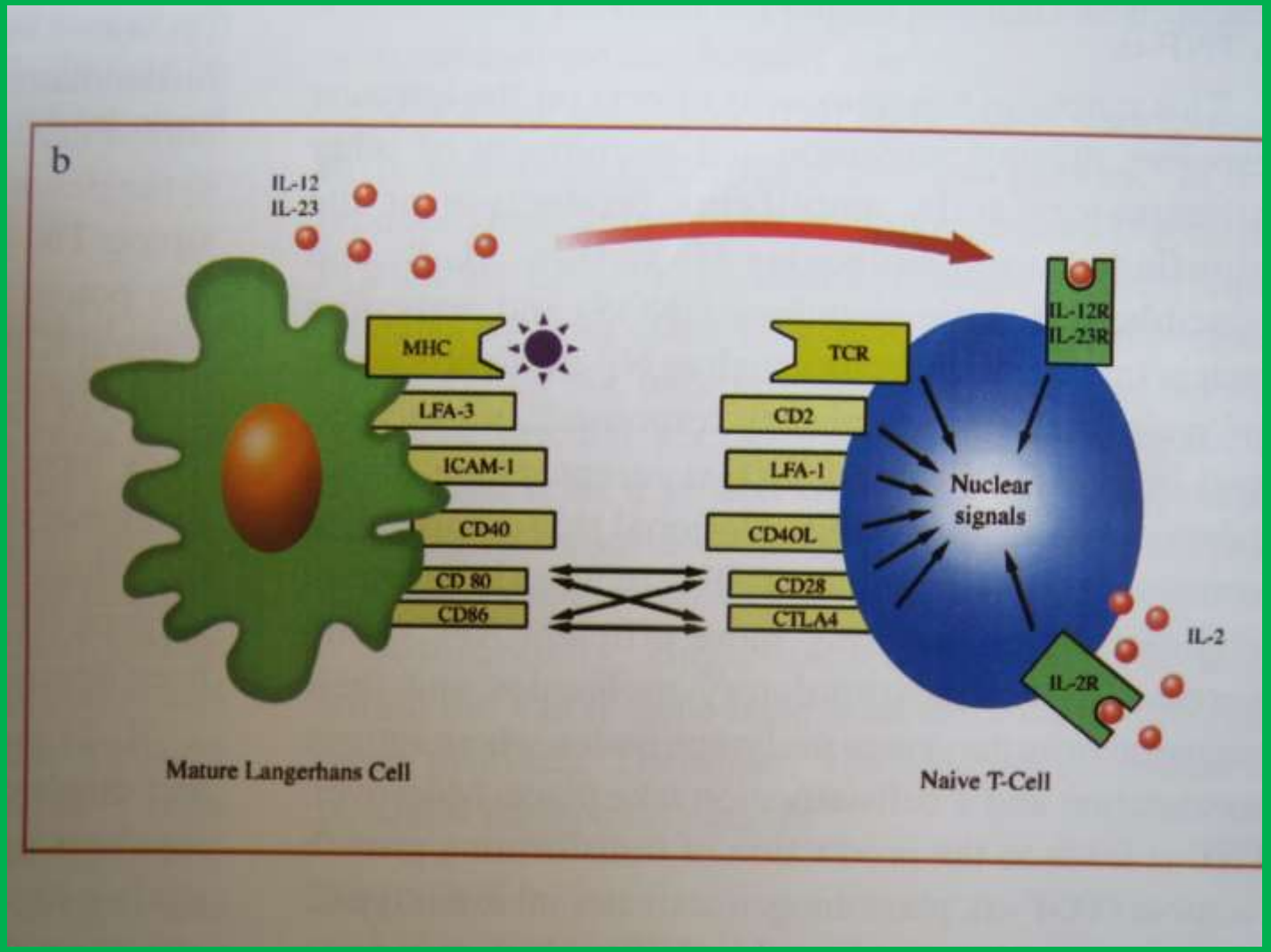
a) Class I or II MHC on APC + TCR (T cell)

b) Non Ag specific costimulation

CD80 & CD86 (B 7 molecules) + CD 28 (T cell)--------

upregulation of CTLA4(cytotoxic T L Ag 4) on T cell

T cell activation



Pathogenesis: T cell migration to skin

Activated T cells in circulation must be slowed

down to be immobillized and bound to endothelium

1) (**Tethering**)-----Cut L Ag (on act. T cells) + E or P selectin on endothelial cells– temporary binding--- rolling -------
2) Arrest of rolling--- flattening of T cells---Diapedesis through vessel wall----- later--- in response to chemotactic gradient (Chemokines)

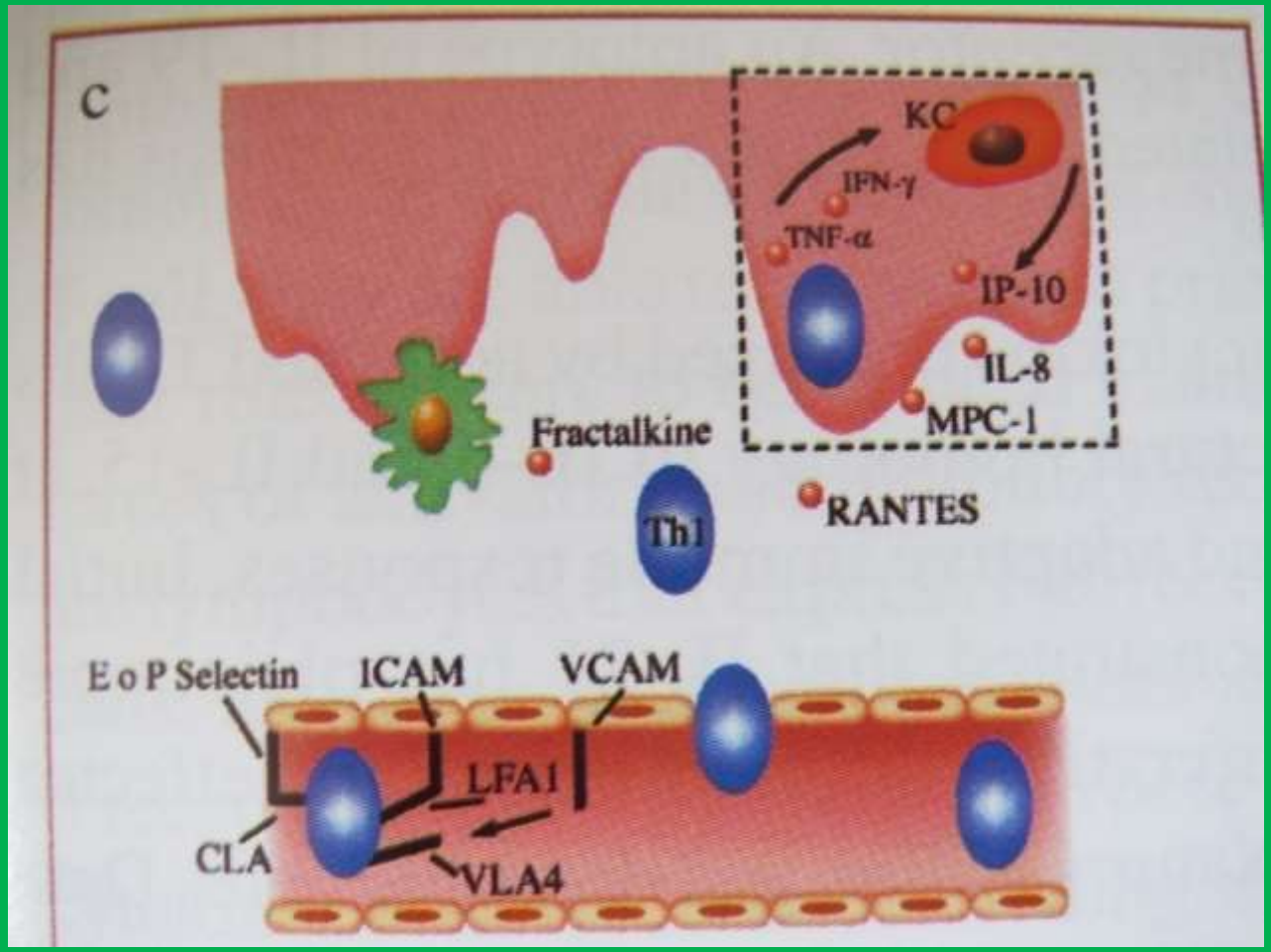
Integrin receptor on T cells (LFA-1 & VLA-4) +

Integrins on endothelial cells (ICAM-1 & VCAM-1)

(High affinity bond)

[Vascular cell adhesion molecule- Very late activation Ag]

Migration of activated T cells to skin



Pathogenesis: chemokines : T cell trafficking

small proteins (67-127 AA)—activation, differentiation & attraction of T cells (endo,LH,keratinocytes & monocytes)

4 groups (relative position of cysteine residues in AA sequence)

CC	CXC	CX3C	C
CCR	CXCR	CX3CR	CR

(7 transmembrane 'G' coupled receptors)

In psoriasis activated Th 1 cells------IFNɣ & TNFα----- keratinocytes----chemokines eg

a) IL8- recruits neutrophils,
b) MCP1, RANTES, IP10- recruits monocytes & Th1 cells
c) CX3CL (fractaline)-recruits monocytes & T cells
d) MIP3α-recruits APCs & CLA T cells

Pathogenesis: Cytokines

Activated T cells ----IL1, IL2, IFNɣ & TNFα (Th1 cytokines) --------Keratinocytes and dendritic cells-----EGF, GM-CSF, IL8 & TNFα---- chronic inflammatory cascade

CD4+ Choregrapher (dermis)

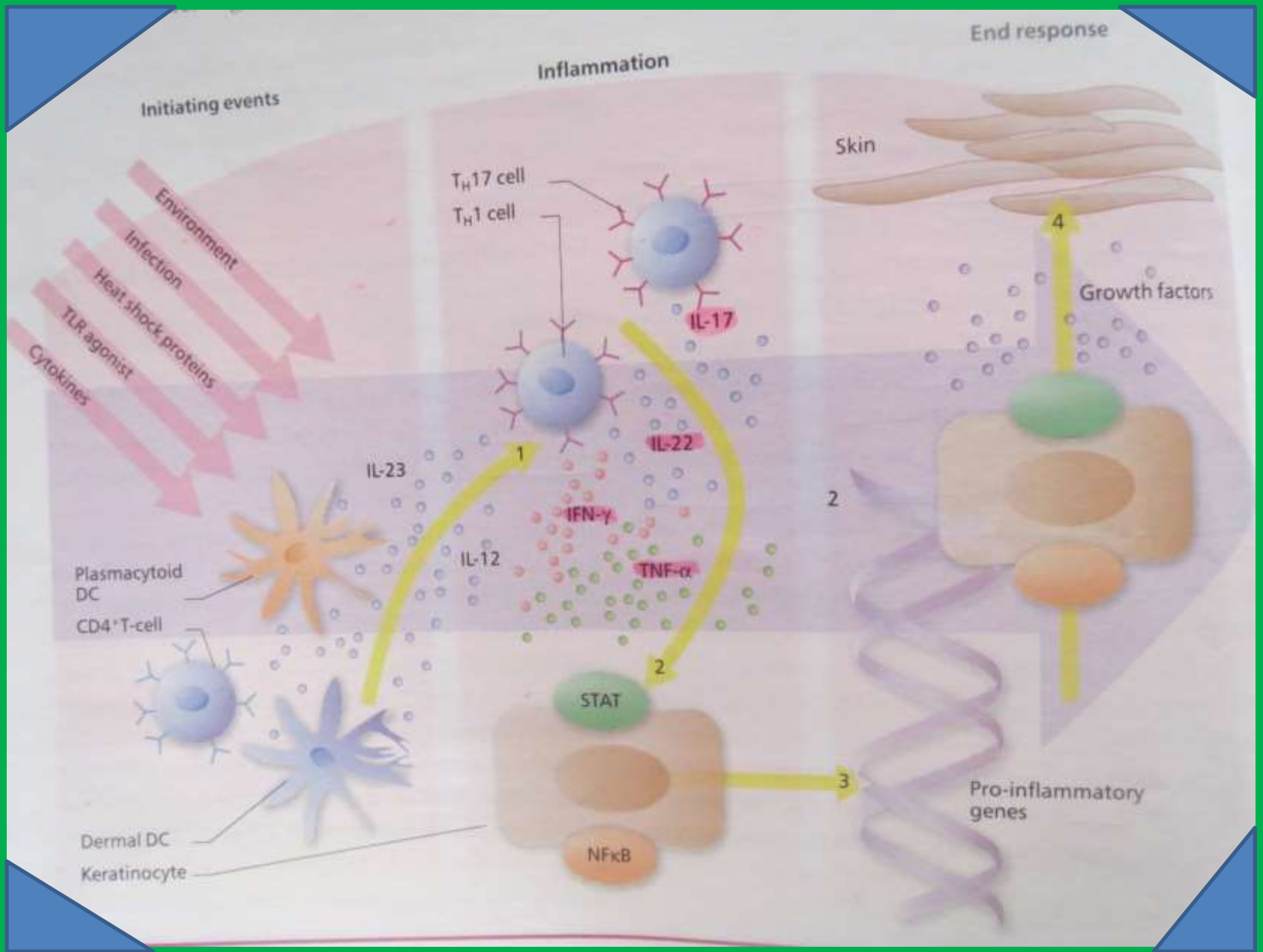
CD8+ Execute (epidermis)

NKT cells secrete IFNɣ

No regulatory T cells (CD10)

Dendritic cells (IL23)-----CD4+ T cells---- IL17 (Th17) --keratinocytes--- proinflammatory cytokines (IL8)

Potential cytokine network in psoriasis



Biologicals

TNFα inhibitors :

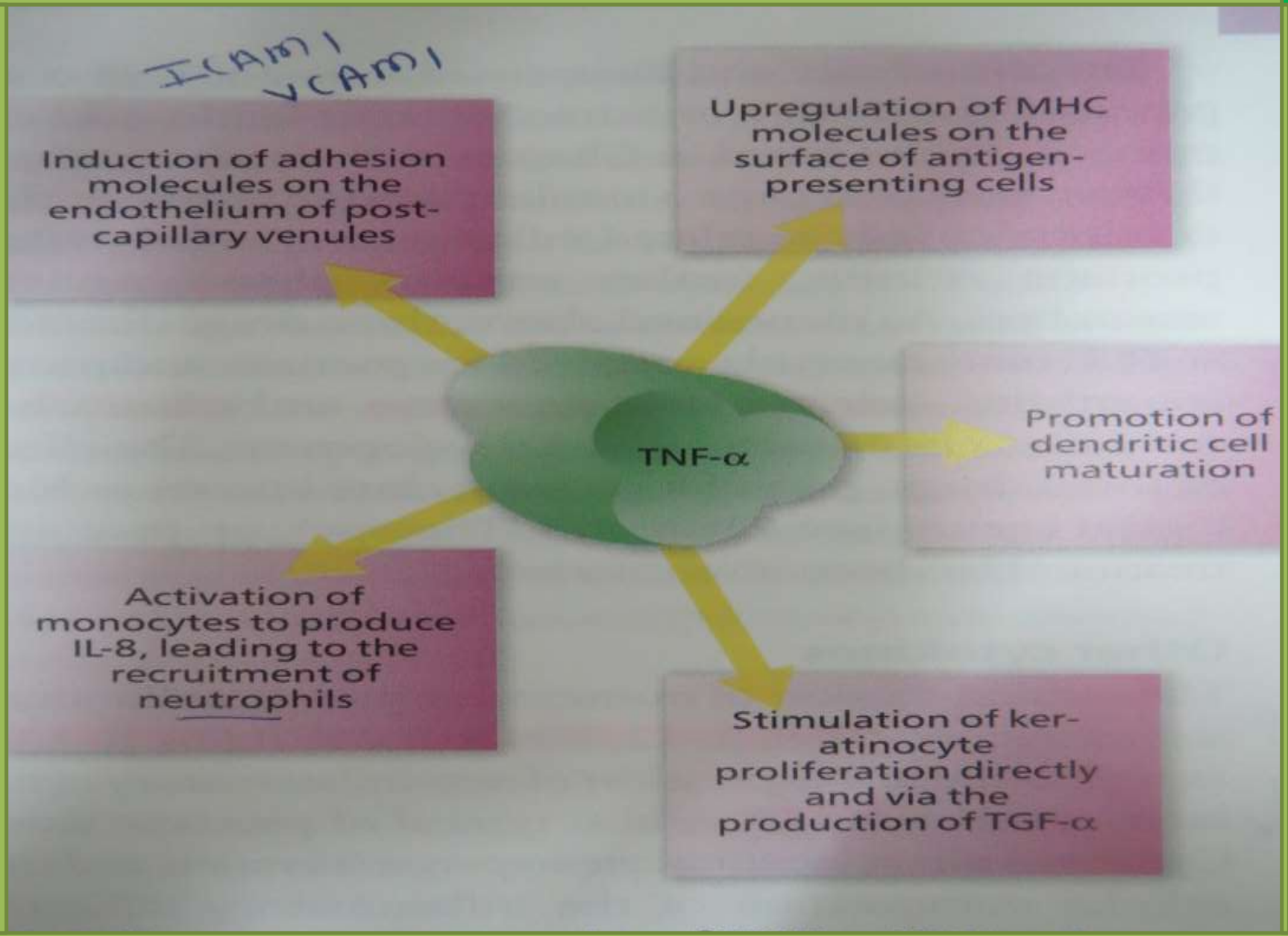
- Adalimumab
- Infliximab (soluble & membrane bound)
- Etanercept (soluble)

T cell modulators :

- Alefacept
- Efalizumab (withdrawn due to PML)

IL 12/23 inhibitors (anti p40 subunit) :

- Ustekinumab


ICAM1
VCAM1
Induction of adhesion molecules on the endothelium of post-capillary venules
Upregulation of MHC molecules on the surface of antigen-presenting cells
TNF-α
Promotion of dendritic cell maturation
Activation of monocytes to produce IL-8, leading to the recruitment of neutrophils
Stimulation of ker-atinocyte proliferation directly and via the production of TGF-α

TNF α inhibitors

1. Fatigue and depression (quality of life)
2. Psoriatic arthritis----------early the better
3. Loss of efficacy in minority
4. Can + methotrexate
5. > 5yrs safety experience (RA,UC,AS, Crohn's)
   - **Adalimumab** (soluble & membrane bound)
   - **Infliximab** (soluble & membrane bound)
   - **Etanercept** (soluble)

Dosages : TNF α inhibitors

Adalimumab

80 mg SC : 0, 1 weeks later 40 mg every 15 days

Infliximab

5mg/kg IV : 0, 2, 6 weeks later 2 monthly

Etanercept

50 mg SC : weekly or twice weekly x 3 months

Efficacy : TNF α inhibitors

Adalimumab

16 weeks : 80%

Infliximab

12 weeks :75% > PASI 75 reduction

Etanercept

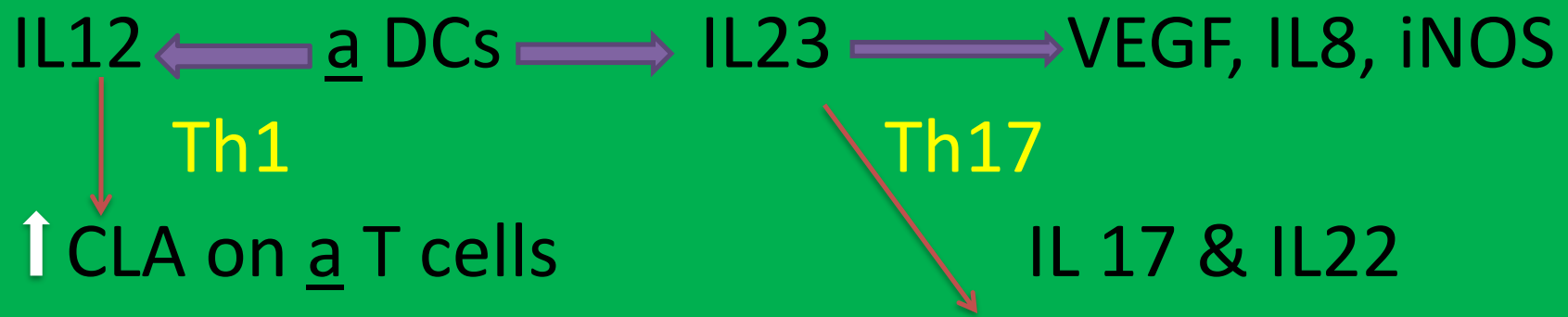
10 weeks :57%

55-60% patients > 20% joint improvement

Side Effects of TNF α inhibitors

- Injection site reactions (30%)
- Cardiac failure (infliximab)
- Infections (acute, TB, histoplasmosis)
- Lymphoma (?)
- Demyelinating neurologic disease(r/o MS)
- Hepatic toxicity

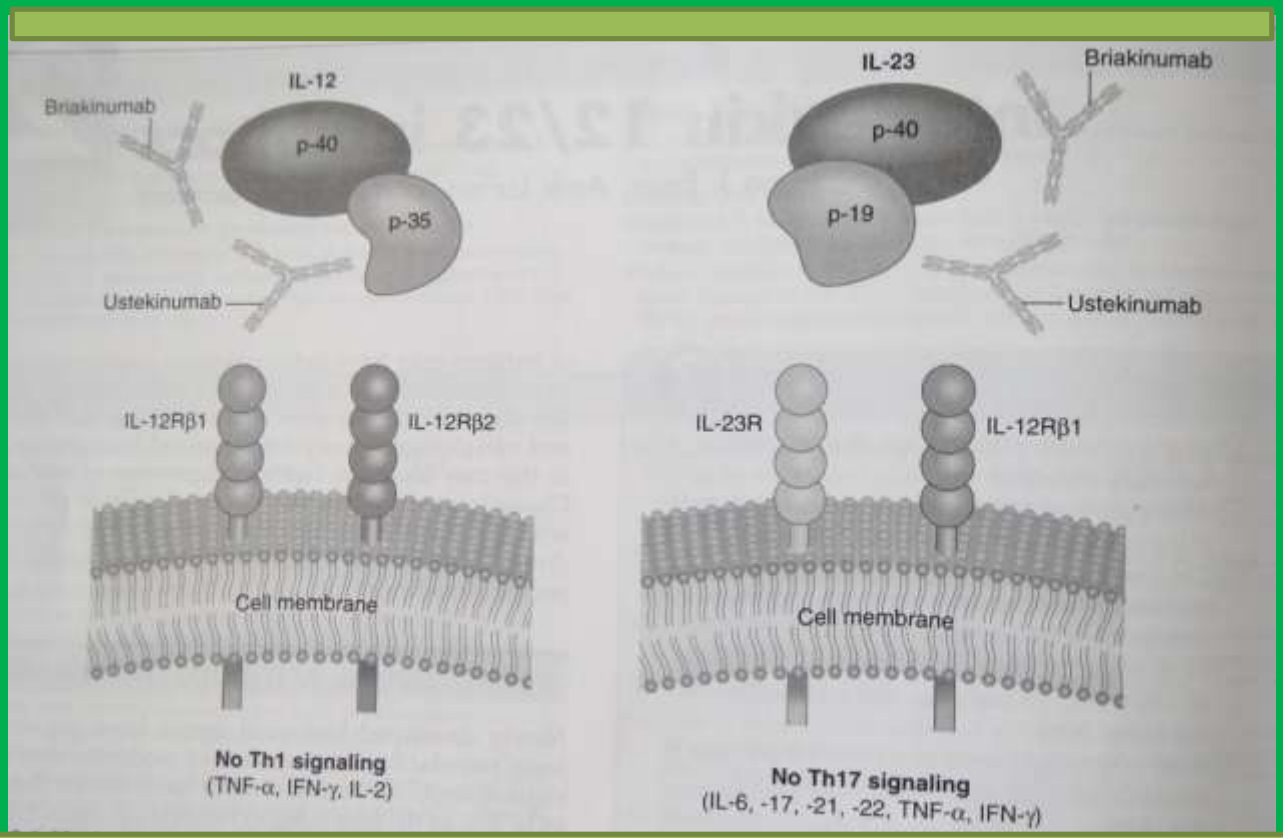
IL 12/23 inhibitors



P40 subunit common to both IL 12 & IL 23

Ustekinumab (anti p40 subunit)

IL 12/23 inhibitors



IL 12/23 inhibitors

Dosage : SC (IV in crohns & UC) 0, 4 and every 12 weeks

Efficacy : 66-76% > PASI 75 reduction 12 weeks

joint improvement +++

Side effects :

-relatively safe

-injection site reactions

-infections

-cardiac

T cell modulators

Efalizumab (withdrawn due to pml) against LFA-1

Alefacept

recombinant fusion protein (human LFA-3-Fc IgG1)

binds to CD2 receptor on T cells thus blocks LFA-3 & CD2interaction and T cell activation

also causes apoptosis of activated T cells

Dose : 15 mg IM weekly x 3 months

Efficacy : 17% (12 weeks) 53% (2^{nd} course) > 50PASI

Side effects of Alefacept

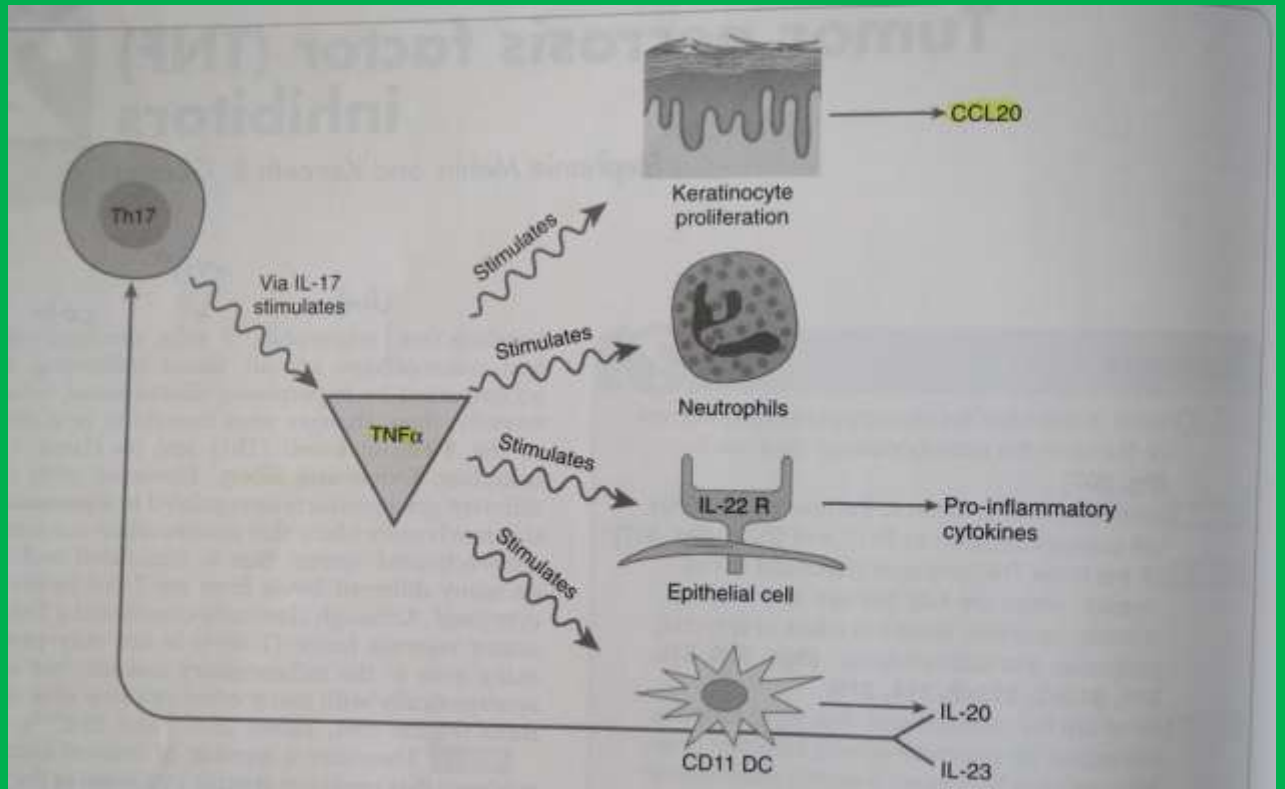
- Lymphopenia
- LFT elevation
- Serious Infections
- Malignancy
- Hypersensitivity
- Flu like syndrome

Conclusions

- **Molecules of the future**
- **Cost**
- **Long term safety**

Thank You

References



-1 Proposed role of TNF in psoriasis pathogenesis. TNF-α stimulates keratinocyte proliferation, which then releases additional natory cytokines – importantly CC20. It can also directly stimulate neutrophils. It upregulates IL-22R on epithelial cells, which via also induces important inflammatory cytokines. The CD11 DC, once stimulated by TNF-α, make IL-20 and IL-23, which are stimulators of the TH17 cell whose product, IL-17, again induces TNF-α.

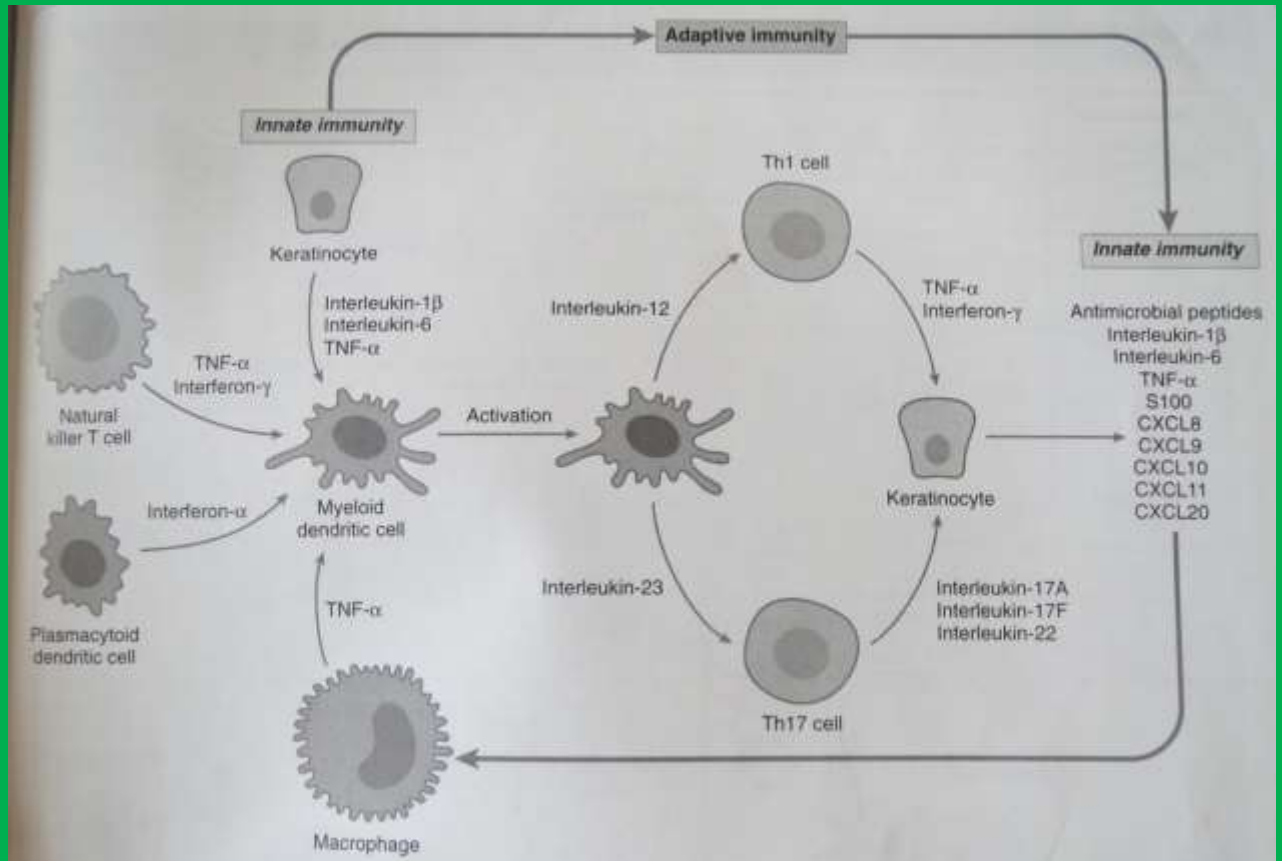


Figure 26-2 Key cells and mediators in the transition from innate to adaptive immunity in psoriasis. Adapted from Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009;361:496–509.

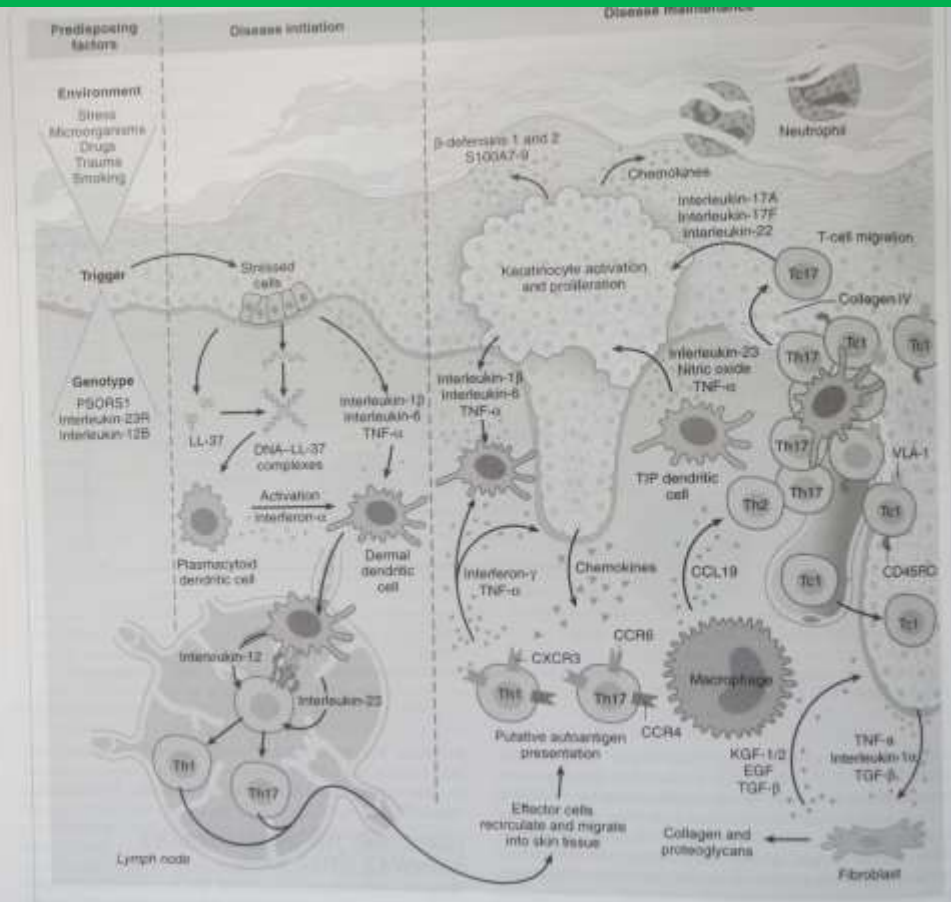


Figure 26-3 Proposed schema of the evolution of a psoriatic lesion from initiation to maintenance of disease. Adapted from Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009;361:496–509.

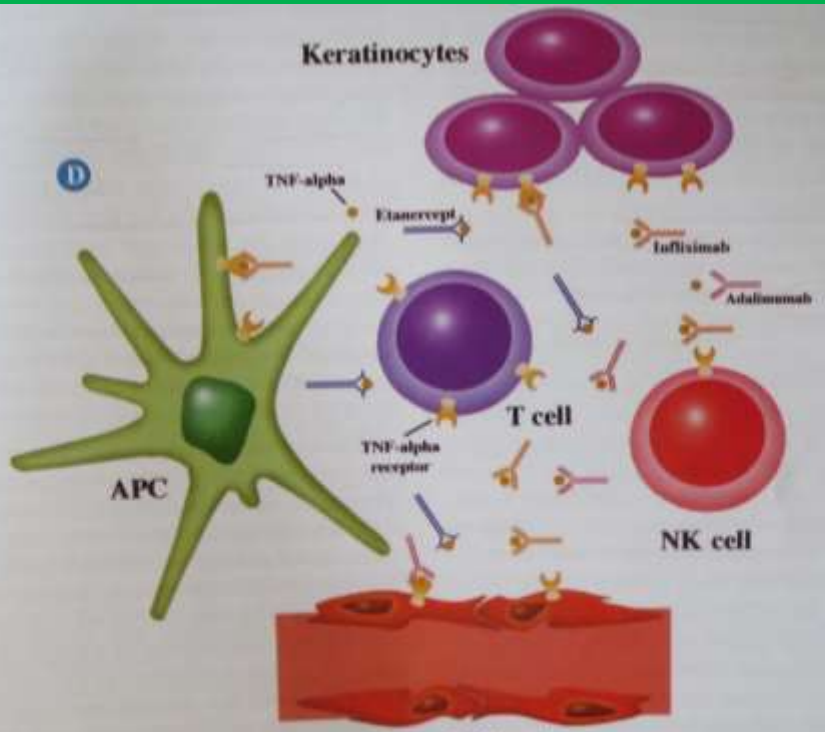
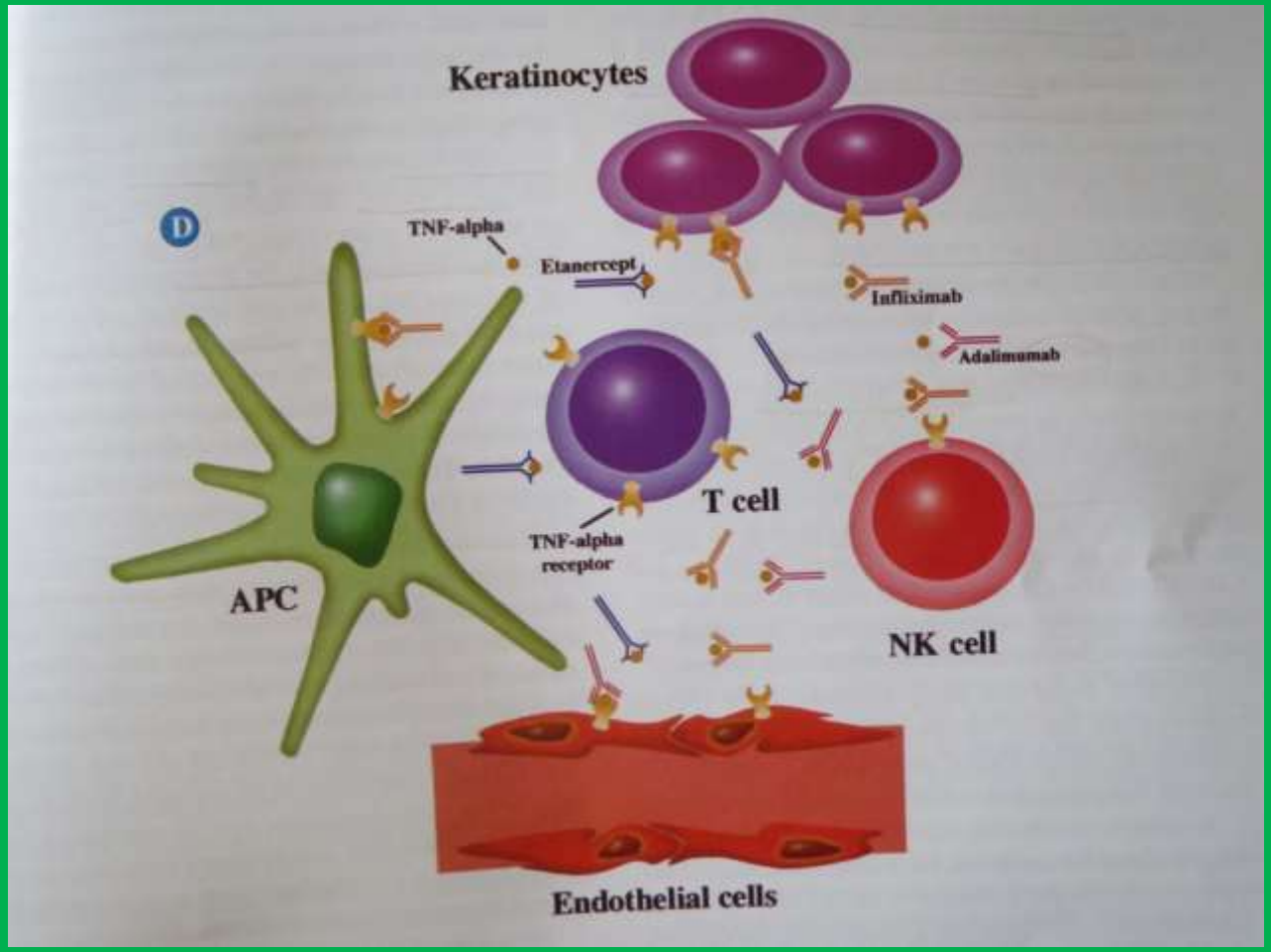
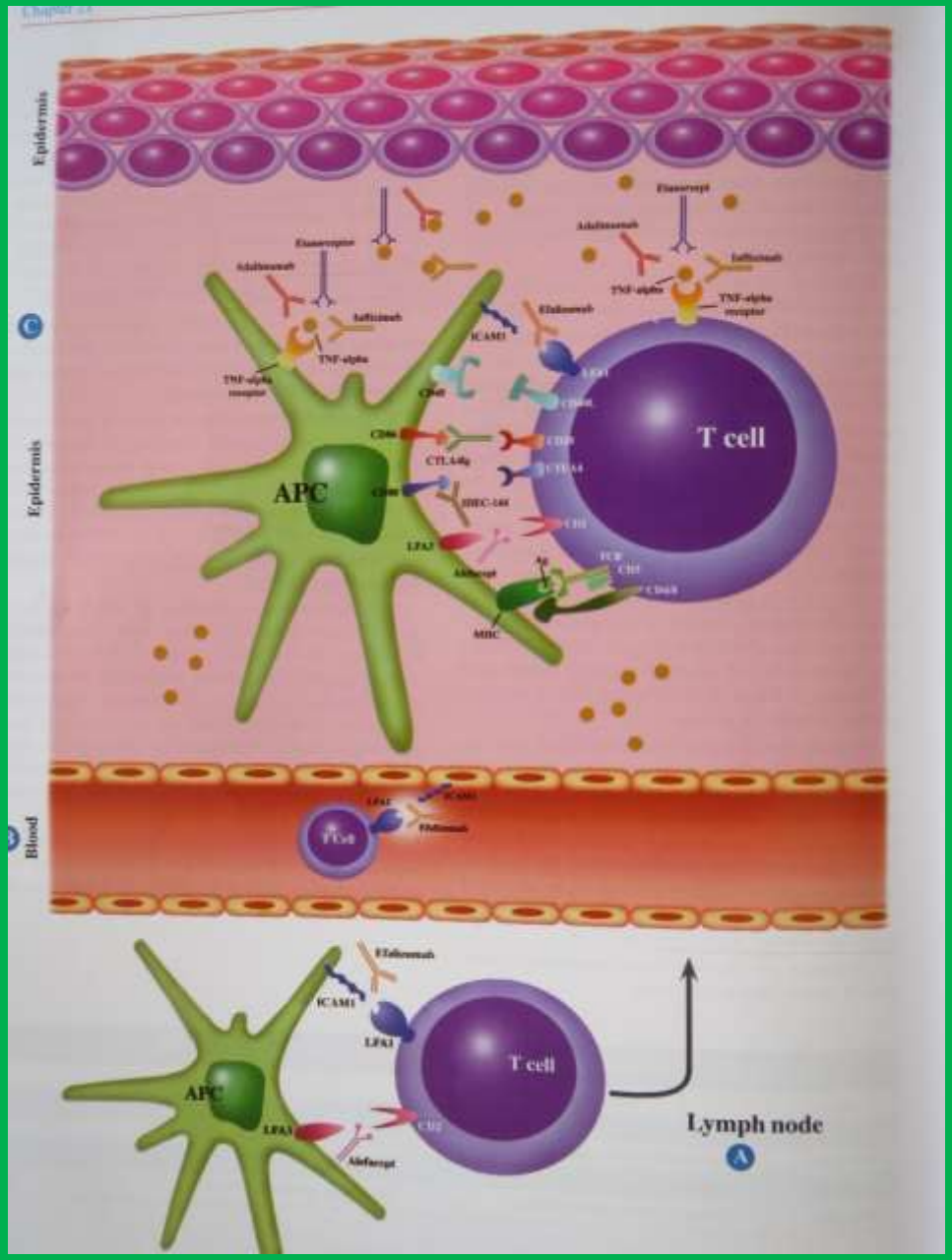
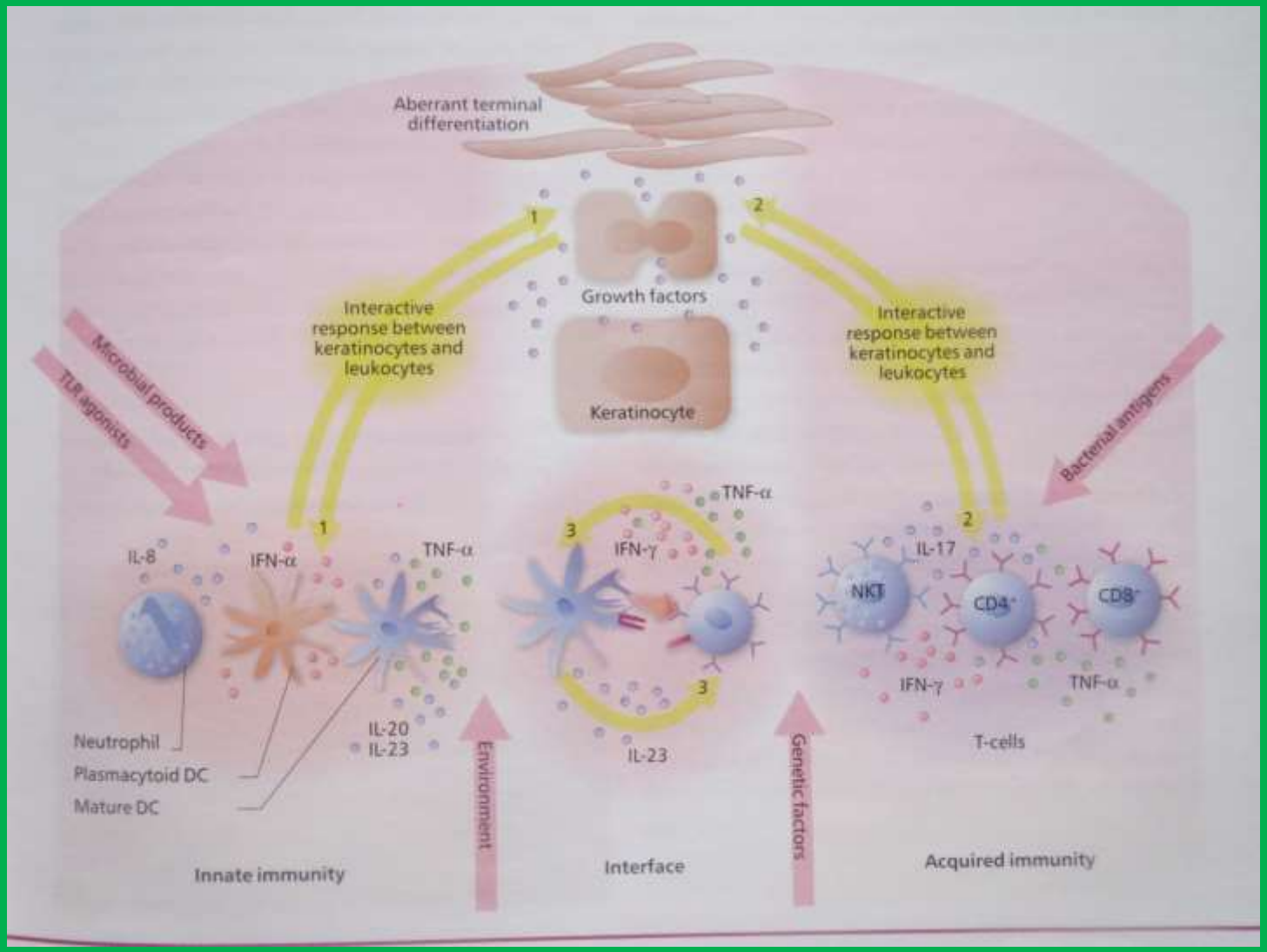


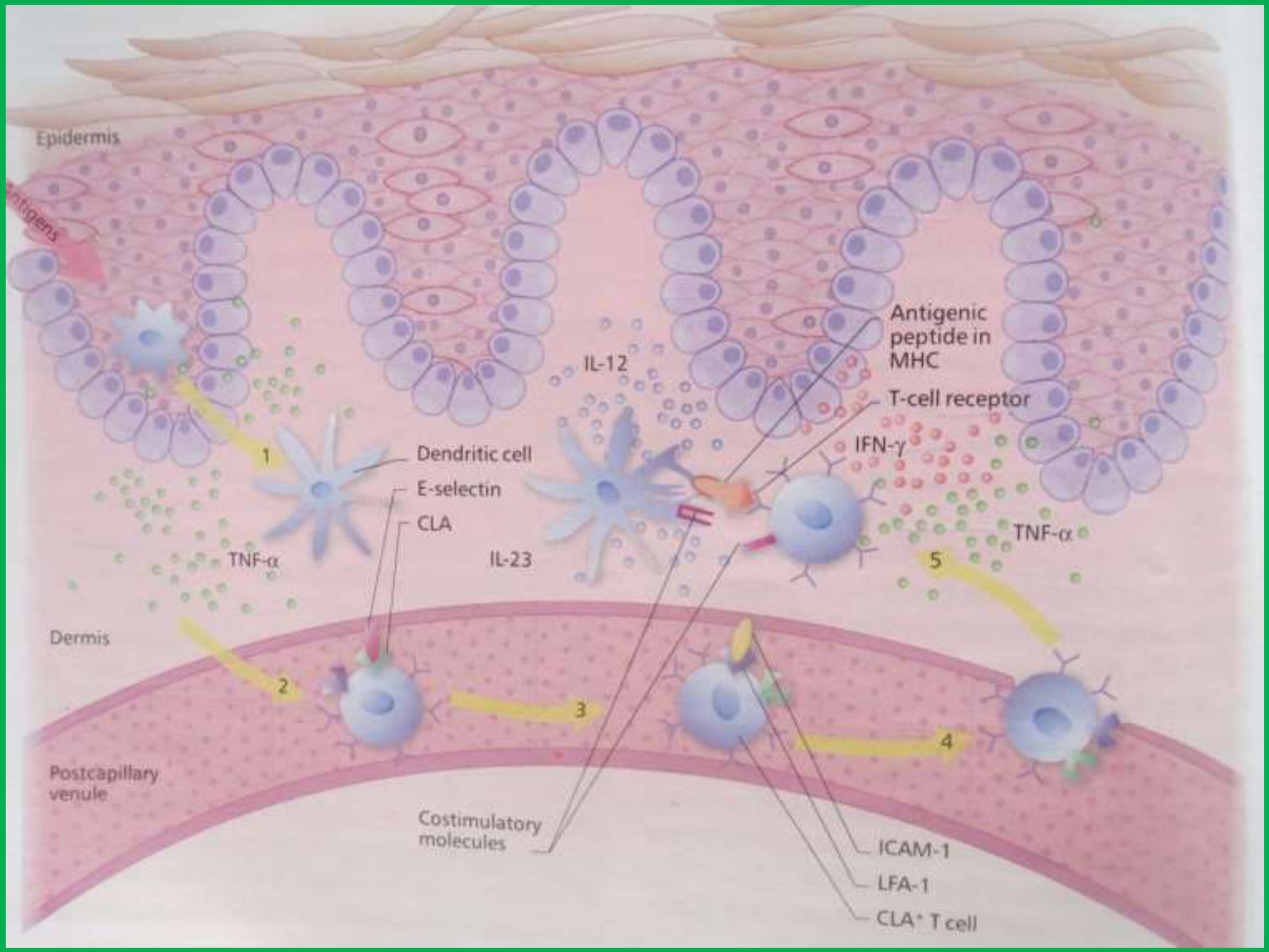
Fig. 21.1 - The interaction between antigen-presenting cells (APCs) and T lymphocytes (A,C) plays a crucial role in the pathogenesis of psoriasis. Several biological agents selectively target molecules expressed on these cells' surface. B) Furthermore, efalizumab, an anti-CD11a, inhibits T cells migration to the skin. D) Target cells of anti-TNF-α agents (adalimumab, etanercept and infliximab)

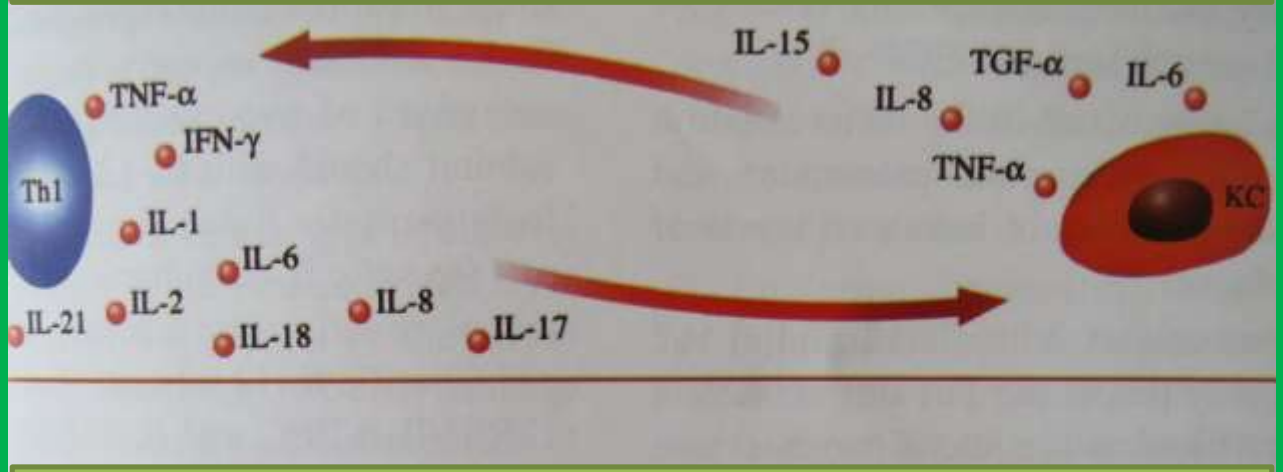

Keratinocytes
D
TNF-alpha
Etanercept
Infliximab
Adalimumab
T cell
TNF-alpha receptor
APC
NK cell
Endothelial cells


Epidermis
Epidermis
Blood
APC
T cell
TNF-alpha
TNF-alpha receptor
ICAM1
CTLA4Ig
HHC-1st
LFA1
MHC
APC
T cell
ICAM1
LFA1
Lymph node
A


Aberrant terminal differentiation
1
2
Growth factors
Keratinocyte
Interactive response between keratinocytes and leukocytes
Interactive response between keratinocytes and leukocytes
Microbial products
TLR agonists
Bacterial antigens
IL-8
IFN-α
TNF-α
1
3
IFN-γ
TNF-α
2
IL-17
NKT
CD4+
CD8+
IFN-γ
TNF-α
IL-20
IL-23
IL-23
Neutrophil
Plasmacytoid DC
Mature DC
T-cells
Environment
Genetic factors
Innate immunity
Interface
Acquired immunity

The interplay of T cells & APCs in psoriasis




IL-15
TGF-α
IL-6
IL-8
TNF-α
TNF-α
IFN-γ
Th1
KC
IL-1
IL-6
IL-21
IL-2
IL-8
IL-18
IL-17