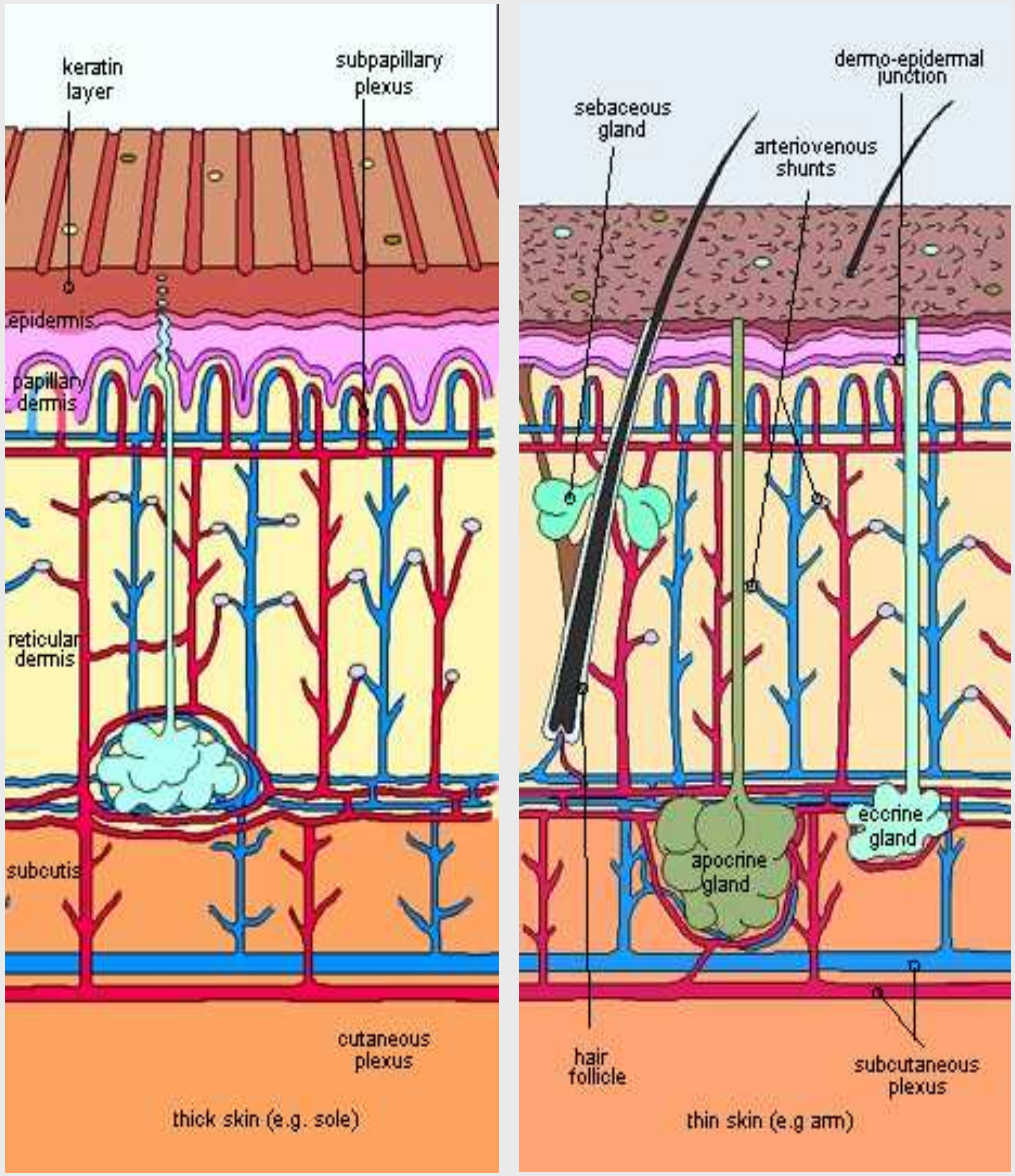
LA PELLE

- Interfacie tra organismo e ambiente esterno
- Costituisce circa 1/6 del peso totale

- Consta di tre strati:
  - epidermide (tessuto epiteliale)
  - derma (tessuto connettivo di sostegno)
  - ipoderma (tessuto connettivo di sostegno)

La pelle:

architettura

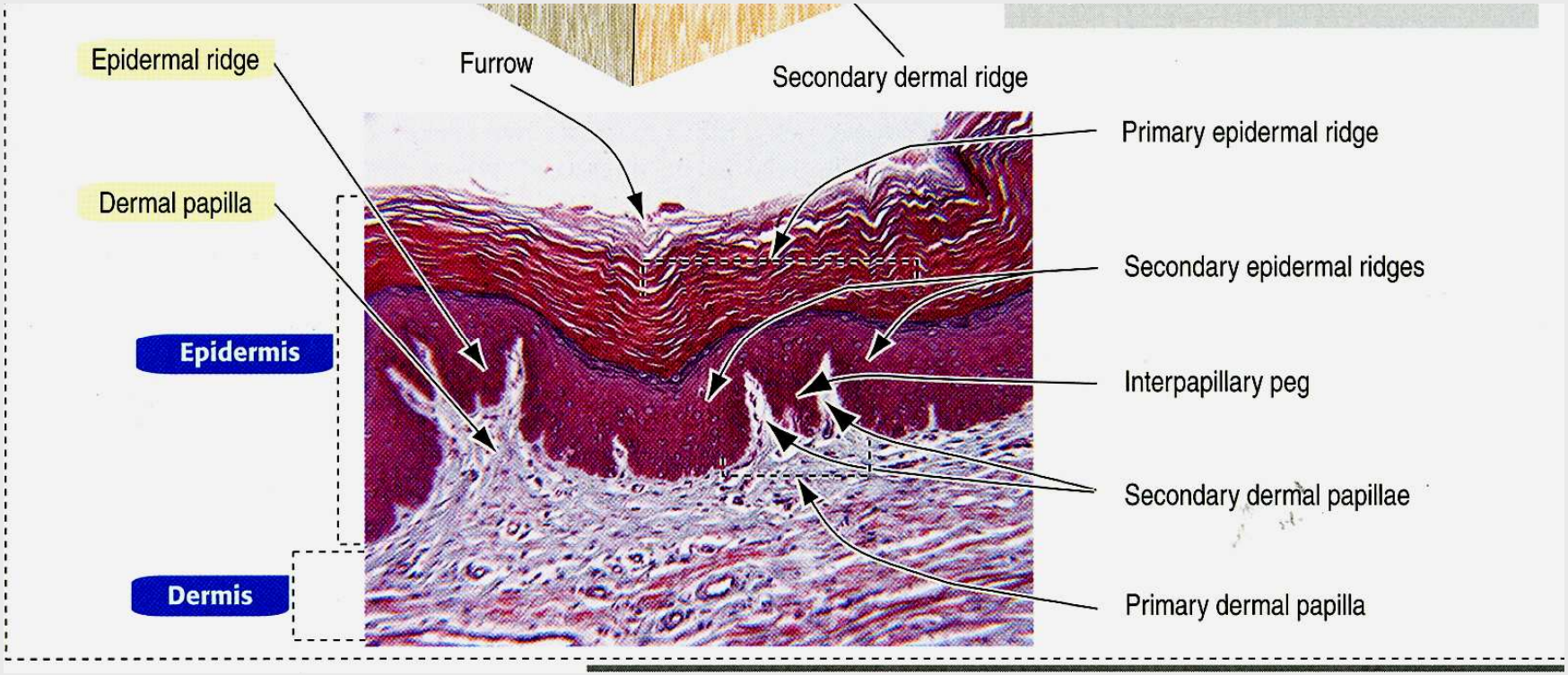


LA PELLE

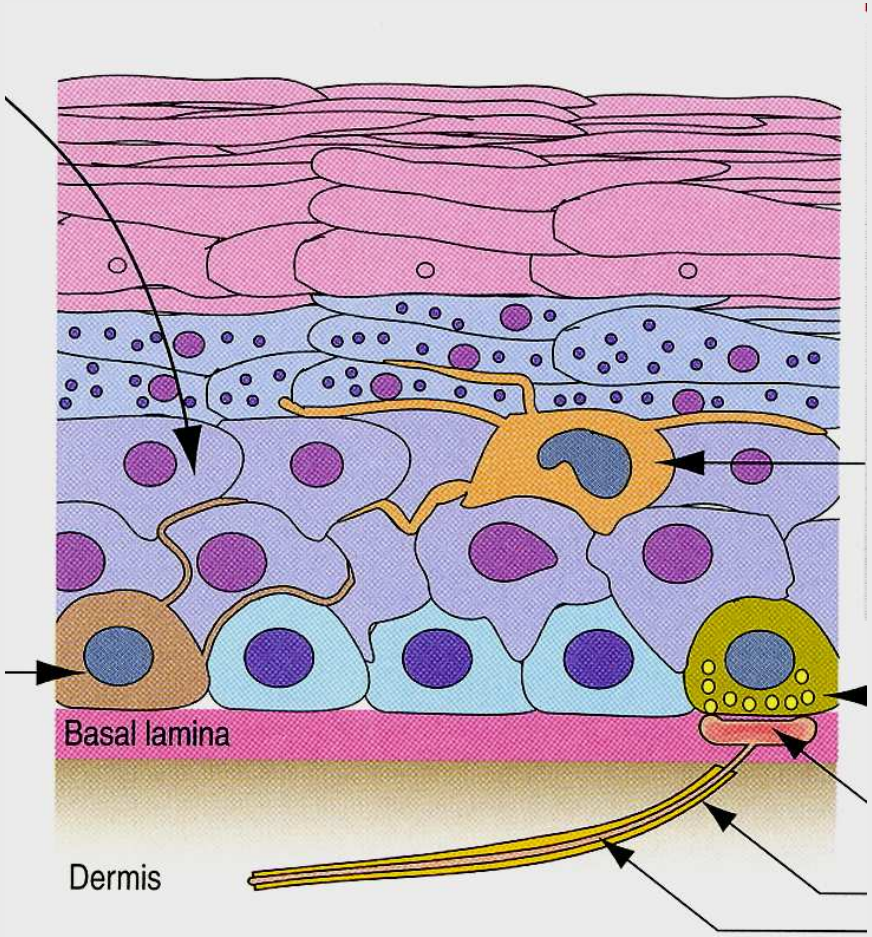
FUNZIONI

- protettiva
- sensoriale
- termoregolatrice
- metabolica
- secretoria

La pelle


Epidermal ridge
Furrow
Secondary dermal ridge
Primary epidermal ridge
Dermal papilla
Secondary epidermal ridges
Epidermis
Interpapillary peg
Secondary dermal papillae
Dermis
Primary dermal papilla

Le cellule dell’epidermide



Epidermide

Ci sono quattro tipi cellulari:

- Cheratinociti
- Melanociti
- Cellule di Langherans
- Cellule di Merckel

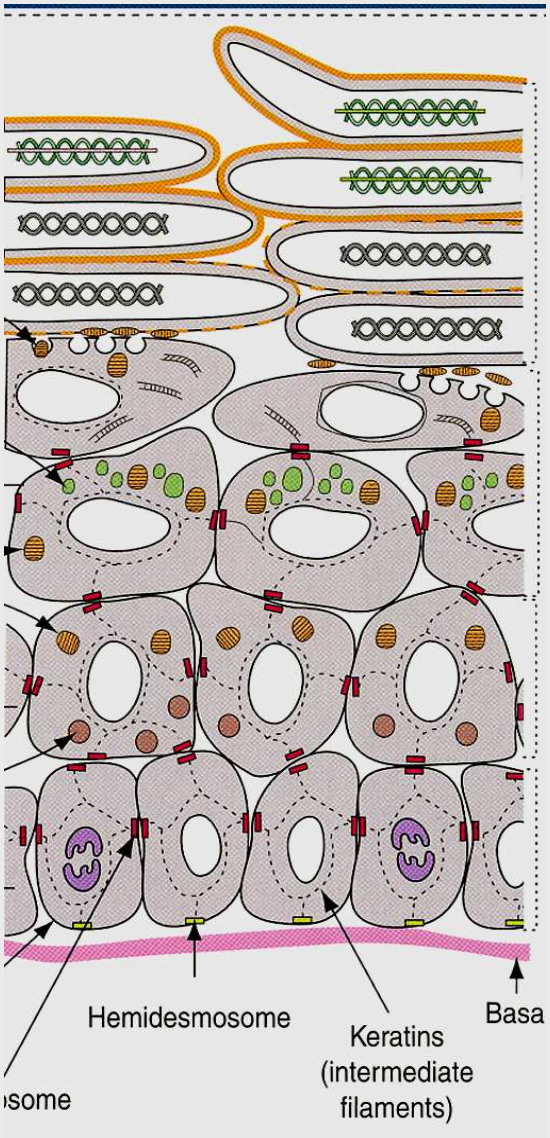
EPIDERMIDE

estrusione di lipidi

granuli di profilaggrina

granuli lamellari

melanosomi



filaggrina

desquamazione

profilaggrina

loricrina, K2e, K9

K1, K10

maturazione

Dsg1, Dsc1

Involucrina, Dsg3, Dsc3

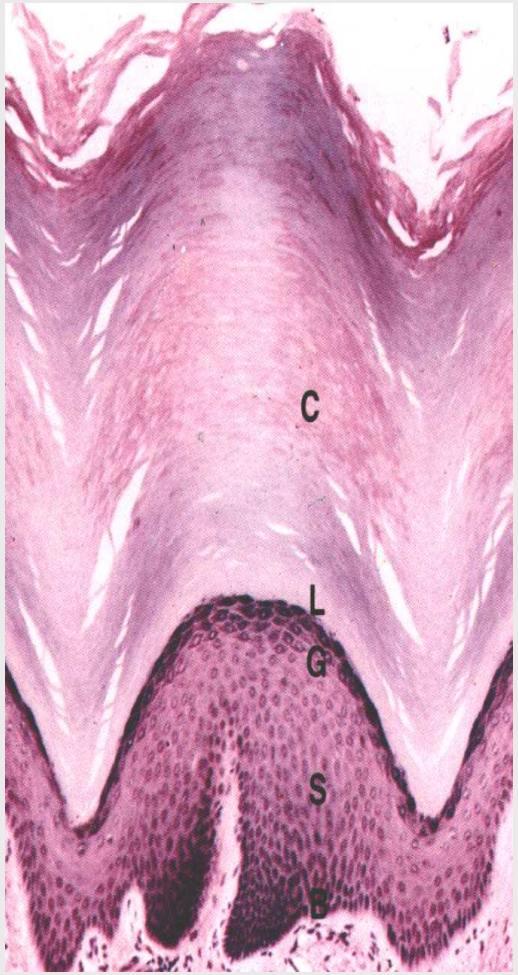
K5, K14

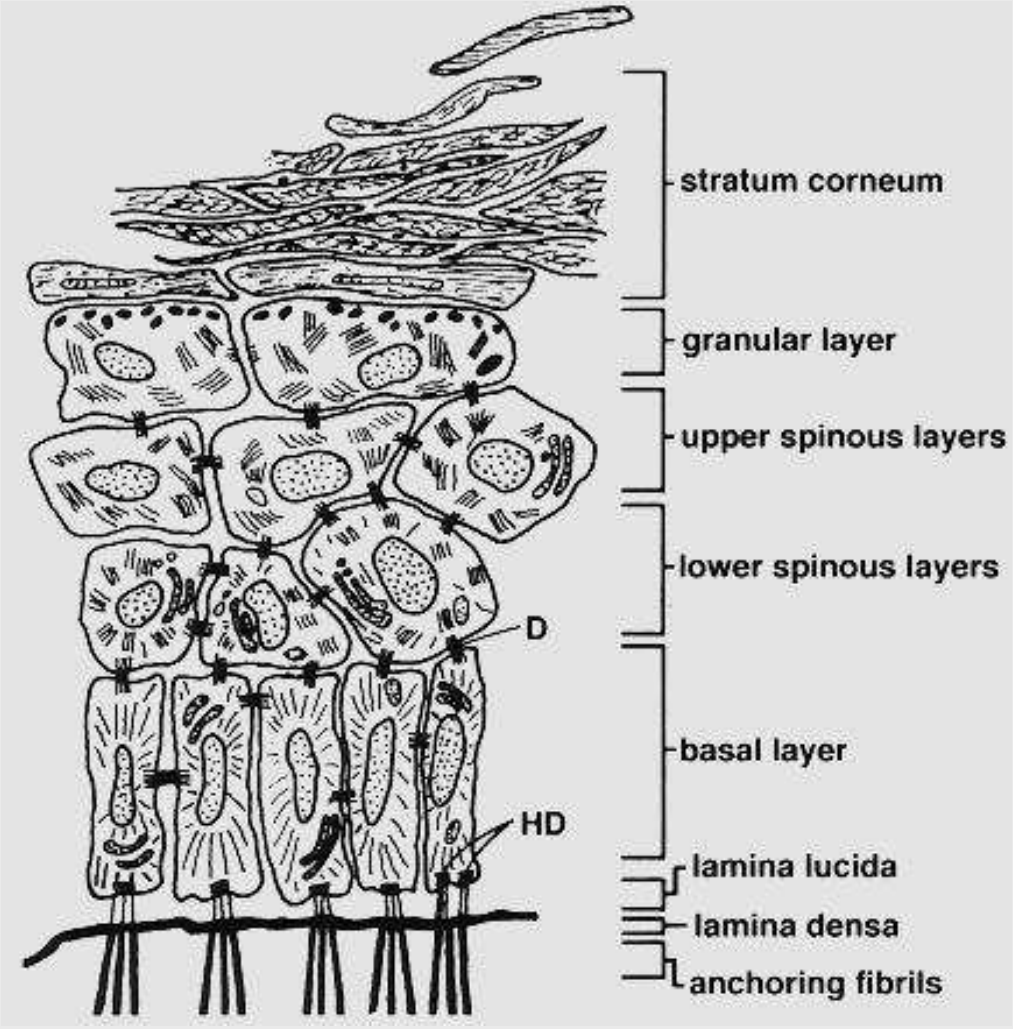
Dsg2, Dsc2

proliferazione

α6β4

L’epidermide spessa: 5 strati



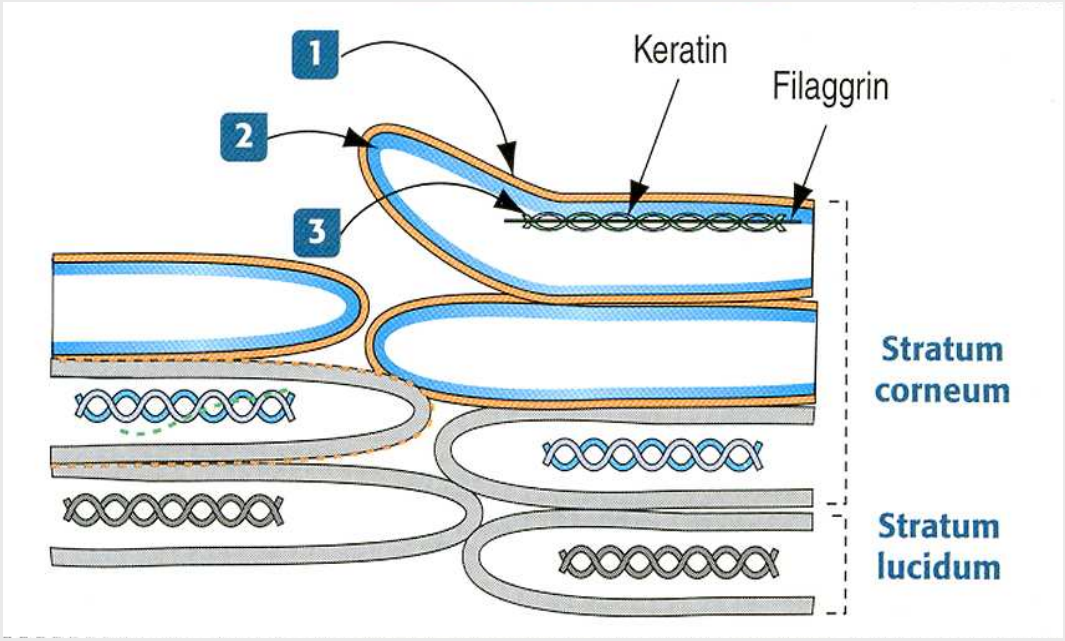


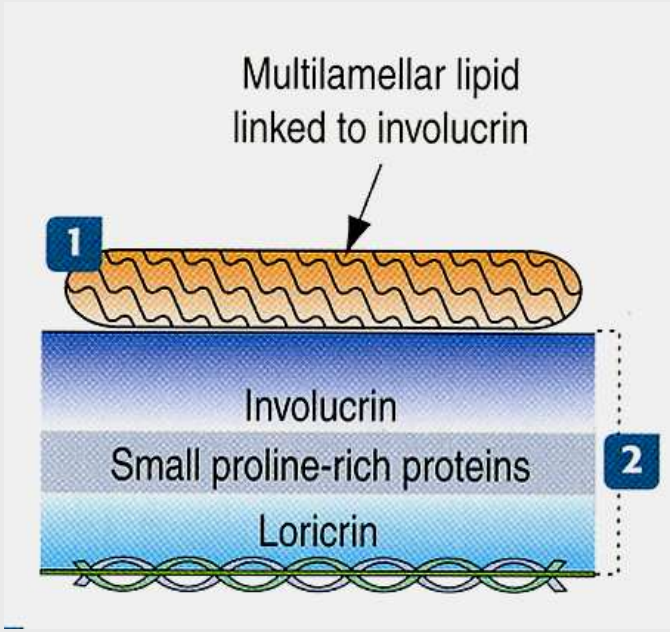
3-5 strati

4-8 strati

1 strato

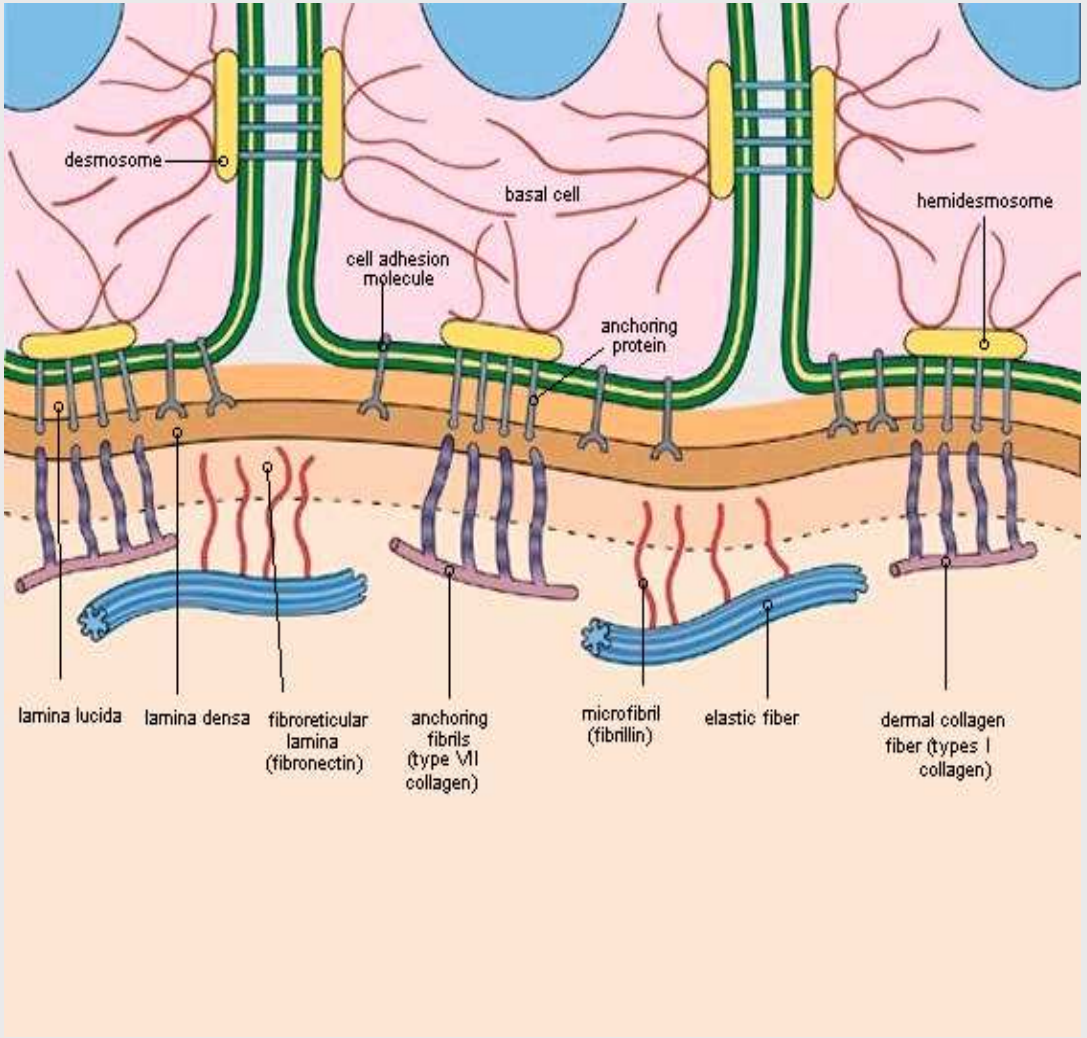
Epidermide come barriera



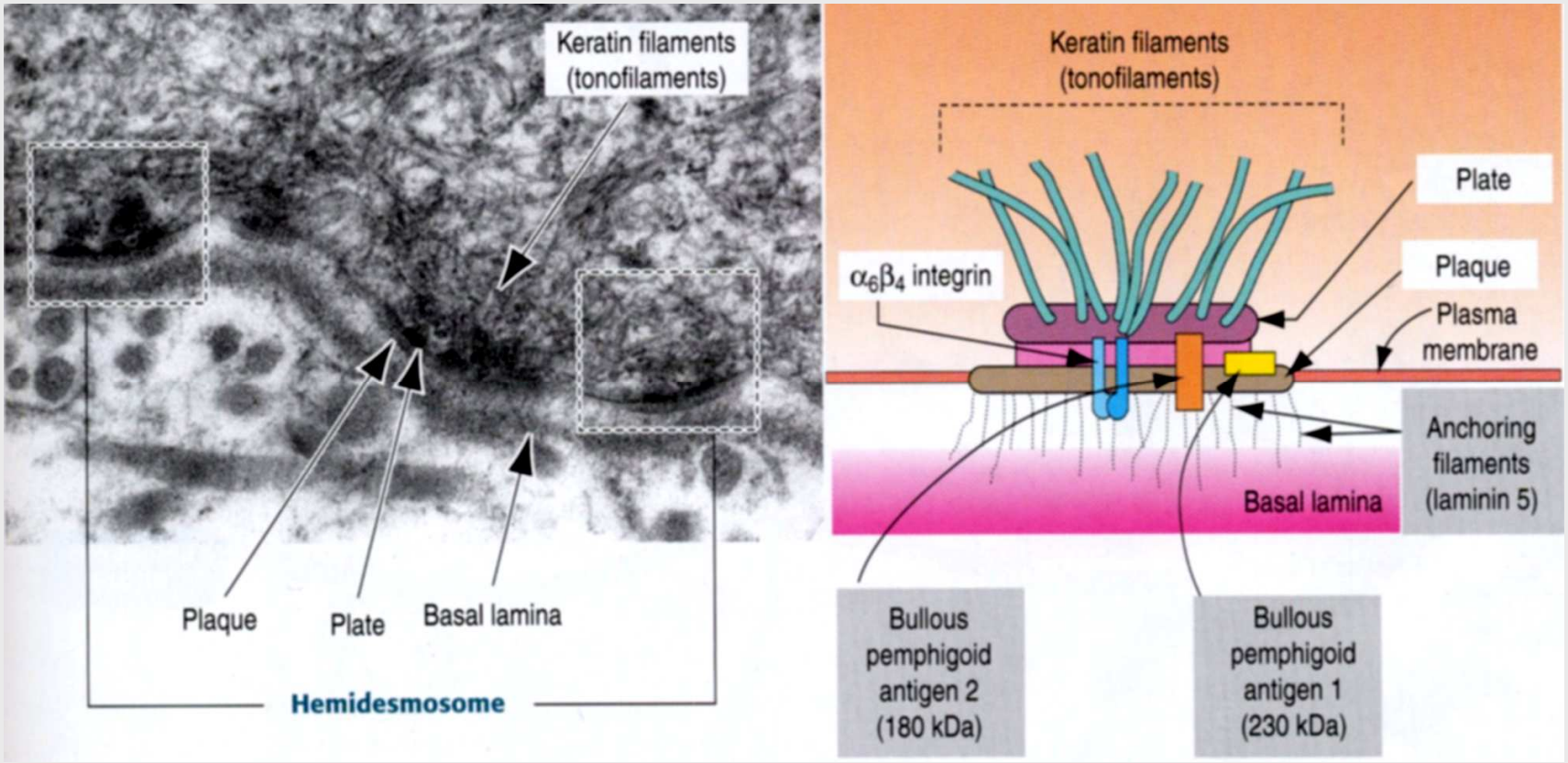


La pelle:

giunzione
dermo-epidermica



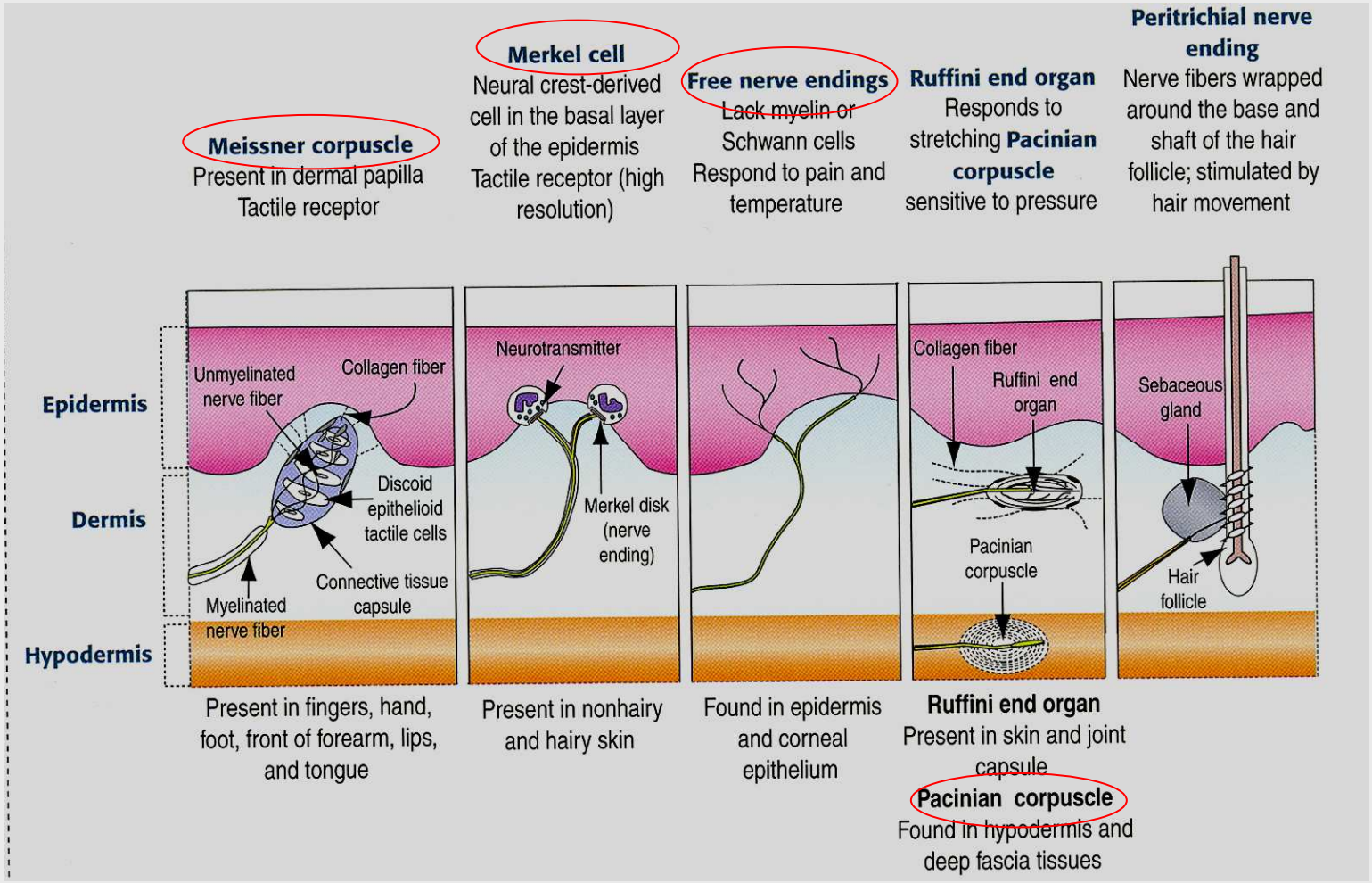
La pelle: giunzione dermo-epidermica



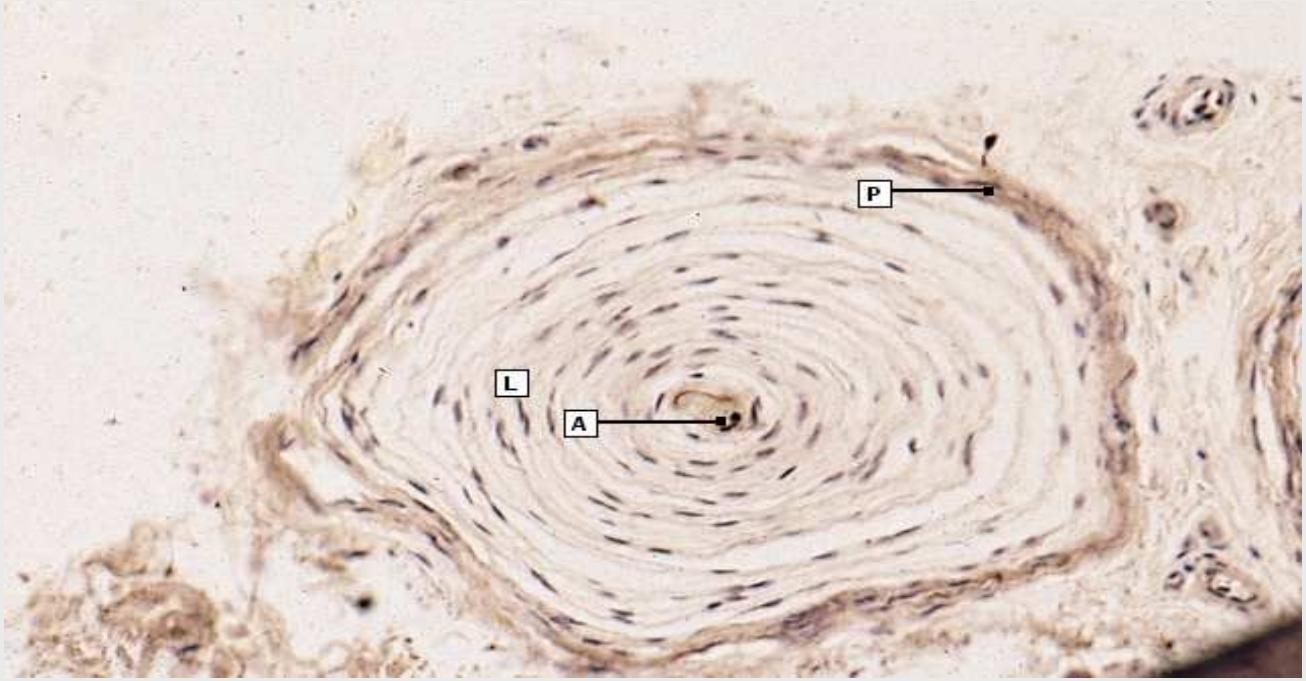
Mutazioni delle cheratine e malattie della pelle

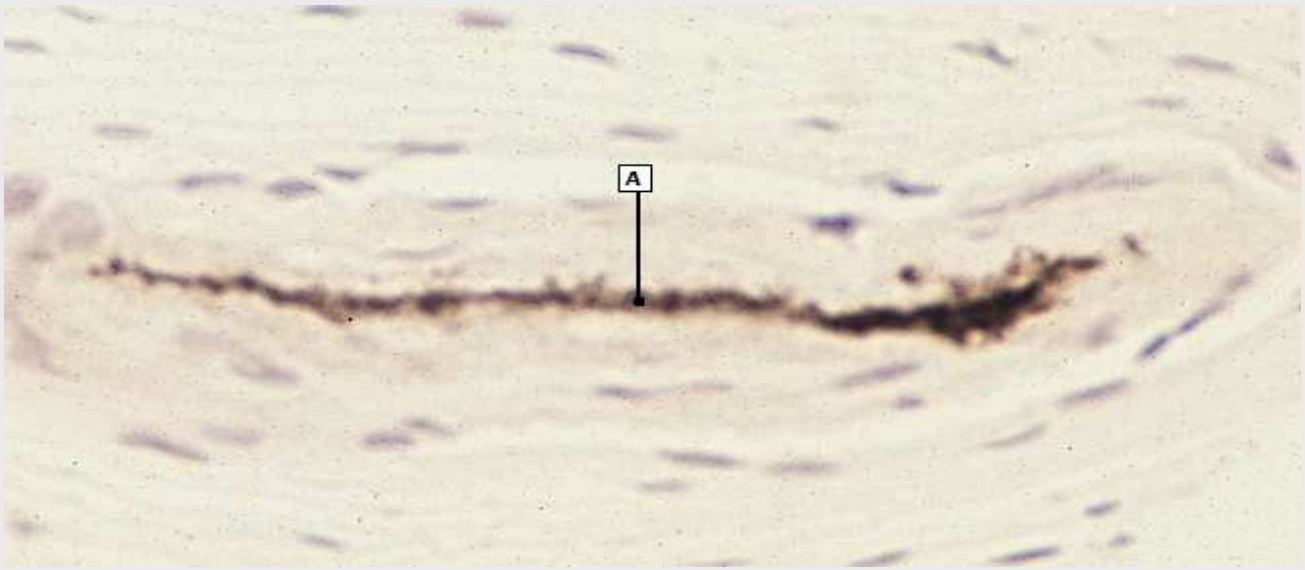
- K2e →ictiosi bullosa di Siemens
- K9 → cheratoderma epidermolitica palmoplantare
- K1 →ipercheratosi epidermolitica
- K5 o K14 → epidermolisi bullosa semplice

Recettori per la sensibilità

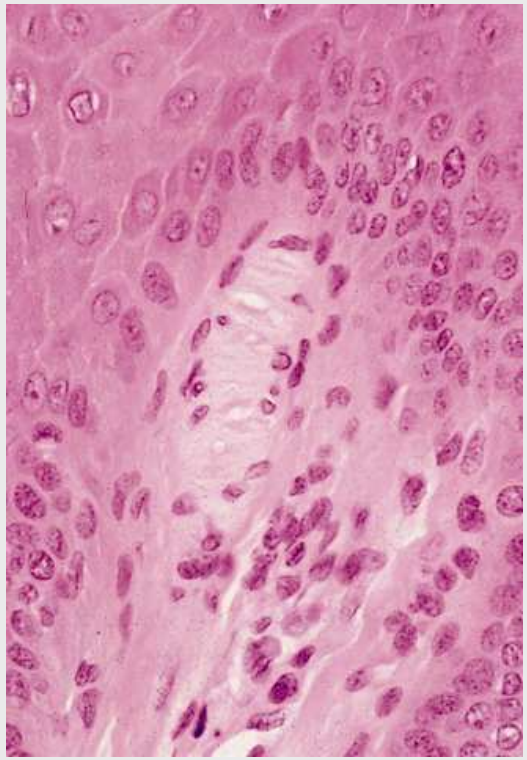


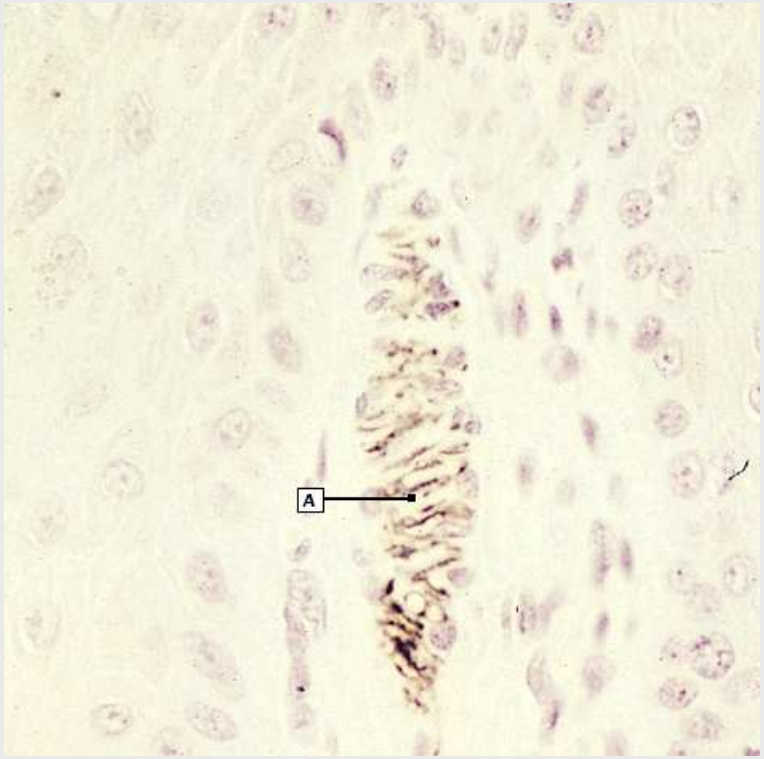
Corpuscolo del Pacini





Terminazioni nervose cutanee: corpuscolo di Meissner

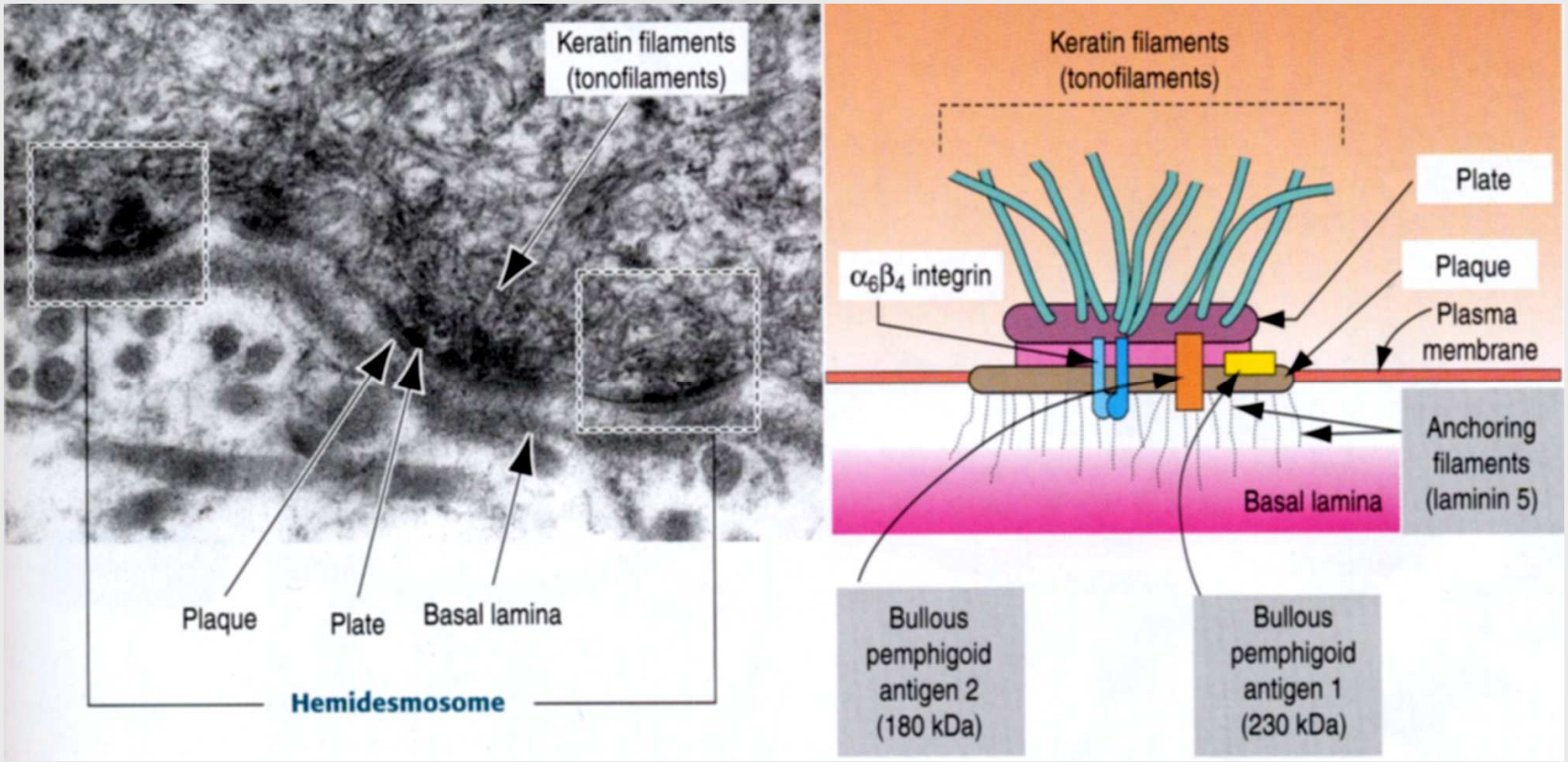




L’EPIDERMIDE: mantenimento

- Emivita del cheratinocita: ca. 30 gg.
- → Turnover dell’epidermide
- → le cellule morte (squame cornee) vengono continuamente rimpiazzate da quelle sottostanti.

La pelle: giunzione dermo-epidermica: antigeni del penfigo, integrine $\alpha 6\beta 4$ e $\alpha\beta 1$



L’EPIDERMIDE: mantenimento

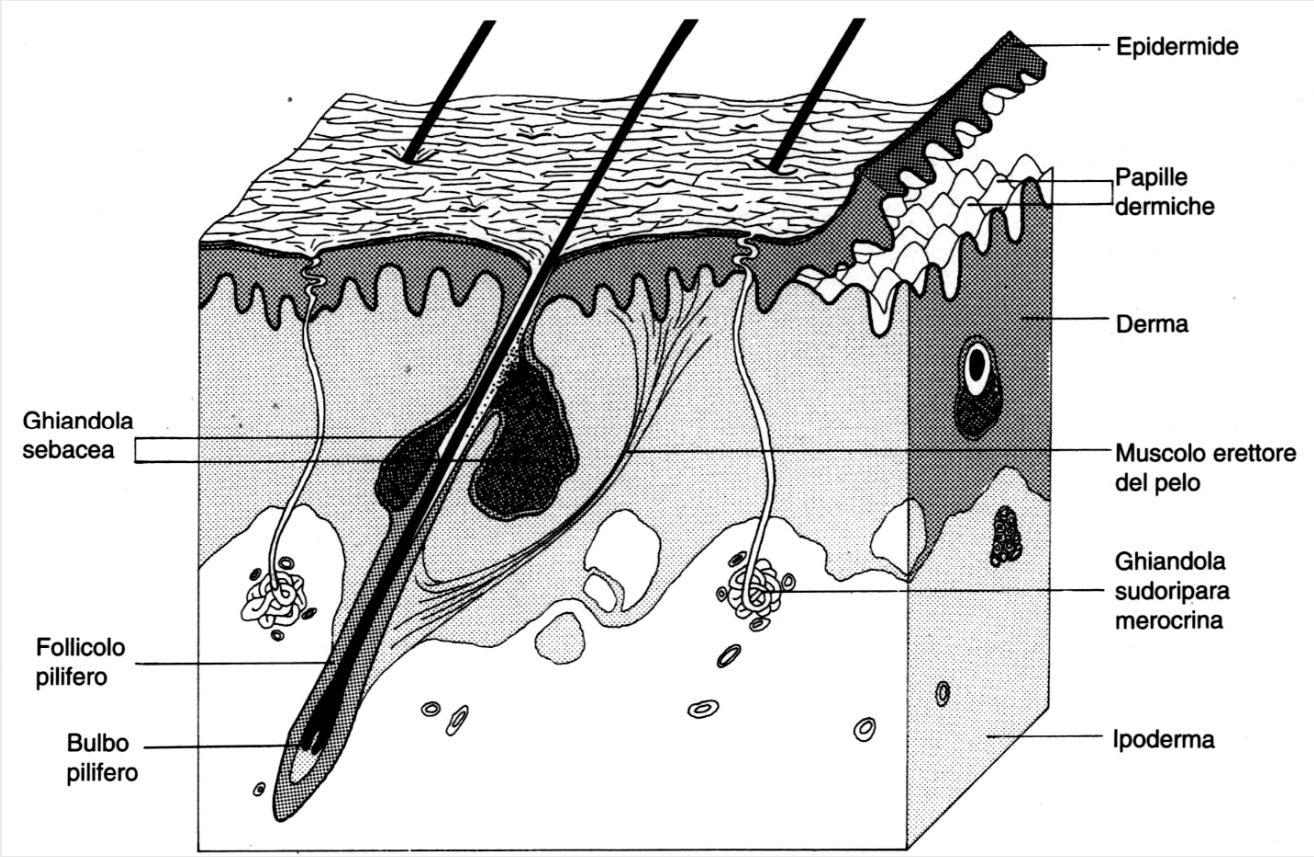
- Ci sono tre tappe nella vita del cheratinocita (vita media di ca. 30 gg), che avvengono in precise localizzazioni:

- Proliferazione (cellula staminale: integrina β1+) nello strato basale
- Maturazione negli strati spinoso e dei granuli (cellule integrina β1-)
- Desquamazione e morte nello strato corneo

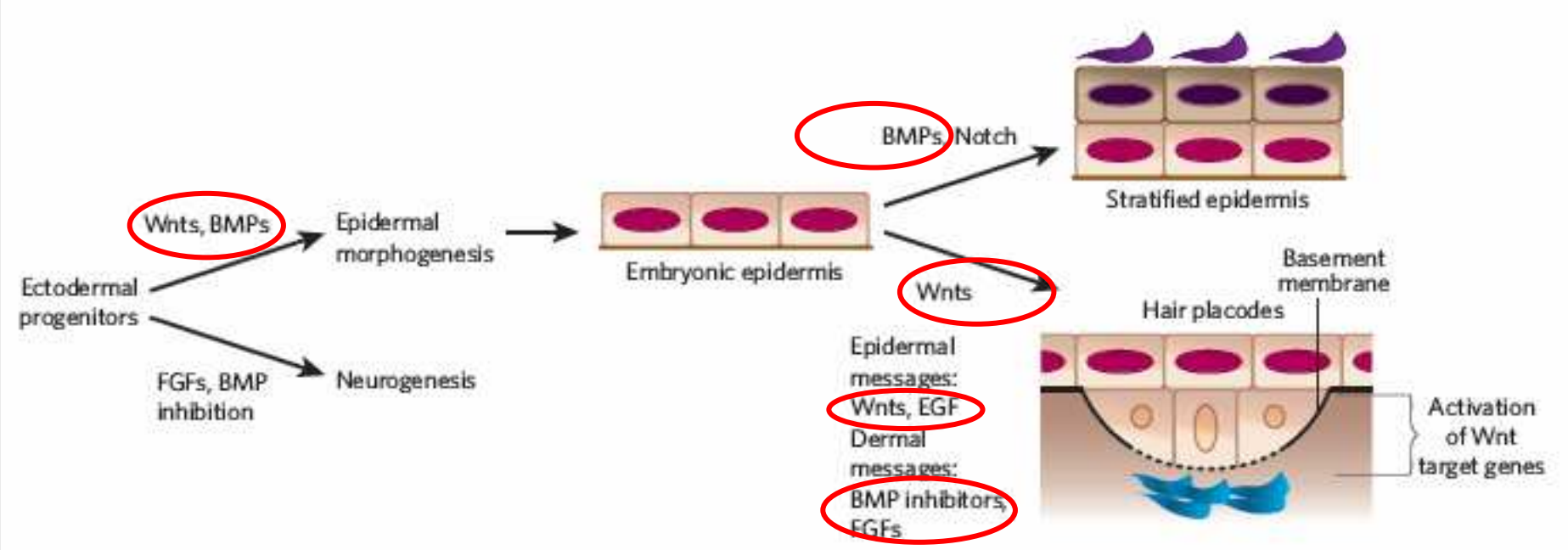
L’EPIDERMIDE: riparazione

- Membrana basale, ECM, ormoni e fattori di crescita stimolano le cellule rimaste.
- Acido retinoico, fattore di crescita epidermico (EGF), fattore di crescita per cheratinociti (KGF)

LA PELLE: annessi cutanei (mantenimento)

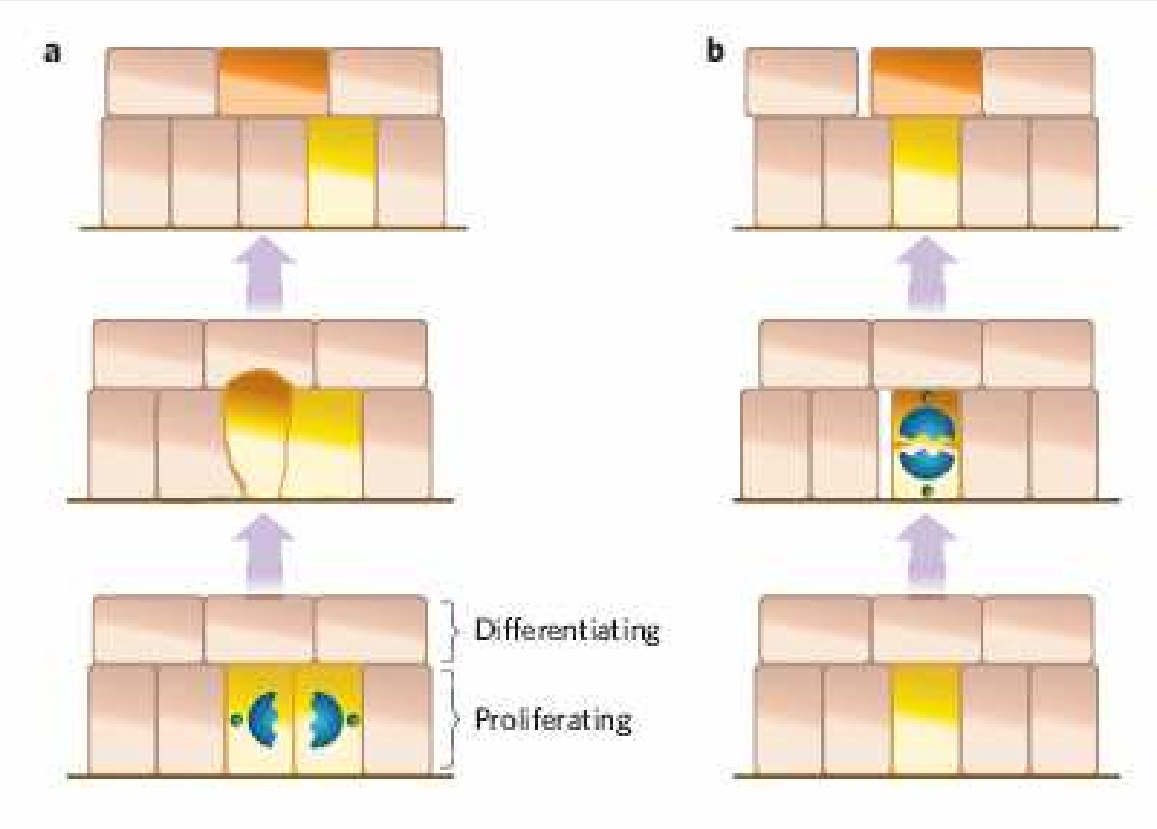


La scelta del destino delle cellule epiteliali



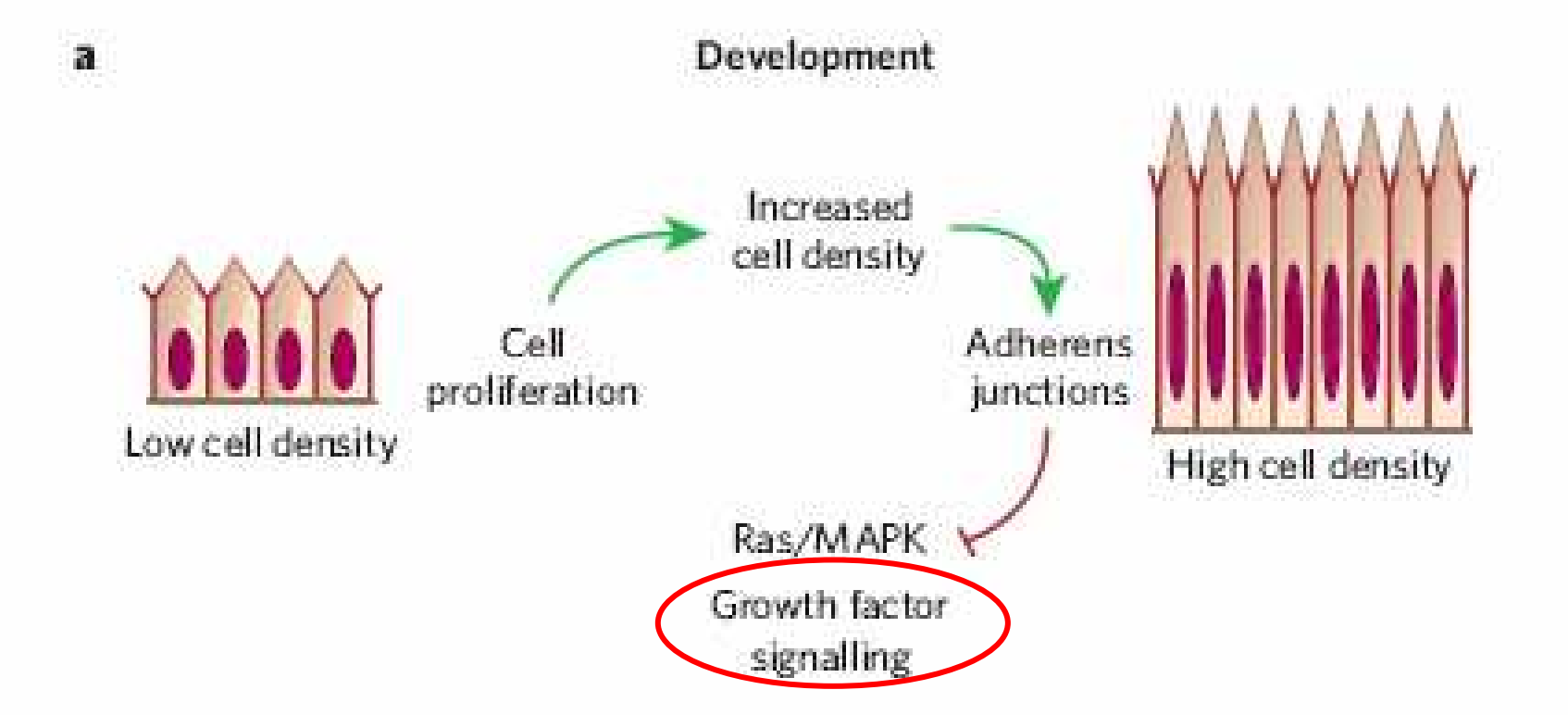
Nature, 2007

Omeostasi – divisione asimmetrica



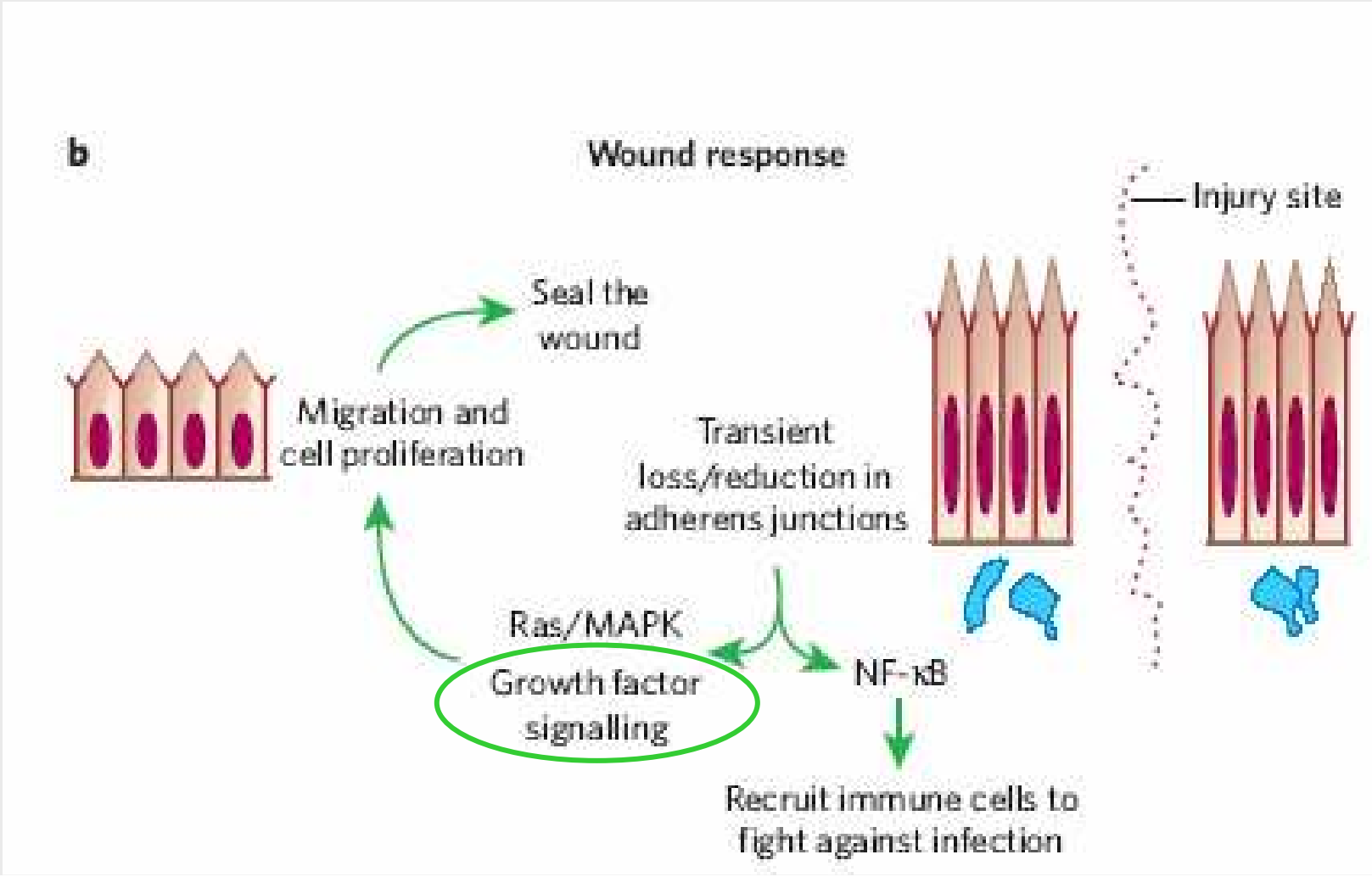
Nature 2007

Controllo della proliferazione dell'epidermide (sviluppo)

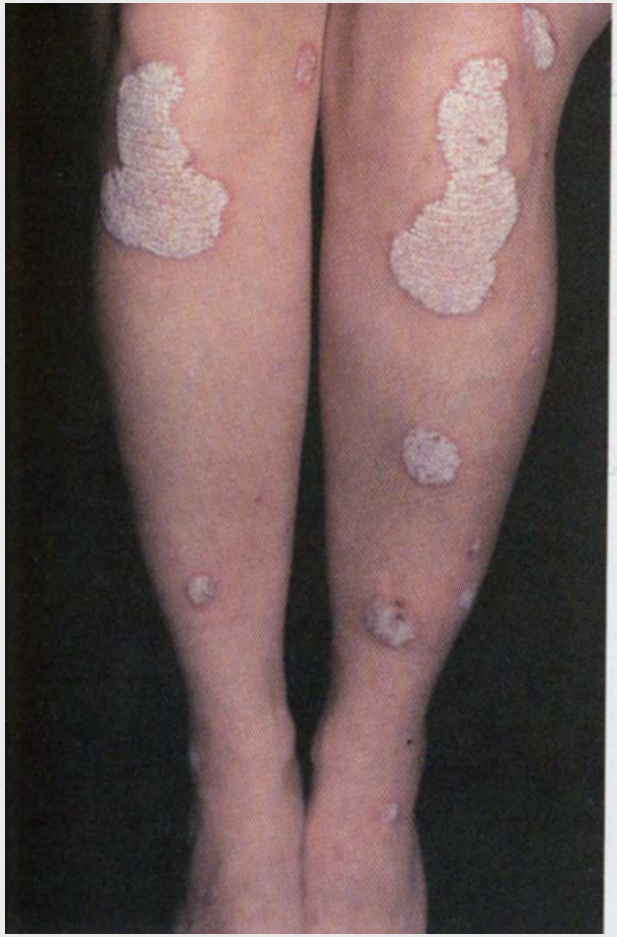


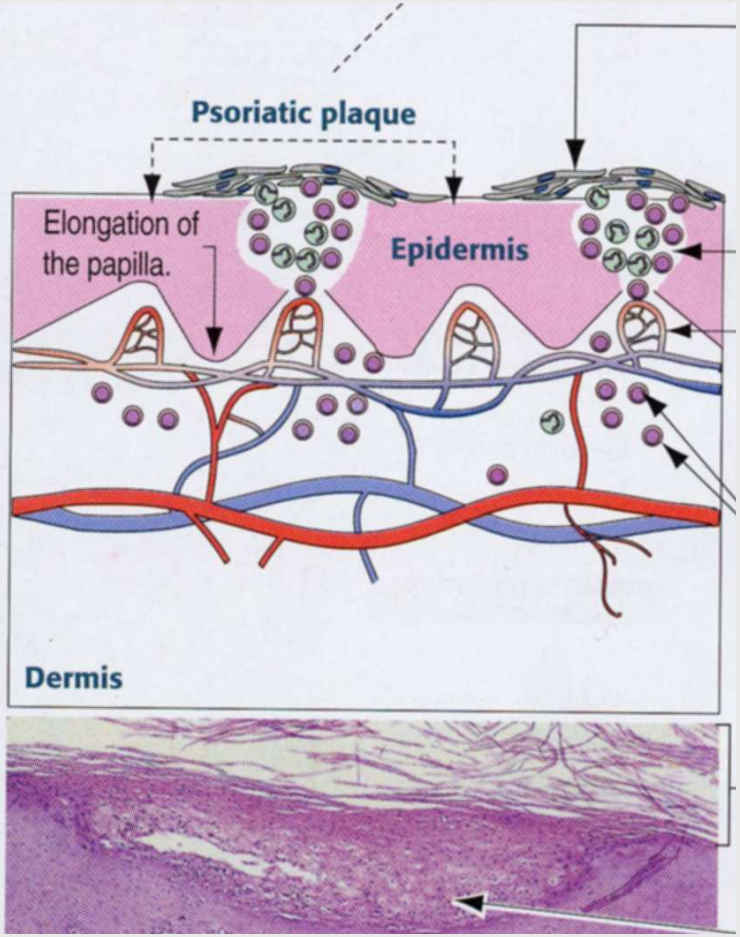
Le giunzioni aderenti sono sensori molecolari

Controllo della proliferazione dell'epidermide (riparazione ferita)

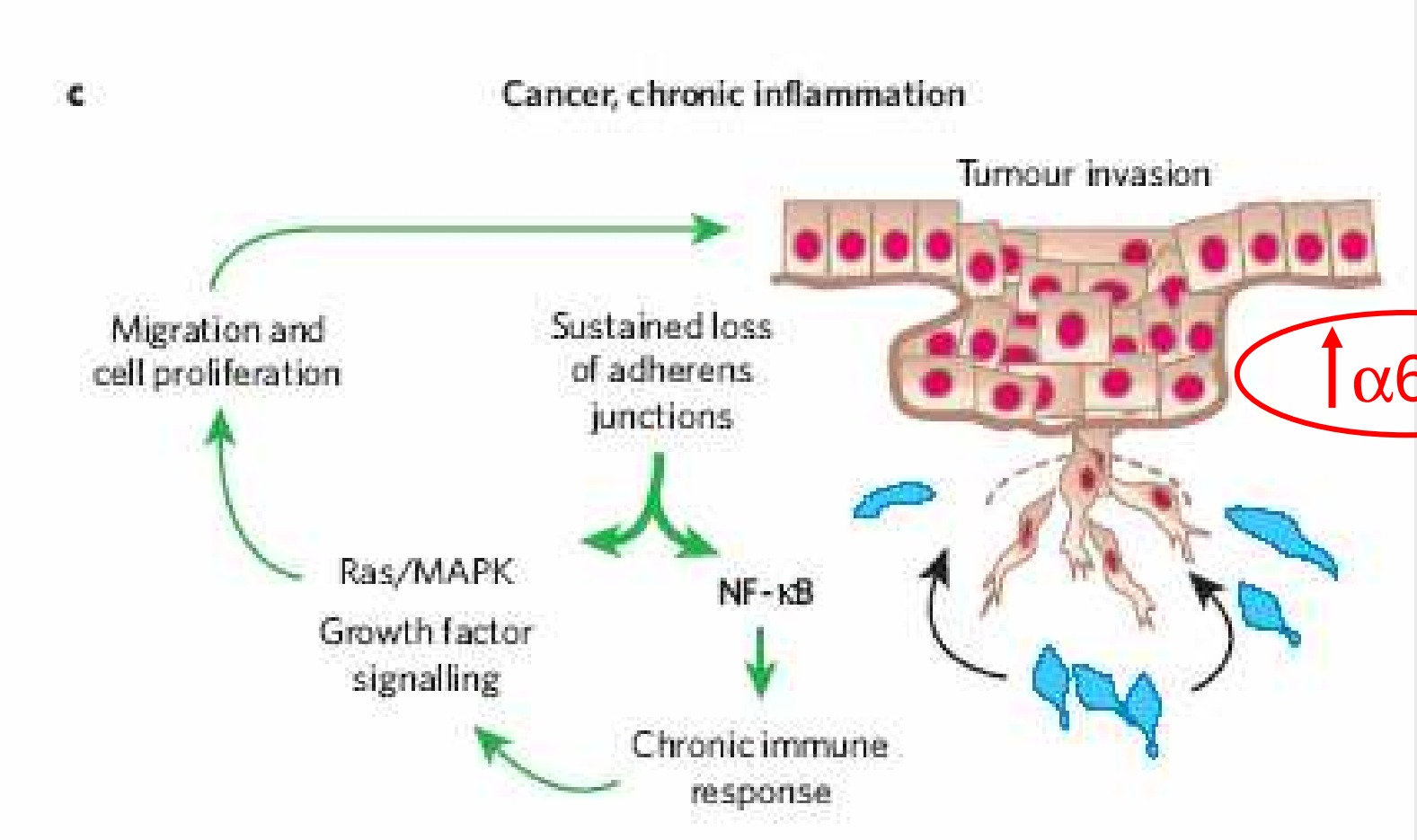


Epidermide: la psoriasi





Controllo della proliferazione dell'epidermide (patologia)

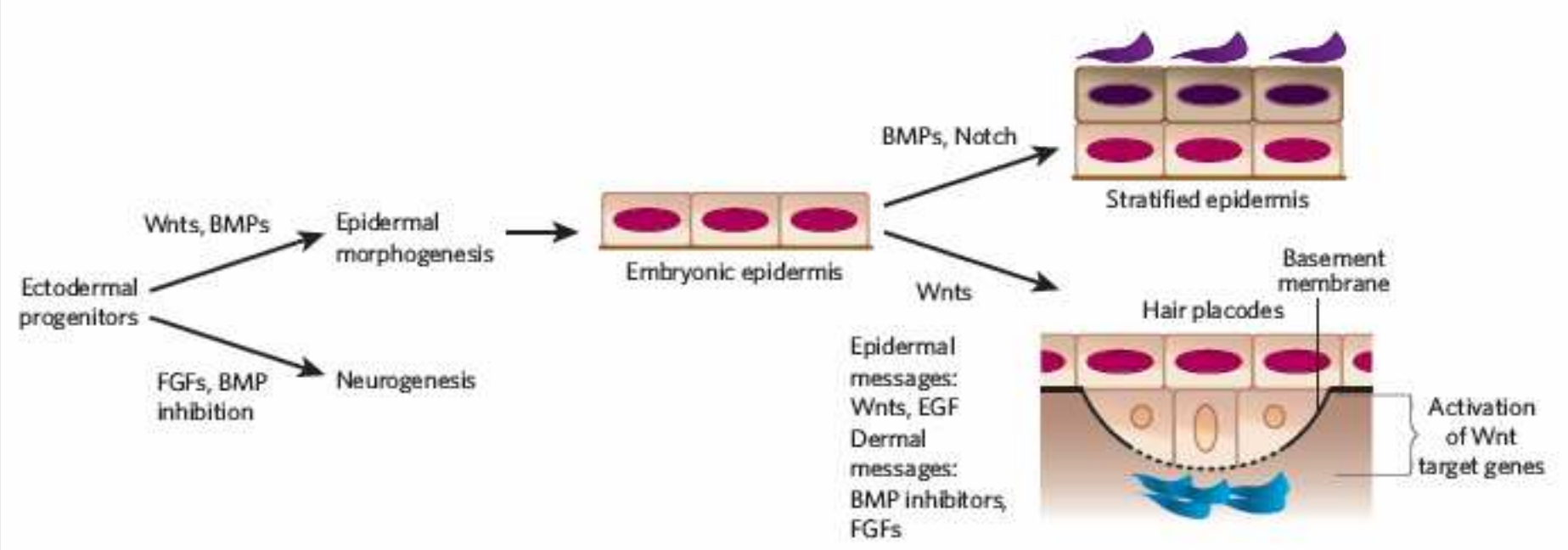


Tumori della pelle

- Carcinoma basale
- Carcinoma squamo-cellulare

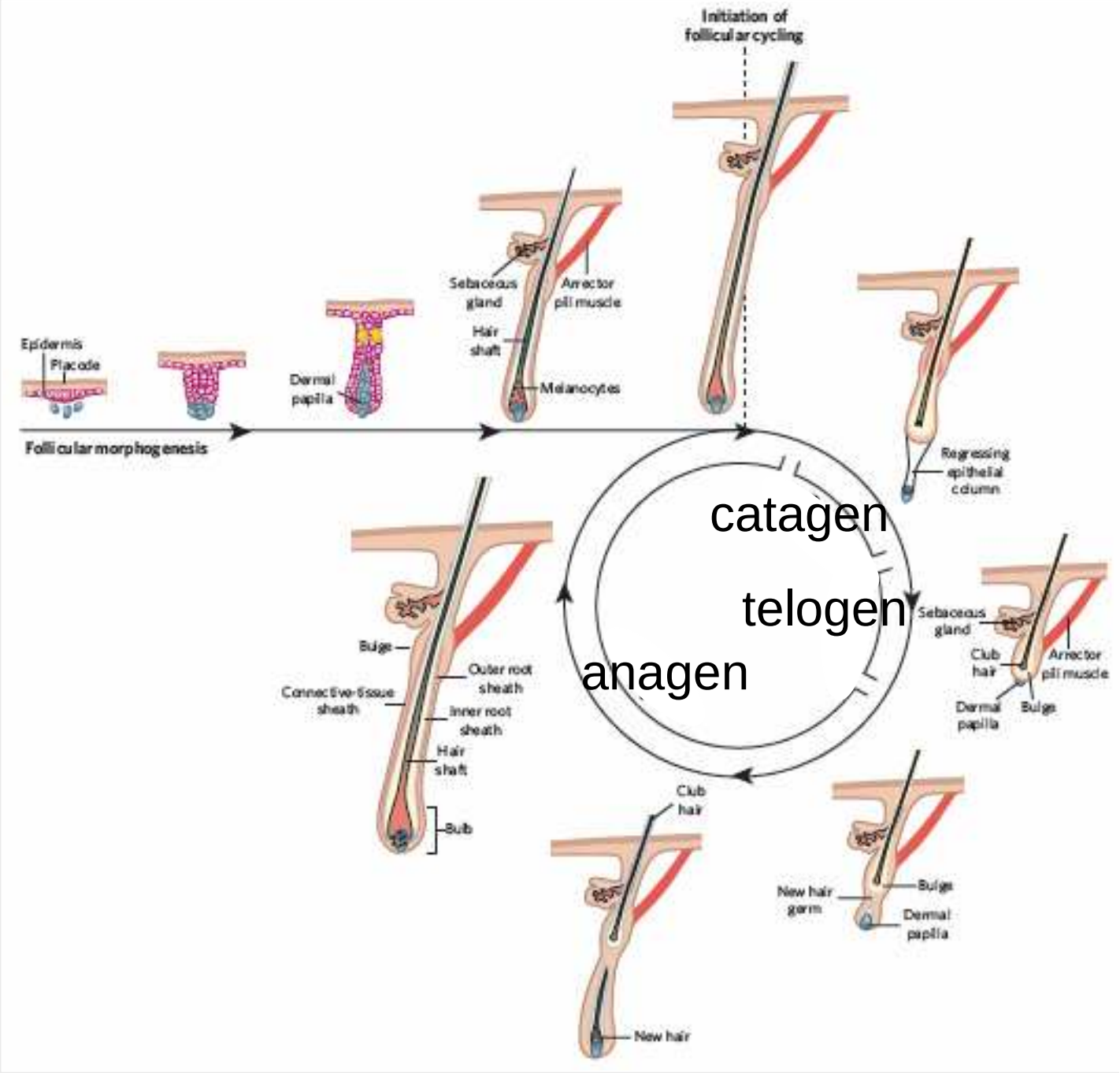
- Neo
- Melanoma

La scelta del destino delle cellule epiteliali

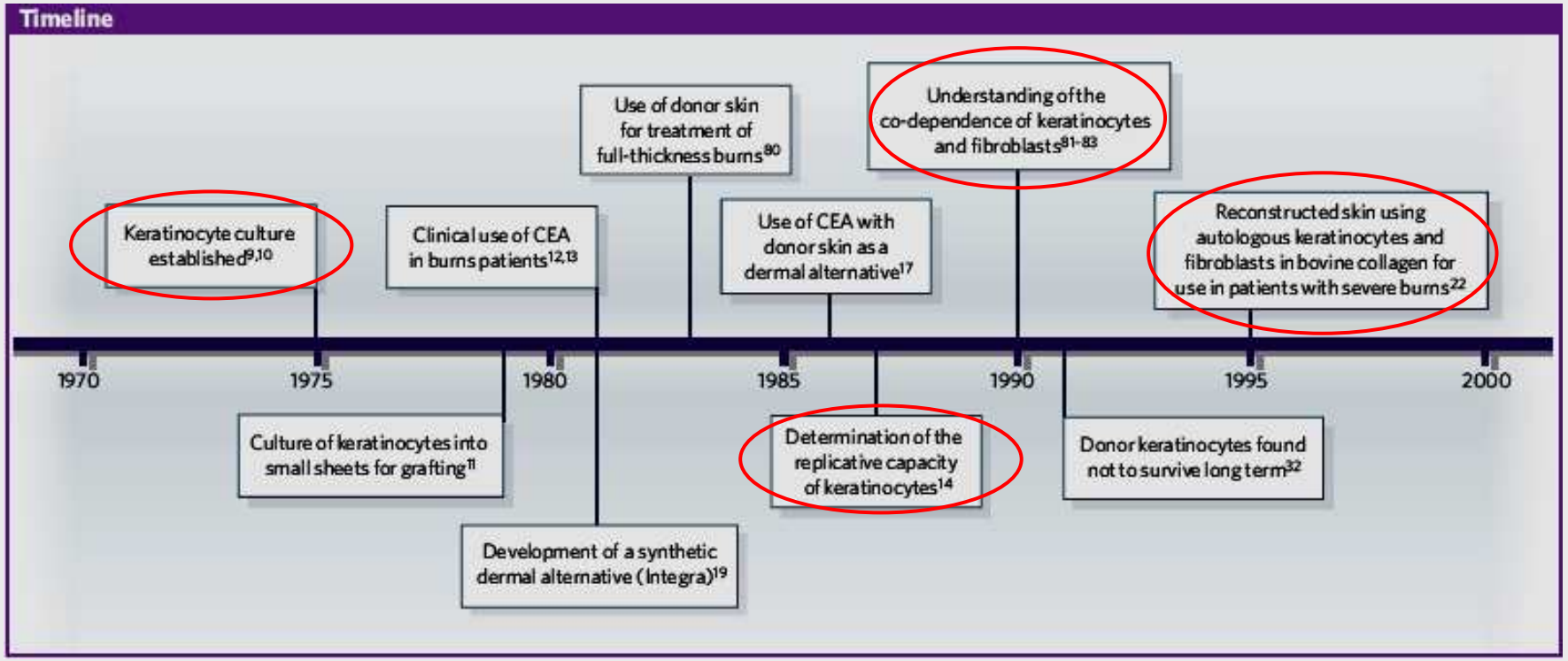


Nature, 2007

Il ciclo del pelo



Ingegneria tissutale applicata alla pelle



Nature 2007

Ingegneria tissutale applicata alla cute

- Per grandi ustionati
- Facilmente accessibile e manipolabile
- Prelievo da cadavere → temporaneo: sopravvive per 3 settimane → permette rivascolarizzazione
- Sostituzione con tessuto costruito ex vivo con cellule prelevate dal paziente
- Vari scaffolds (collagene bovino, silicone, GAGs)

Nature 2007

Medicina rigenerativa

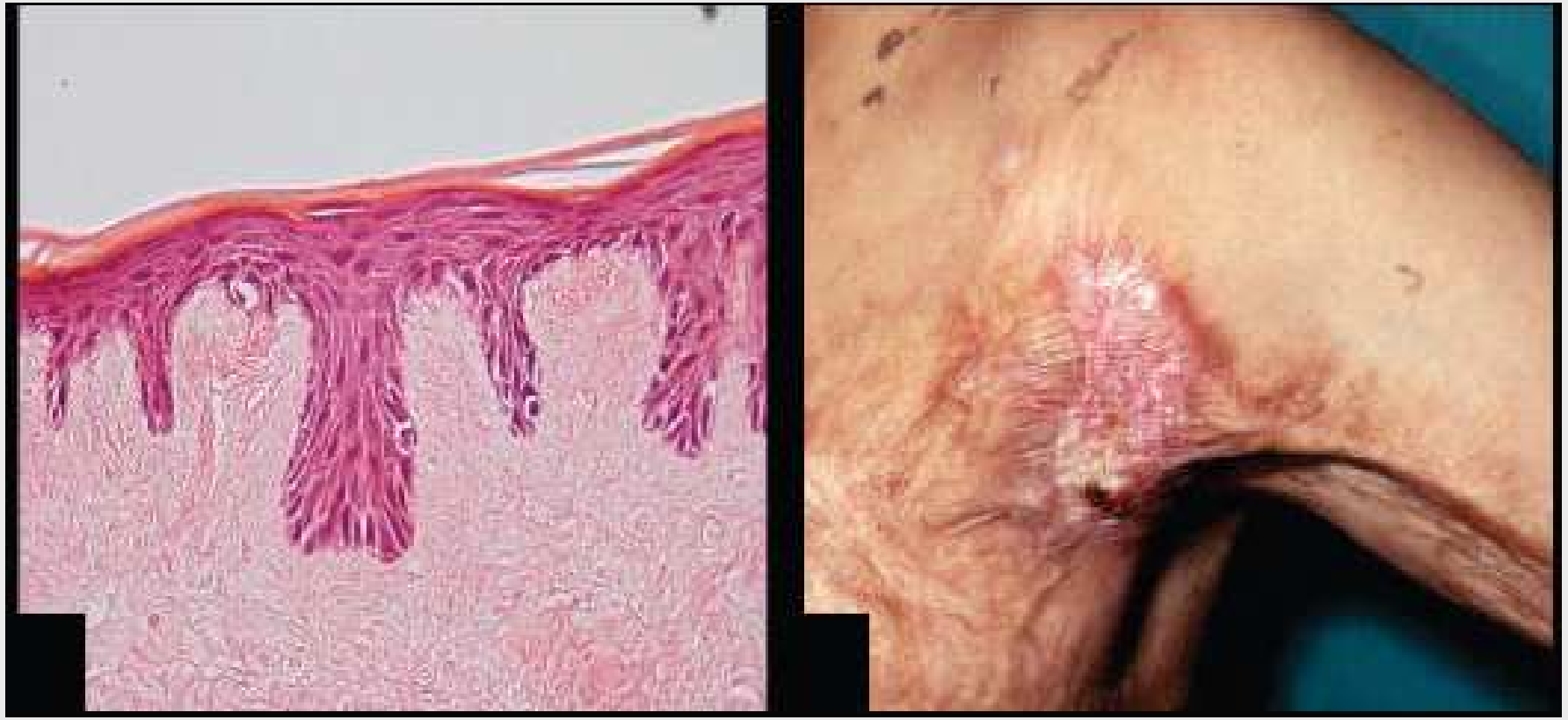
- Perdita di frammenti > 4 cm diametro → cute non guarisce
- → prelievi di cute (epidermide + strati superficiali di derma)
- Paziente ustionato riceve cute allogenica da cadavere, che sarà rigettata in ca. 3 settimane (anche Integra: bovine collagen + shark CIS)
- Espansi ex vivo e trapiantati sul paziente
- Applicazioni: ulcere, chirurgia ricostruttiva, cicatrici, malattie bollose

Paramount factors in the development of tissue-engineered

- materials,
- safety of the patient,
- clinical efficacy and convenience of use

- → must attach to the wound bed,
- be supported by new vasculature,
- not be rejected by the immune system
- be capable of self repair throughout a patient's life.

Clinical use of TE skin



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Limits

- The maximum thickness of skin-replacement material that can easily become vascularized is about 0.4 mm,
- failure to take this into consideration when using reconstructed skin based on human allodermis can result in delayed angiogenesis and loss of graft
- aesthetic appearance can be far from ideal (contracture of grafts, abnormal pigmentation..

Scaffold

- must not induce a toxic or immune response or result in excessive inflammation
- slowly biodegradable
- readily available and capable of being prepared and stored with a long shelf life
- FDA-approved bovine collagen or hyaluronic acid, or acellular natural human or porcine matrices and synthetic FDA-approved biodegradable scaffolds (such as poly-l-lactide, already used in dissolvable sutures or related polymers) are in use.

Skin replacement

- epidermal layer only
- dermal substitute only
- Both

- Before-around 1980’
- Murine fibroblasts
- Pig skin
- after 25 years there is still no uniform international approach to this issue

Epithelial cover (autologous)

- An integrated sheet such as Epicel (Genzyme Tissue Repair). This is developed from the methodology originally pioneered in 1981- A biopsy of the patient's cells is grown into an integrated sheet and enzymatically detached for delivery to the patient.
- Subconfluent cells on a carrier such as Myskin (CellTran). Cells are delivered to the patient before they reach confluence on a chemically defined carrier dressing.
- Small sheets cultured from a patient's hair follicles such as Epidex (Modex Therapeutics).
- A spray such as CellSpray (Clinical Cell Culture). Subconfluent cells are expanded in the laboratory and made into a suspension in which they are transported. They are then delivered to the patient as a spray.

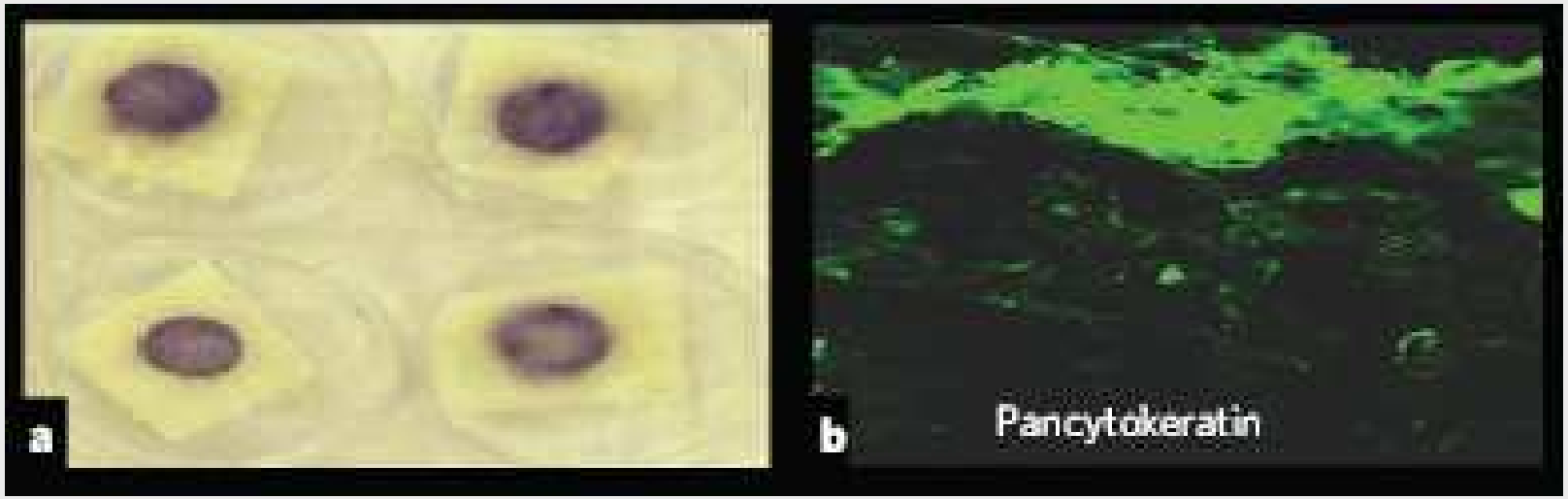
Dermal replacement materials

- Donor skin: skin from screened skin donors can be used to provide either a temporary wound cover or a permanent source of allodermis.
- Integra (Integra LifeSciences): an alternative to donor skin that provides a vascularized dermis for a subsequent split-thickness skin graft.
- Alloderm (Lifecell): freeze-dried human donor dermis.
- Dermagraft (Advanced Biohealing): a synthetic material conditioned with donor fibroblasts.
- Transcyte (Advanced Biohealing): similar to Dermagraft but with a silicone membrane to act as a temporary epidermal barrier.
- Permacol (Tissue Science Laboratories): porcine skin that provides a temporary wound dressing.

Epidermal/dermal replacement materials

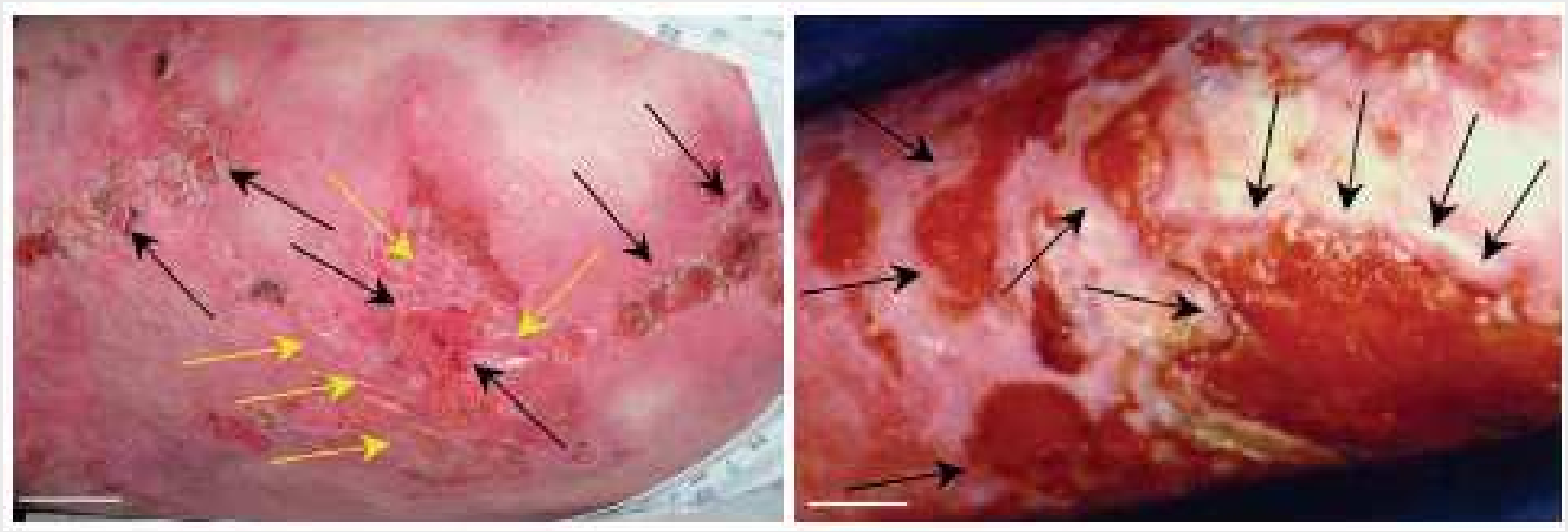
- Apligraf (Organogenesis): this combines allogeneic keratinocytes and fibroblasts with bovine collagen to provide a temporary skin-replacement material suitable for use in chronic wounds but not major burns.
- Orcel (Ortec International): combines allogeneic keratinocytes and fibroblasts with bovine collagen to provide a temporary skin replacement material suitable for use in chronic wounds.
- Cincinnati skin substitute, or Permaderm (Cambrex): comprises autologous keratinocytes and fibroblasts crafted into reconstructed skin with bovine collagen.

Reconstruction of tissue-engineered skin using a synthetic scaffold (polystirene)



Nature 2007

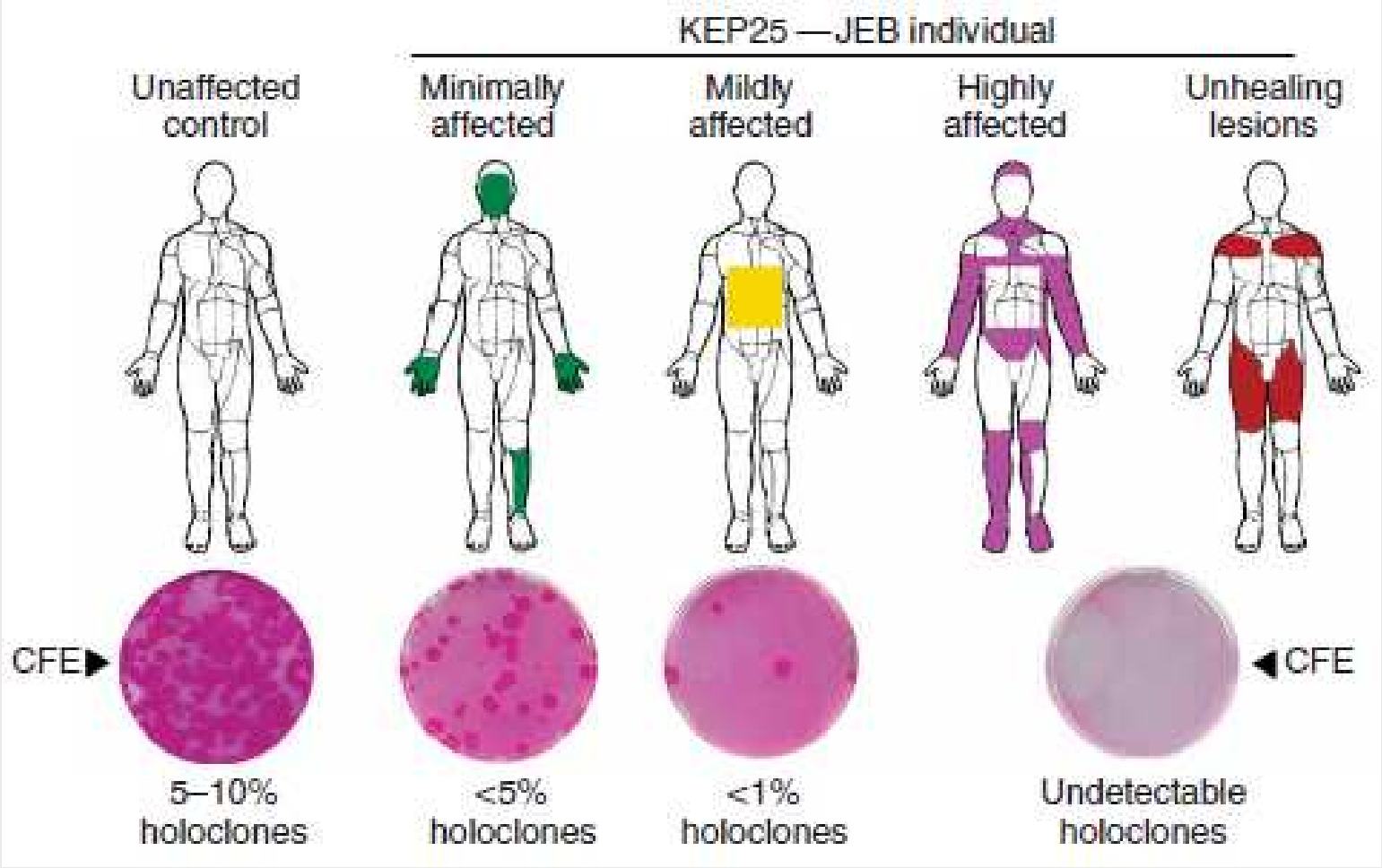
Epidermolisi bullosa giunzionale (JEB)



Difetto del gene β3 (integrina recettore di LAM5)

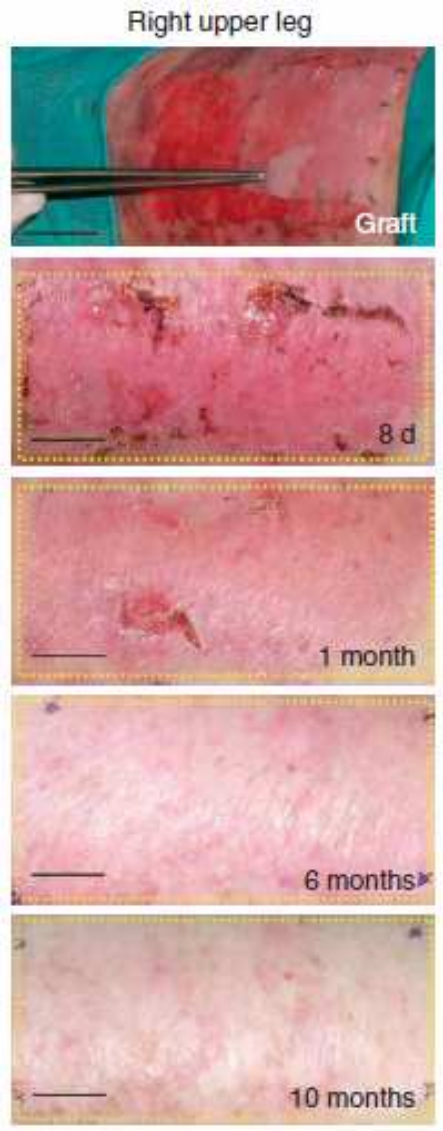
Mavilio et al, Nat Med dic 2006

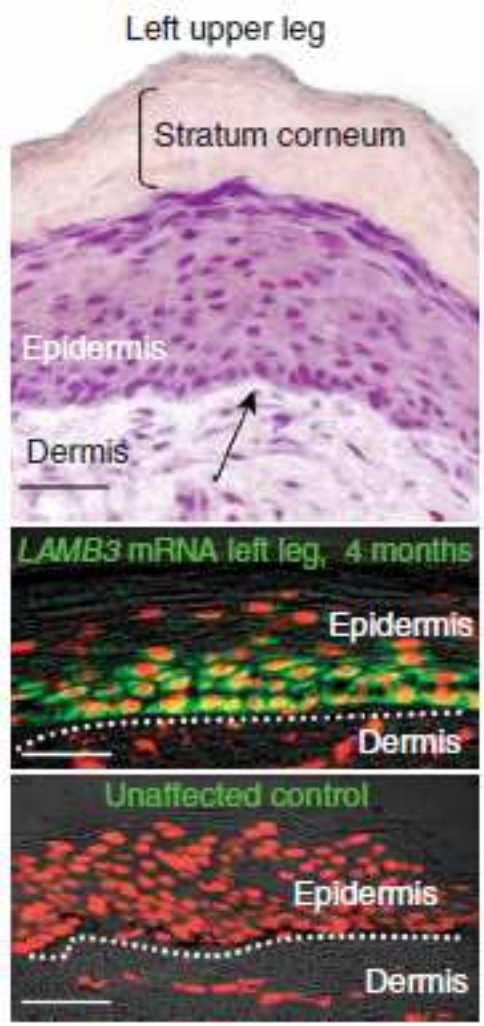
Epidermolisi bullosa giunzionale (JEB): da dove prendere le cellule??



Epidermolisi bullosa giunzionale (JEB)

Risultato del trapianto dell'epidermide ingegnerizzata

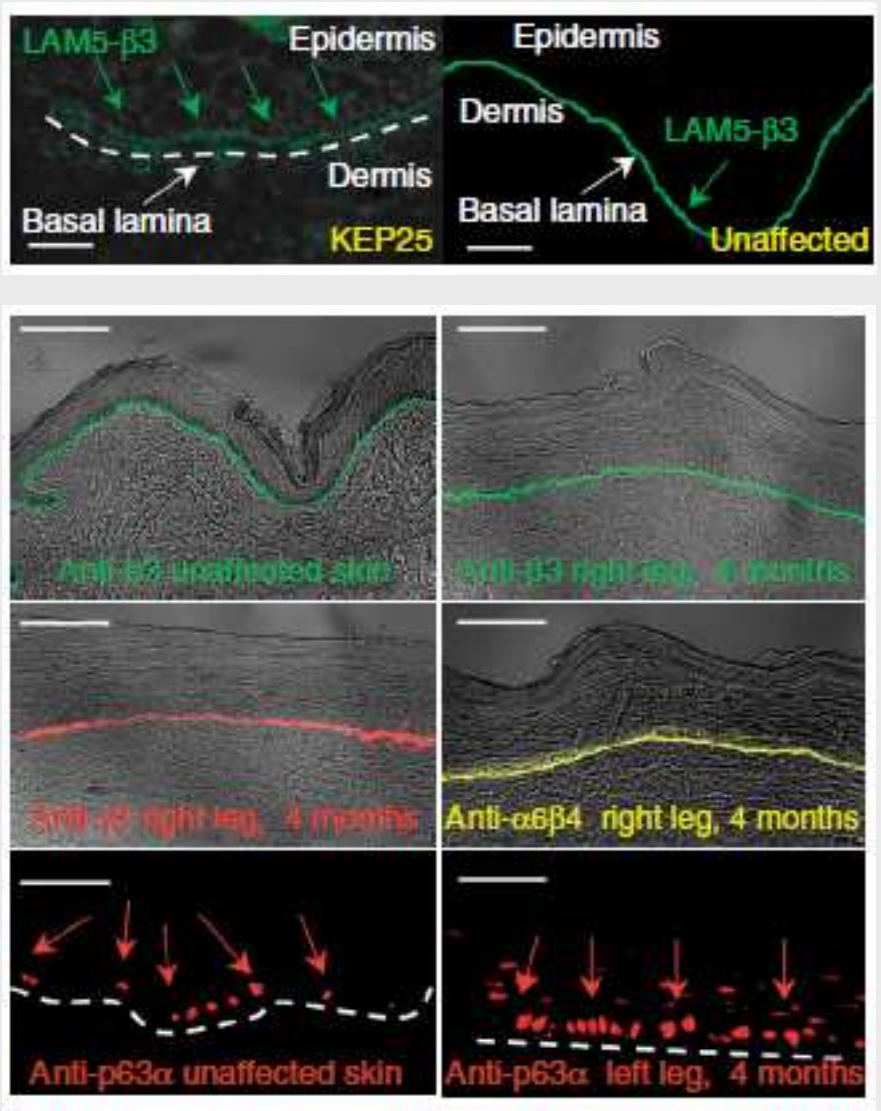




istologia

espressione delle proteine

Epidermolisi bullosa giunzionale (JEB)



Ligandi di β3

Marcatore di prolif

Epidermolisi bullosa giunzionale (JEB)

- Esempio di terapia genica ex vivo
- La pelle ha le caratteristiche della palma della mano
- Assenza di risposta infiammatoria o immune