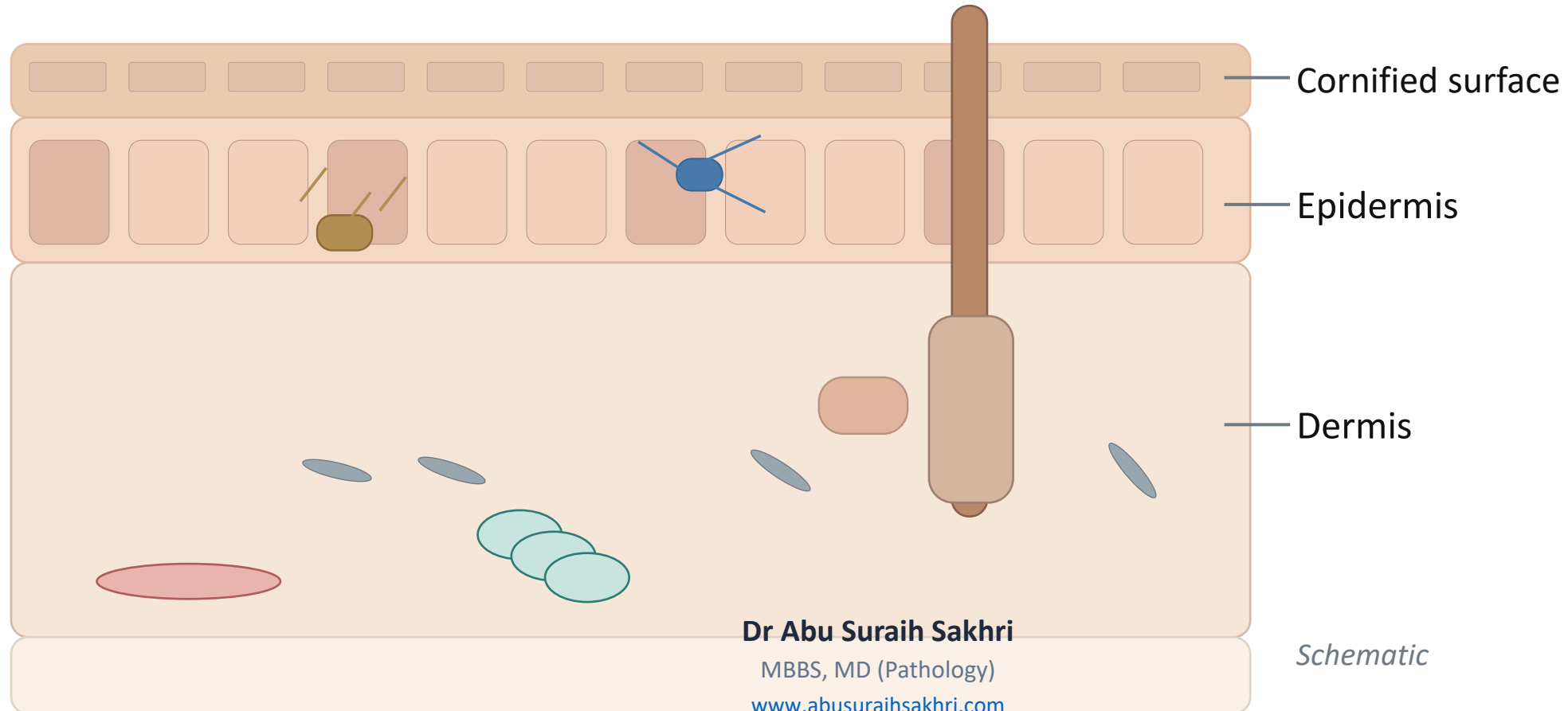


More Than a Mechanical Barrier

Skin as an integrated protective, immune, sensory, and regenerative organ



What this lecture explains

Four questions organize the functional anatomy of skin.

Structure

How do keratinocytes, melanocytes, and adnexa build a protective surface?

Immunity

How does the skin recognize antigens and recruit lymphocytes?

Integration

How do microbiota, nerves, and appendages support homeostasis?

Pathology

How do function, lesion morphology, and systemic disease connect?

From passive covering to active organ

Earlier viewpoint

Mechanical protection against injury

A barrier against fluid loss

Little emphasis on cellular cross-talk

Contemporary viewpoint

Interdependent epithelial, neural, immune, and adnexal systems

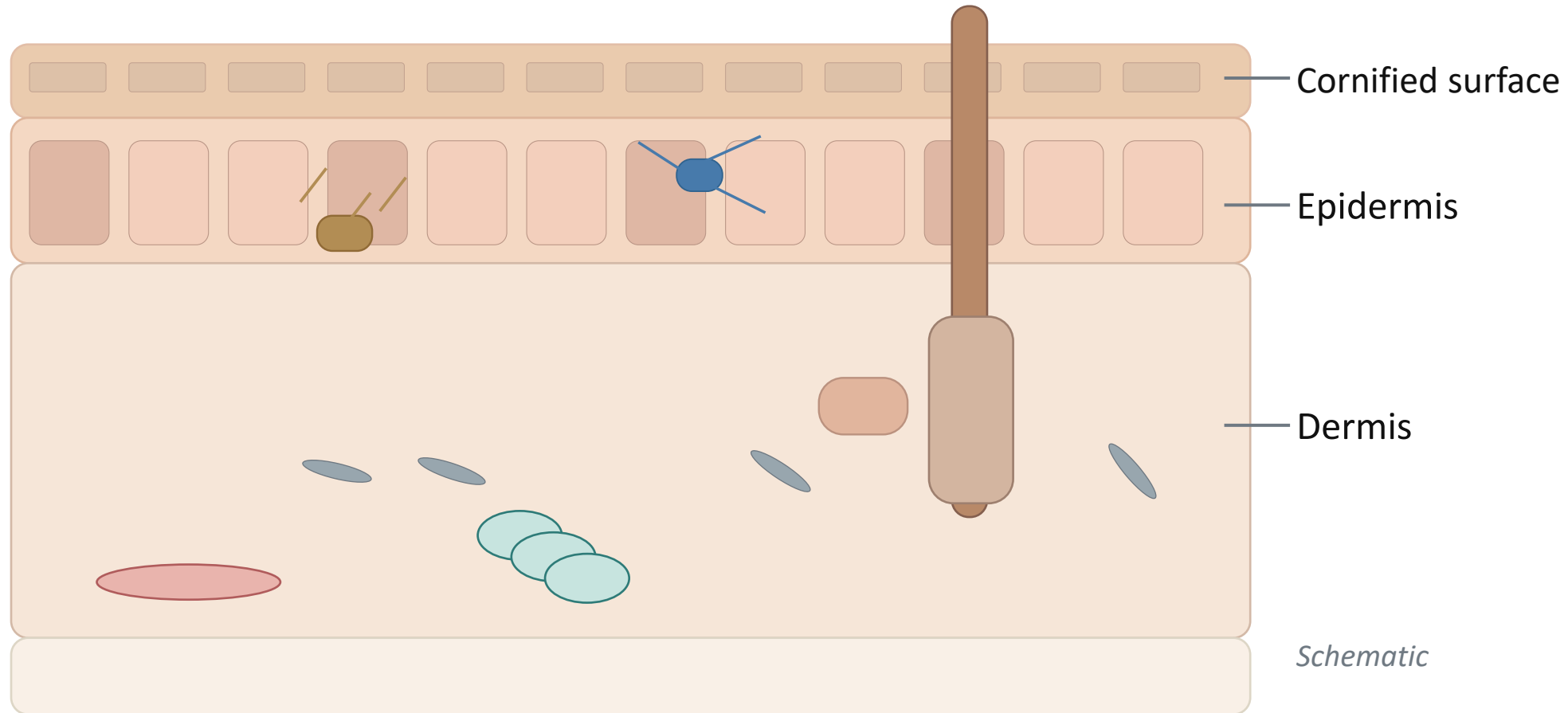
Defense against physical and infectious agents

Regulated signaling governs homeostasis

The skin is the body's largest organ—not an inert wrapper.

Two compartments, many interacting cell types

The epidermis overlies a dermis containing vessels, supporting cells, nerves, and adnexal structures.



The functional roles of skin are interconnected

Each function emerges from cooperation among more than one cell type.

Barrier

Keratinocytes, keratin, desmosomes

Photoprotection

Melanocytes and melanin-bearing keratinocytes

Immune surveillance

Keratinocytes, dendritic cells, lymphocytes

Sensation

Nerve fibers and neural end organs

Thermoregulation

Sweat glands and autonomic nerves

Repair

Follicular stem-cell niches and dermal support

Epidermal and dermal compartments

Epidermis

Squamous epithelial cells and their maturation

Melanocytes in the epidermal compartment

Langerhans cells within epidermis

Dermis

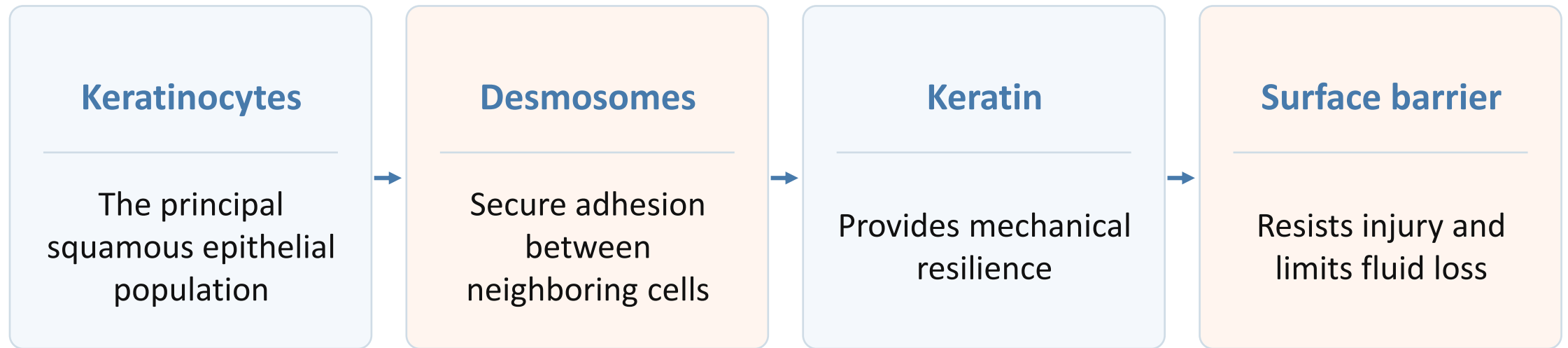
Fibroblasts, vessels, mast cells, dendrocytes

Skin-homing T cells and small numbers of B cells

Adnexal extensions, nerves, and stromal support

Keratinocytes construct the physical barrier

Barrier strength depends on cellular cohesion and durable structural protein.



The two structural components work together rather than independently.

Desmosomes provide cohesion

Adherent epithelium

Neighboring keratinocytes are joined at desmosomes

Cohesion resists mechanical disruption

Disrupted cohesion

Loss of effective cell–cell adhesion weakens the epithelial barrier

Separation can contribute to blister formation

Barrier failure may reflect failure of cell adhesion, not merely surface damage.

Keratin supplies durable strength

The structural protein of squamous epithelium makes the keratinocyte sheet mechanically robust.



Desmosomal adhesion and keratin production are complementary.

Epidermal maturation progresses upward

Basal keratinocytes mature toward cornified surface cells.



The stratum corneum is the differentiated surface

Superficial position

Forms the outermost cornified epithelial zone

Represents progressive keratinocyte maturation

Barrier significance

Contributes to protection against physical agents

Helps constrain loss of water from the body

Physical damage exposes the limits of the barrier

Perturbations in epithelial integrity create opportunities for tissue injury.



Structural resilience is necessary—but is only one of several skin defenses.

Keratinocytes are immunologically active

Structural role

Production of keratin

Desmosomal cohesion

Maintenance of the physical interface

Signaling role

Secretion of cytokines

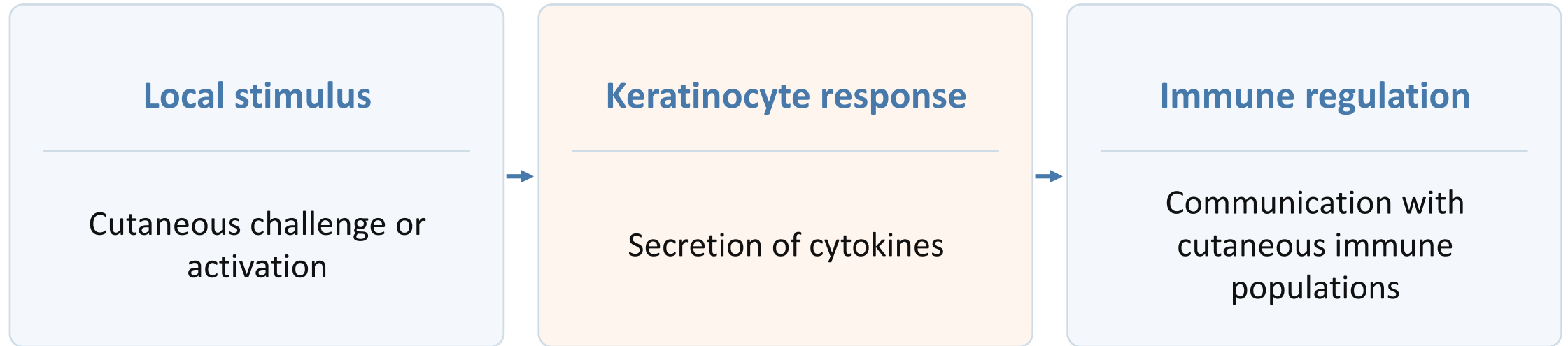
Production of defensins

Regulation and augmentation of immune responses

The same cell population links physical protection to immune defense.

Cytokines connect keratinocytes to immune cells

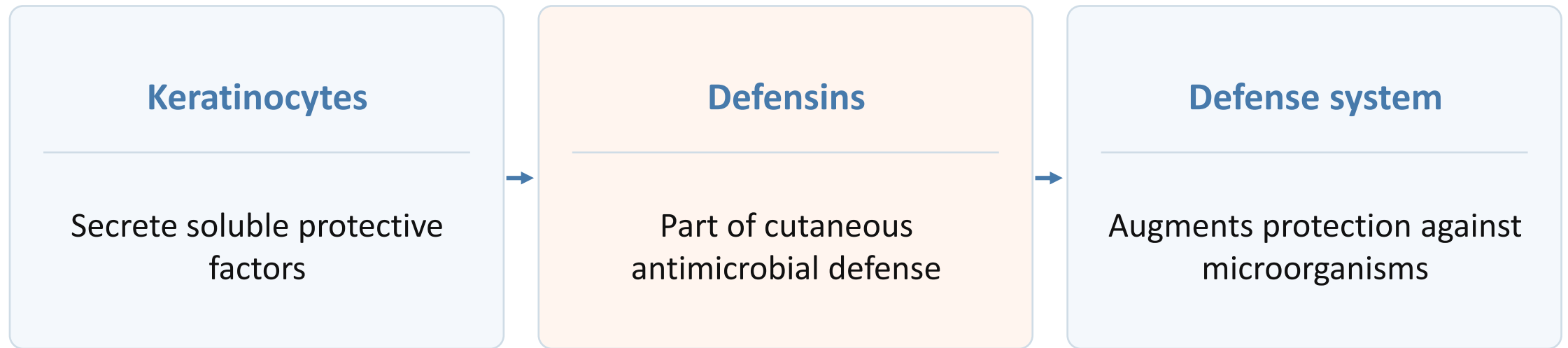
Keratinocyte-derived soluble mediators help coordinate responses in skin.



The source emphasizes immune signaling, not only keratin production.

Defensins contribute to local protection

Keratinocytes produce molecules that complement the physical epithelial barrier.



Physical and immune defenses reinforce each other

The cutaneous surface combines distinct but cooperating protection mechanisms.

Structural exclusion

Cohesive keratinized epithelium

Soluble response

Cytokines and defensins from keratinocytes

Cellular surveillance

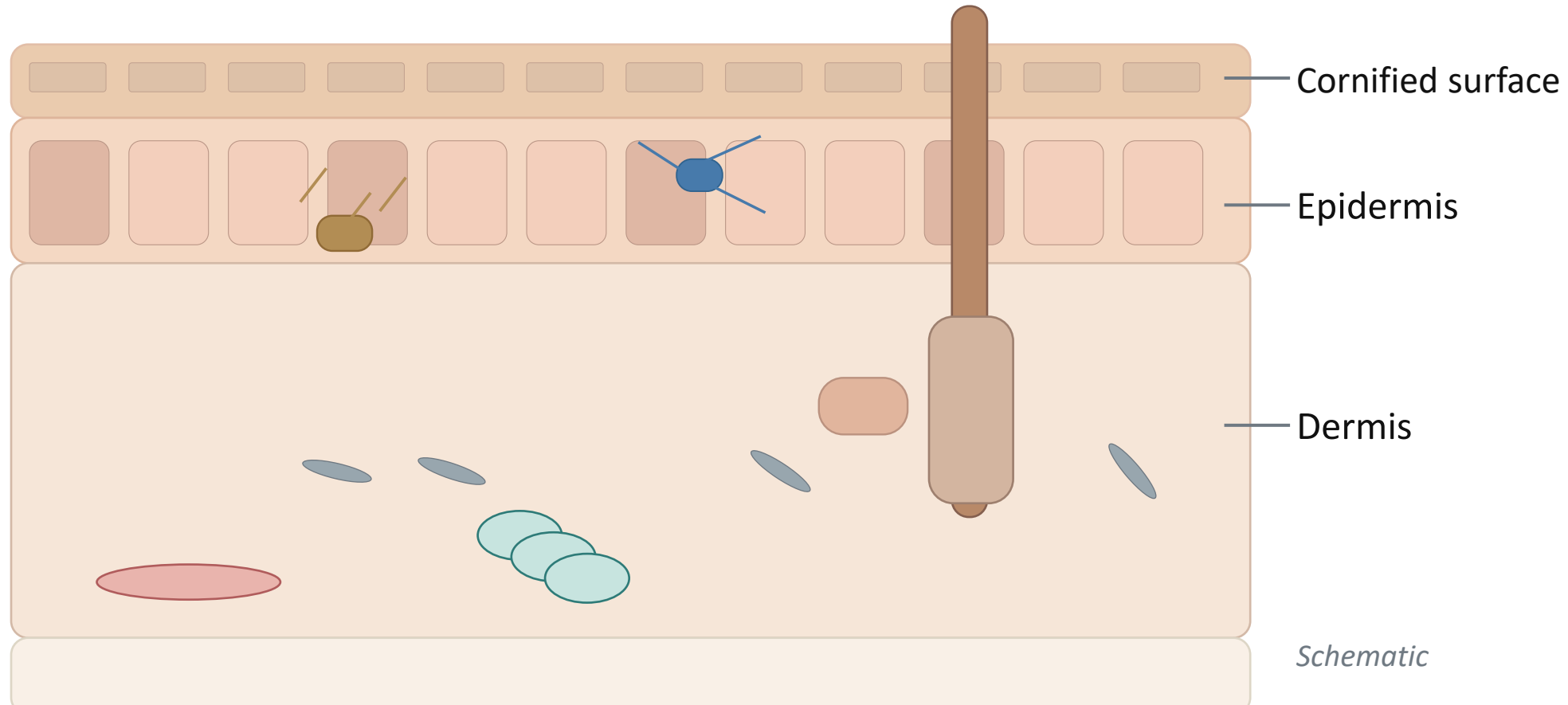
Dendritic-cell processing of antigens

Adaptive response

T-cell responses after regional-node priming

Melanocytes reside within the epidermis

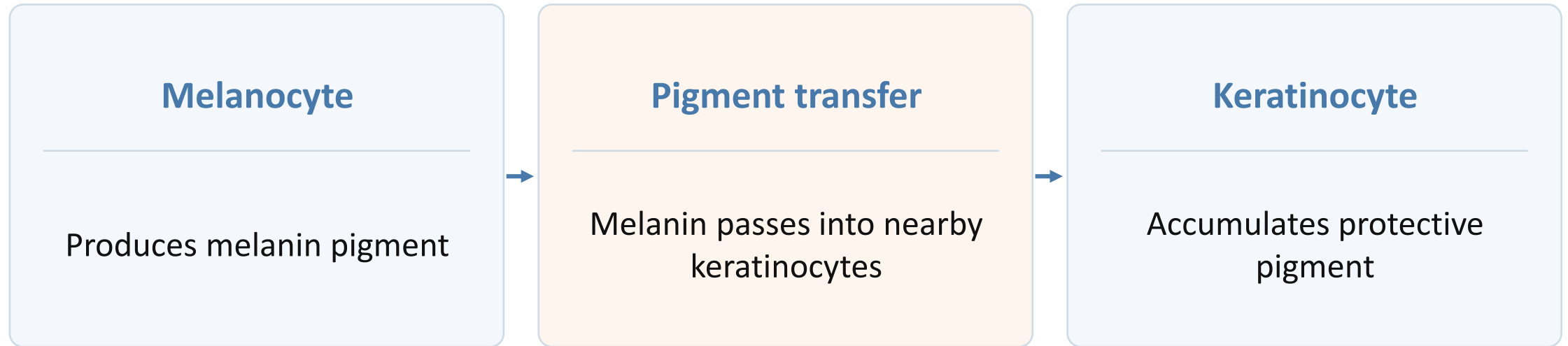
Melanin-producing melanocytes cooperate with the keratinocytes that receive their pigment.



Melanocyte: Melanin synthesis • Keratinocytes: Pigment recipients

Melanin is transferred to keratinocytes

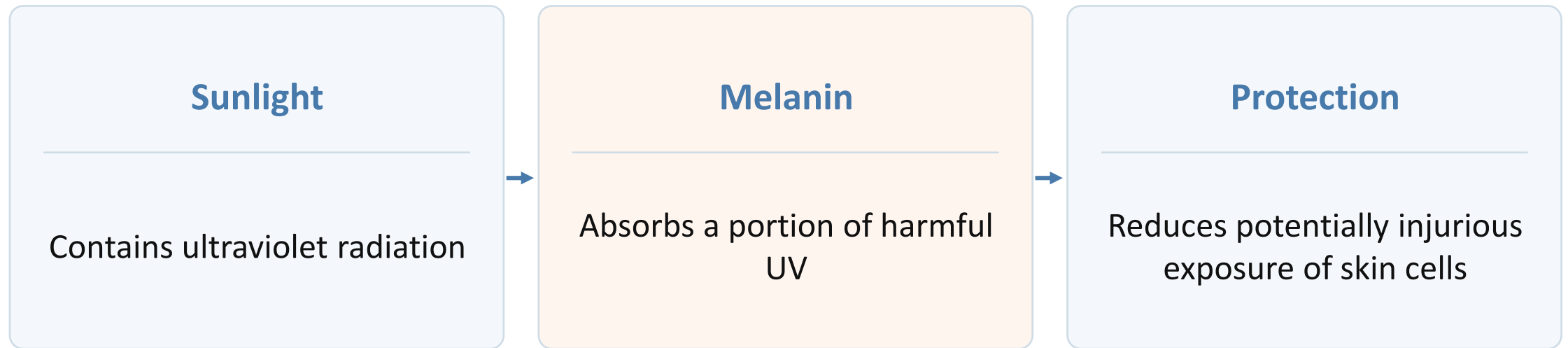
Protection depends on pigment production and transfer between cell types.



Epidermal pigmentation is a cooperative cellular process.

Melanin absorbs potentially harmful UV radiation

Pigmentation mitigates radiation-associated injury but does not eliminate every UV effect.



Skin color reflects pigment distribution

Pigment source

Melanocytes manufacture melanin

Melanin is a brown pigment

Pigment-bearing compartment

Keratinocytes receive melanin

Its accumulation contributes to visible skin color

Sunlight has both physiological and pathological effects

Physiological role

Sun exposure supports cutaneous vitamin D synthesis

The skin participates in endocrine physiology

Potential harm

UV radiation injures skin

Prolonged exposure is linked to premature aging and cutaneous malignancy

Benefit and hazard coexist; They are not equivalent endpoints.

Skin is exposed continuously to antigens

Cutaneous immunity must recognize both microbial and nonmicrobial challenges.

Microbial challenge

Exposure to organisms on the body surface

Nonmicrobial antigen

Environmental antigens may also be encountered

Local surveillance

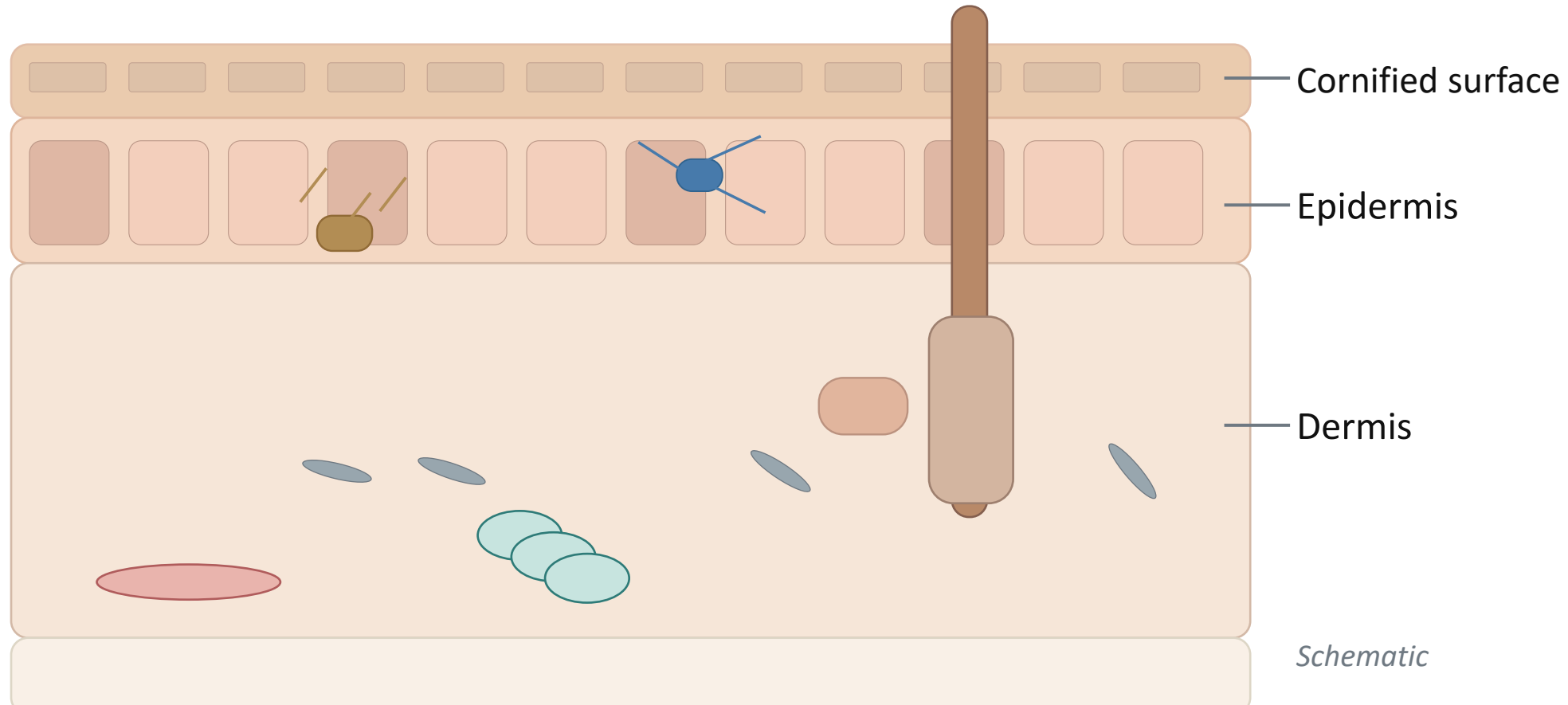
Intraepidermal and dermal dendritic cells process antigens

Systemic connection

Regional lymph nodes initiate adaptive responses

Langerhans cells survey the epidermis

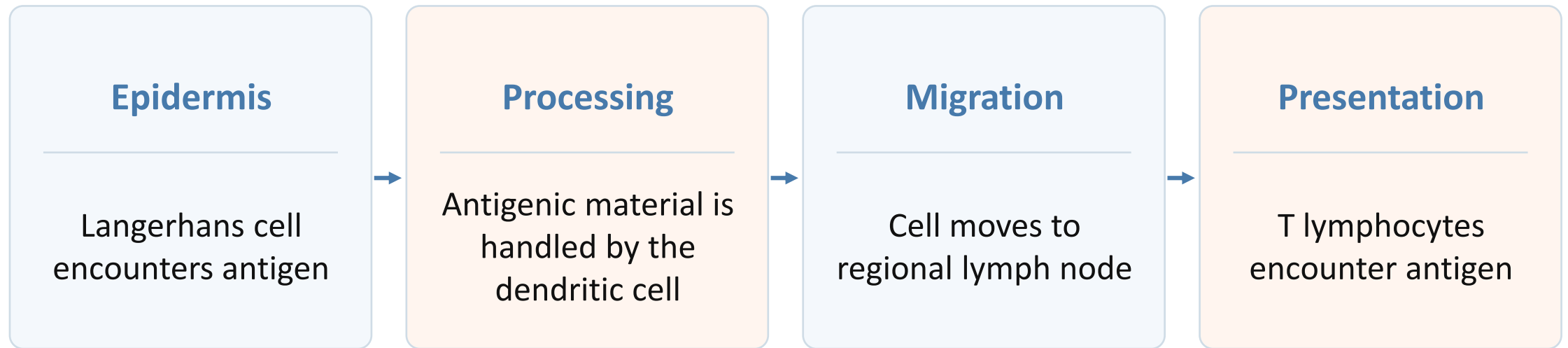
Intraepidermal dendritic cells take up antigens and initiate immune communication.



Langerhans cell: Antigen handling • Epidermal immune surveillance

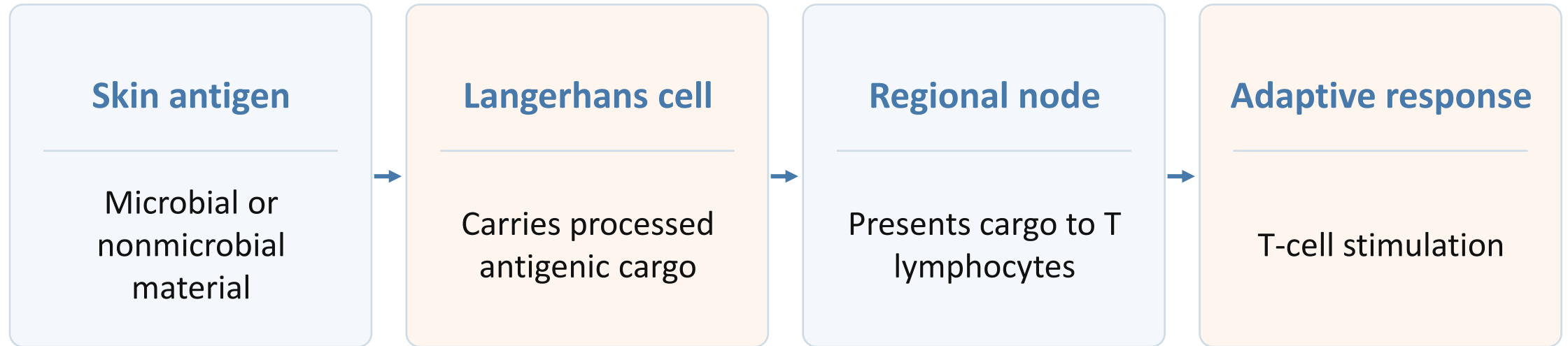
Antigen capture precedes adaptive priming

A cutaneous antigen can be processed locally and then presented away from the skin.



Regional lymph nodes link skin to adaptive immunity

Dendritic-cell migration extends a local exposure into an organized adaptive response.



Dermal dendritic cells have related functions

Langerhans cells

Intraepidermal distribution

Process encountered antigens

Can migrate to regional nodes

Dermal dendritic cells

Located in underlying dermis

Participate in antigen handling

Support cutaneous immune response

Innate and adaptive defense are connected

Innate arm

Keratinocyte-derived soluble mediators

Local factors secreted by Langerhans cells

Early defense at the interface

Adaptive arm

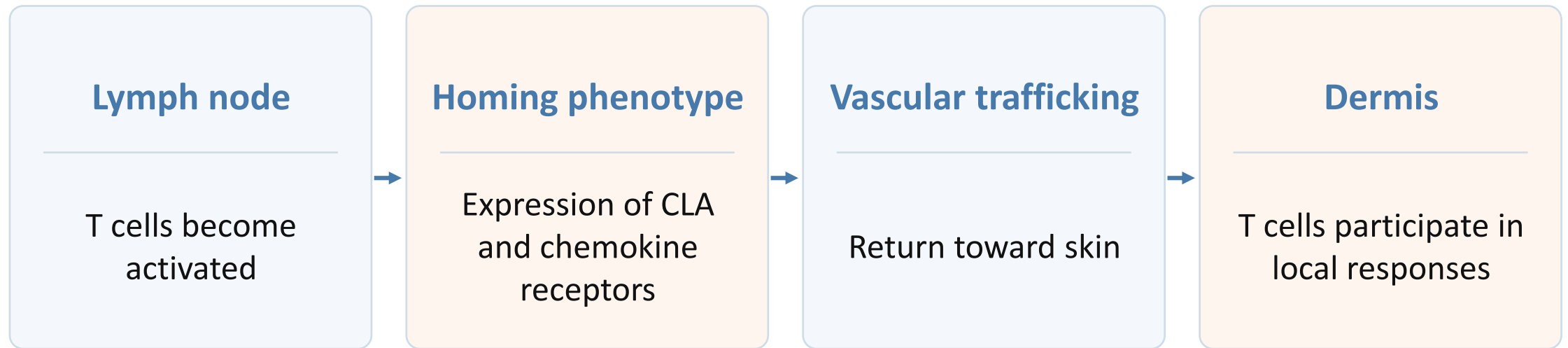
Antigen presentation in regional nodes

Activation of T lymphocytes

Return of tissue-directed T cells to skin

Activated T cells can return to skin

After stimulation in lymph nodes, certain T cells home back to the dermis.



CLA contributes to cutaneous lymphocyte homing

CLA

Cutaneous lymphocyte-associated antigen

An adhesion molecule on a subset of T cells

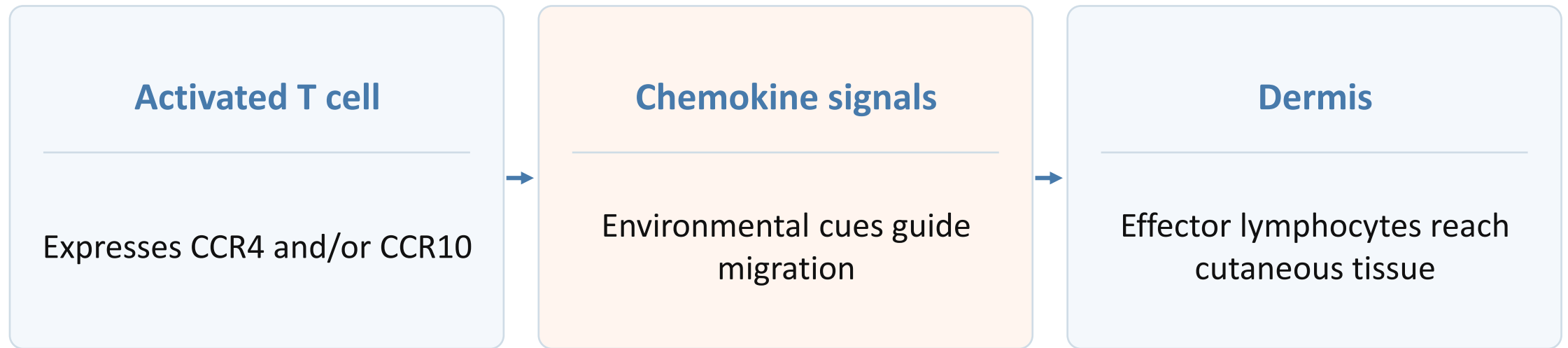
Functional context

Associated with skin-directed trafficking

Acts with chemokine receptors during homing

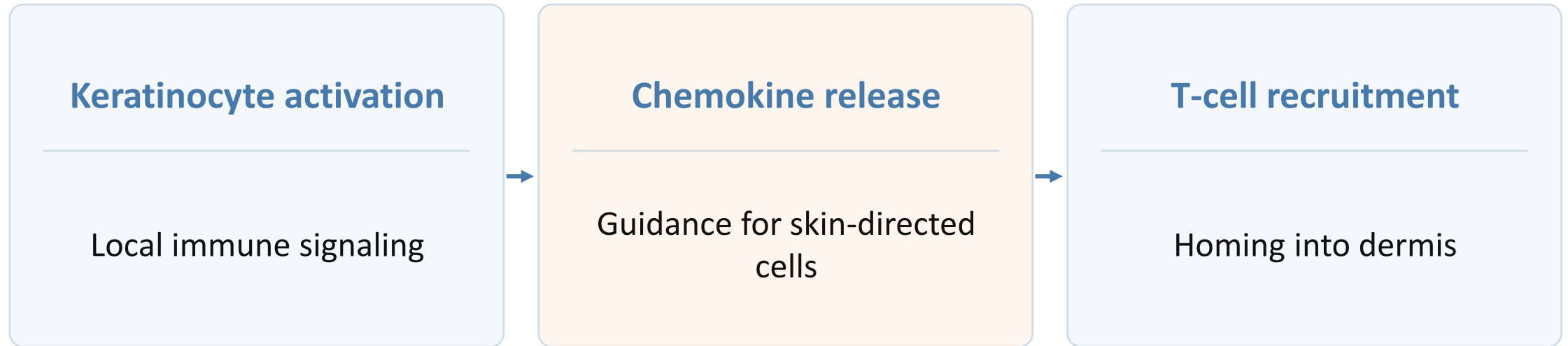
CCR4 and CCR10 are skin-homing receptors

Chemokine receptor expression contributes to positioning immune cells within skin.



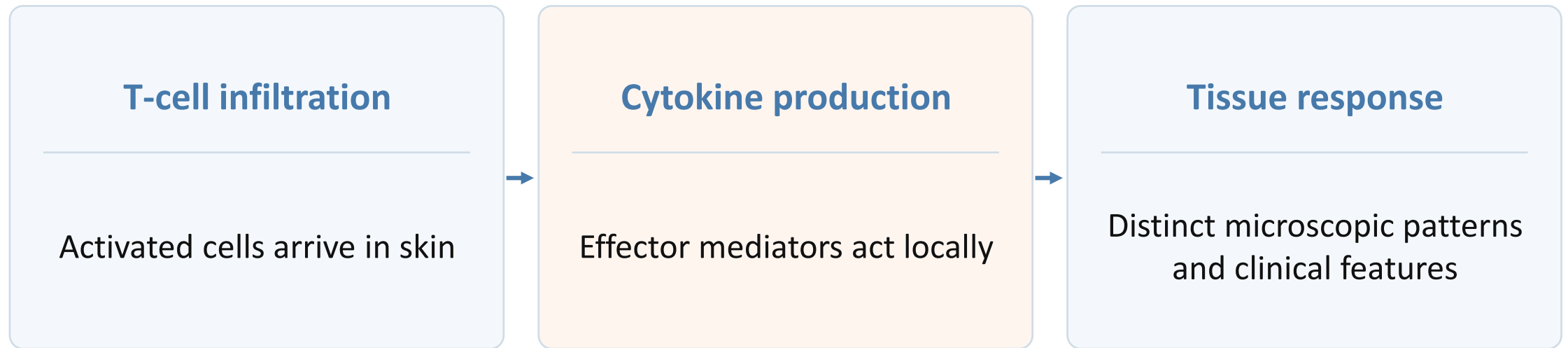
Activated keratinocytes help recruit lymphocytes

Inflamed or activated epithelium can shape where T cells migrate.



T-cell cytokines shape inflammatory morphology

Cutaneous lesions reflect the consequences of specific cellular immune signals.



Inflammatory morphology can be viewed as the tissue record of immune signaling.

Dermal B cells participate in humoral responses

T lymphocytes

Receive antigenic stimulation through dendritic cells

Return to skin and produce cytokines

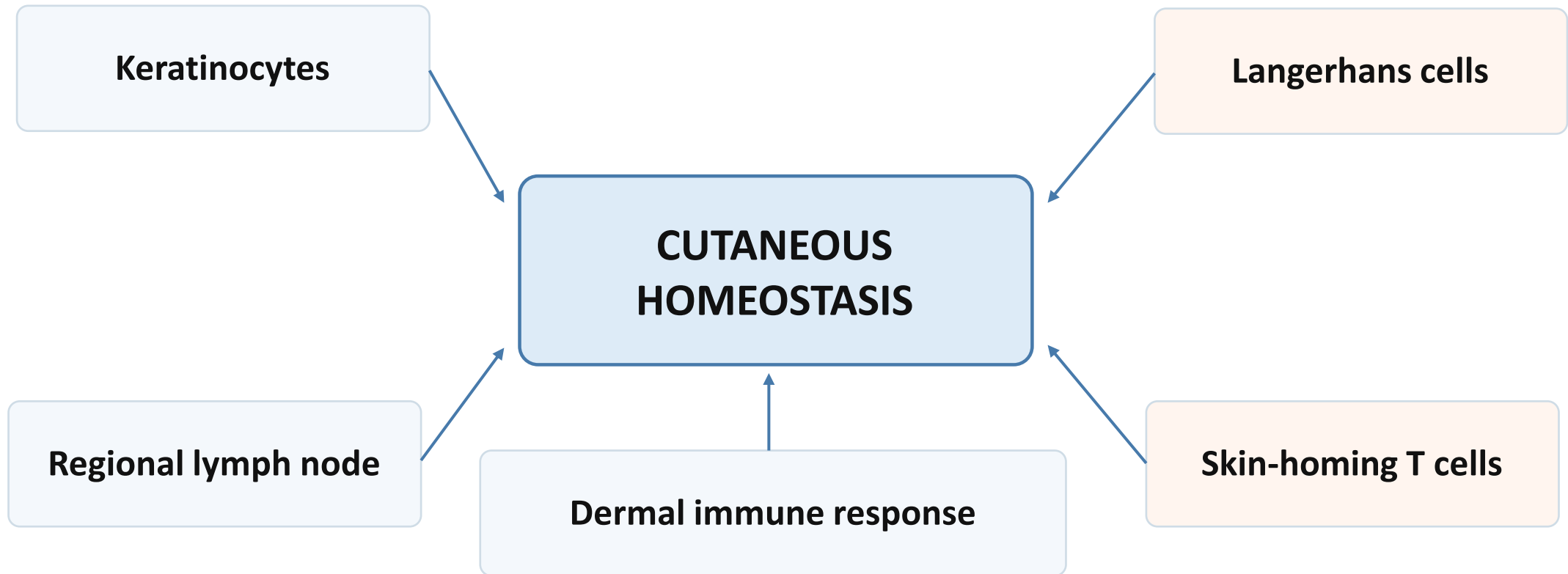
B lymphocytes

Present in smaller numbers within dermis

Can contribute to humoral responses to encountered antigens

Cutaneous immune activity is a distributed circuit

Protection requires exchange among skin, regional nodes, and returning effector cells.



Immune dysregulation creates visible disease

Inflammatory and infectious lesions arise from locally patterned immune responses.

Initiation

Environmental exposures and antigen capture

Amplification

Keratinocyte-derived mediators and recruited leukocytes

Expression

T-cell cytokines change the tissue response

Clinical appearance

Rash patterns reflect underlying pathology

The skin is a biological ecosystem

Many organisms inhabit cutaneous niches and coexist with their human host.

Bacteria

Part of normal skin ecology

Fungi

Can occupy cutaneous niches

Viruses

Included in the organisms found at the skin surface

Mites

Arthropods may share skin niches

Different skin niches support different organisms

The surface and its specialized microenvironments create habitats for the microbiome.



The microbiome can resist pathogen colonization

Resident communities occupy ecological space that otherwise could be available to harmful organisms.



The textbook explicitly draws a parallel with colonization resistance in the gut.

Microbiota complement epithelial and immune defense

Three types of protection operate at the same skin interface.

Barrier

Keratin and desmosomal cohesion

Immune surveillance

Antigen processing and local signaling

Ecological protection

Normal organisms occupy potential pathogen niches

Sensation is an essential cutaneous function

Cutaneous sensory pathways register diverse external stimuli.

Touch

Detection of tactile contact

Vibration

Detection of oscillatory mechanical input

Itch

Pruritic sensation

Pain

Noxious sensation

Cold

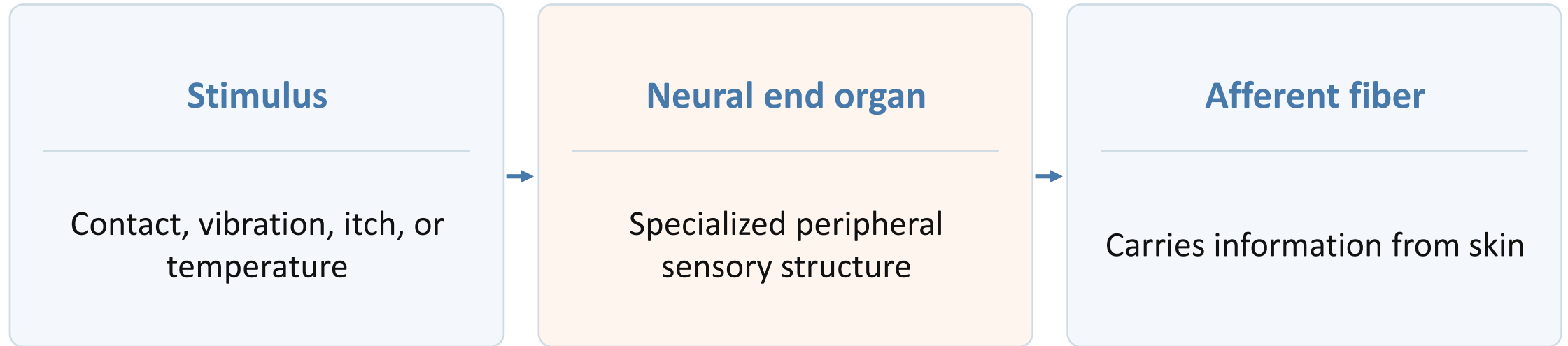
Low-temperature sensation

Heat

High-temperature sensation

Afferent nerve fibers carry cutaneous sensation

Specialized neural end organs and associated afferent fibers support sensory experience.



Autonomic fibers regulate adnexal function

Afferent pathways

Carry information about the skin

Support somatosensory awareness

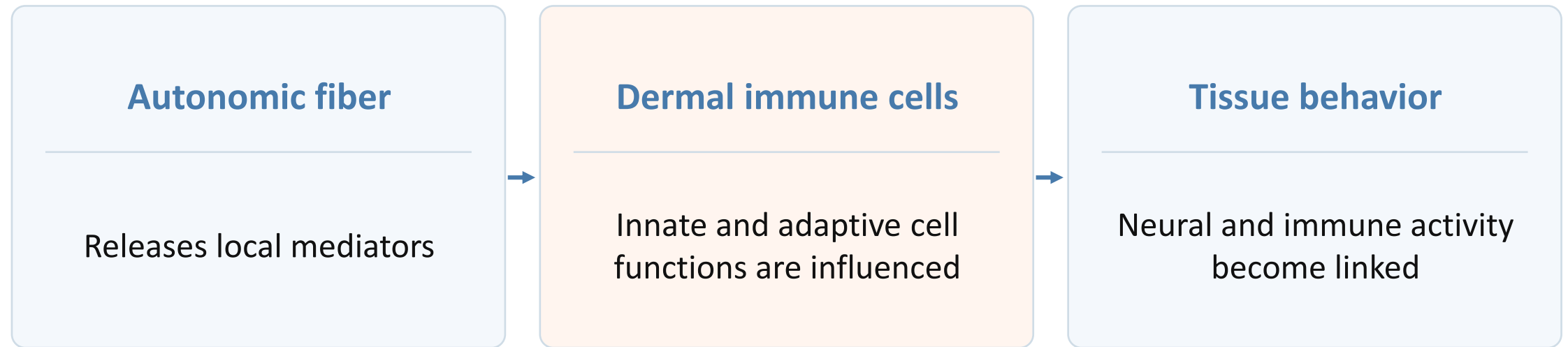
Autonomic efferents

Regulate sweat glands and arrector pili muscles

Also release factors influencing dermal immune cells

Cutaneous nerves interact with immune cells

Skin innervation has regulatory actions beyond sensory transmission.



Merkel cells are distinctive basal cells

Anatomic location

Rare cells within basal epithelial layer

Associated with neurosecretory granules in the figure description

Possible functions

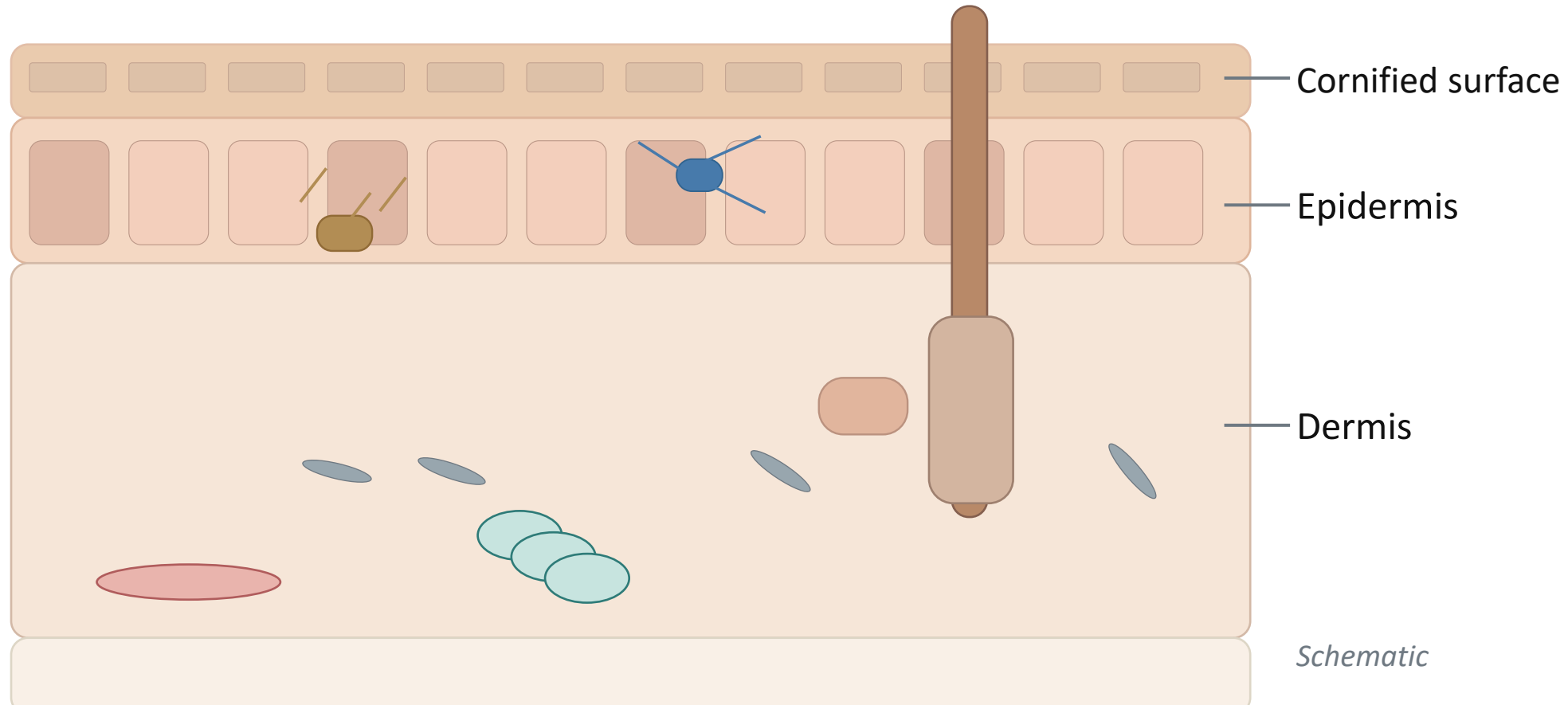
Potential neuroendocrine activity

Potential mechanoreceptor role

Persistent uncertainty

Adnexa are specialized functional extensions

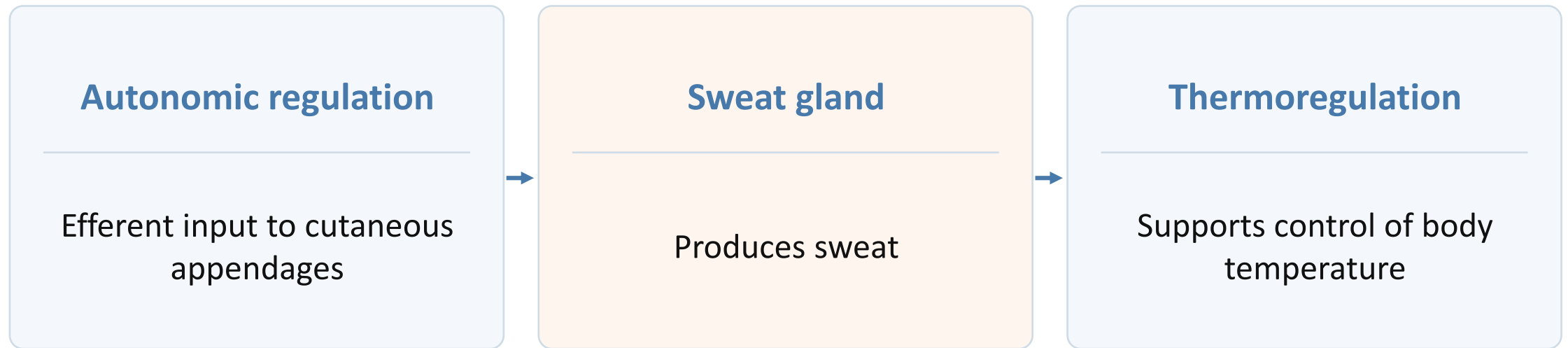
Follicles and glands extend from the epidermal surface into the dermis.



Hair follicle and glands • Epithelial extensions into dermis

Sweat glands support temperature regulation

Autonomic control acts on sweat glands to coordinate heat regulation.



Sebaceous glands protect and lubricate skin

Sebum contributes several complementary functions.

Lubrication

Maintains a lubricated cutaneous surface

Surface protection

Supports the protective interface

Water conservation

Helps limit water loss

Antimicrobial effect

Contributes to defense against microbes

Hair follicles are more than hair factories

Productive function

Manufacture hair shafts

Form specialized epidermal appendages

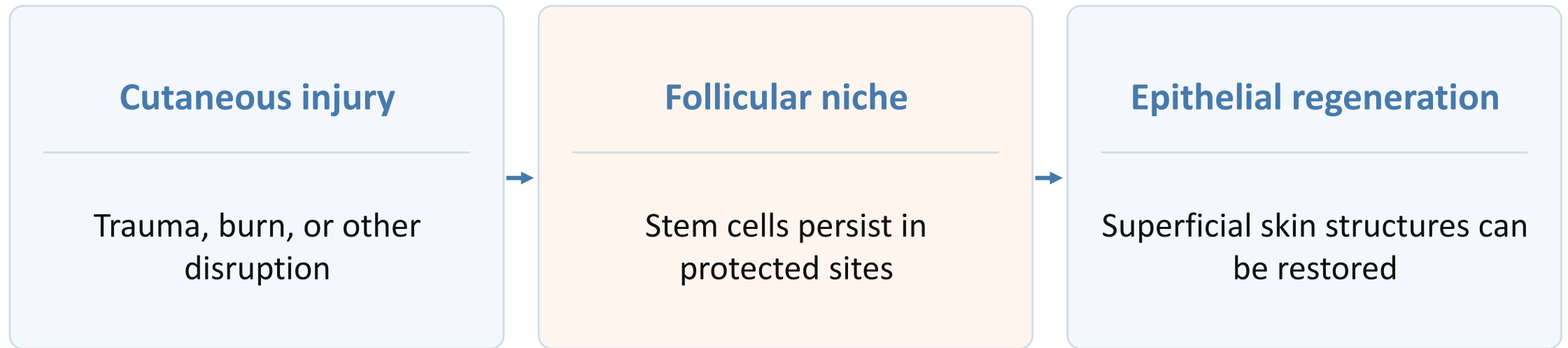
Regenerative function

Contain protected stem-cell niches

Support rebuilding of superficial epithelium after injury

Follicular stem cells support epithelial repair

Protected niches in hair follicles help reconstitute the surface after damage.



Repair depends on intact supporting compartments

The source places regenerative capacity in an anatomical network.

Follicular niche

Reservoir of epithelial stem cells

Epidermis

Superficial structure requiring replacement

Dermis

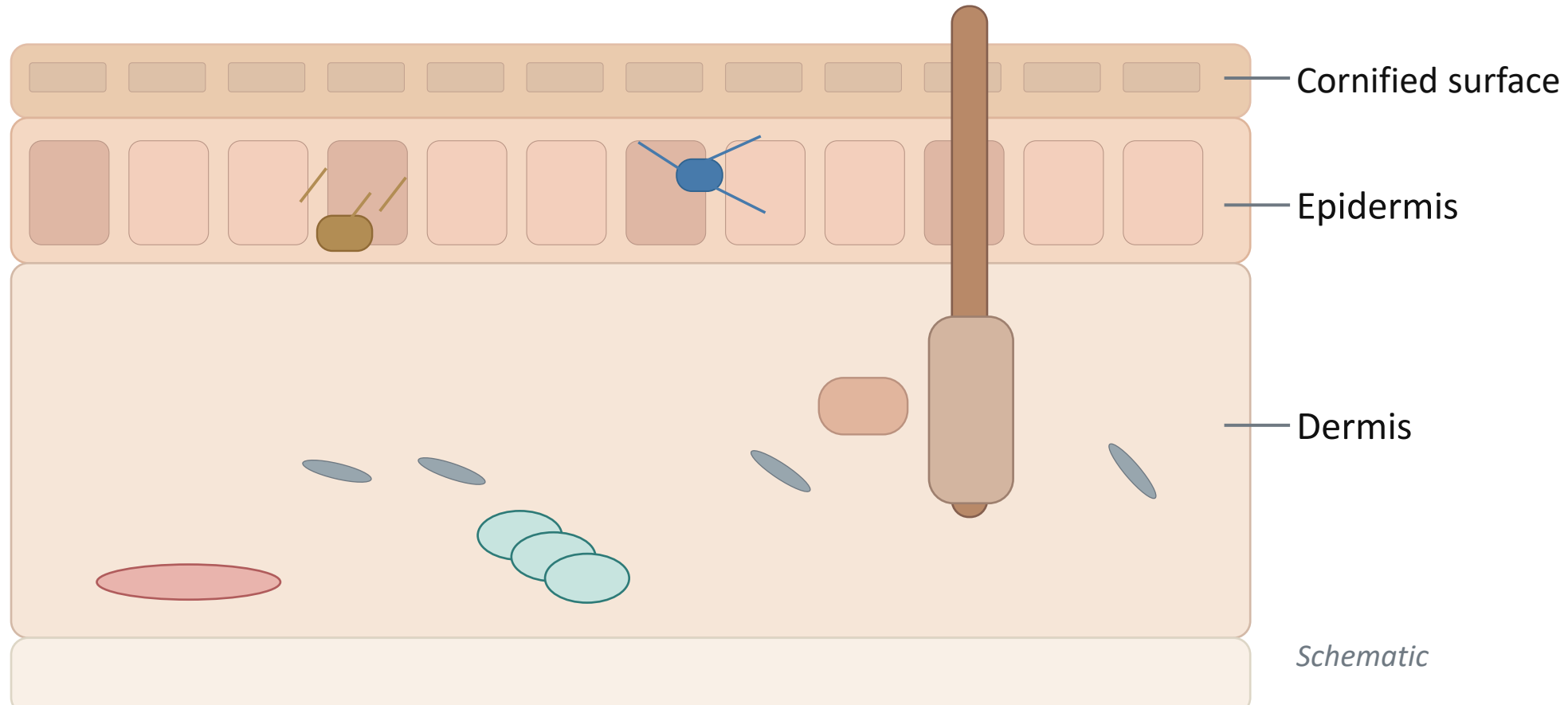
Contains supporting fibroblasts and vessels

Integrated response

Repair follows coordinated compartmental function

The dermis contains a diverse support population

Vessels, fibroblasts, mast cells, and dendrocytes support immune responses and repair.



Vessels and fibroblasts • Dermal immunity and repair

Fibroblasts and vessels belong to the dermal network

Fibroblasts

Located within dermal connective tissue

Part of dermal support and repair environment

Small vessels

Present in dermis

Situated near immune cells, including perivascular mast cells

Perivascular mast cells and dermal dendrocytes

Mast cells

Described as perivascular in Fig. 25.1

Contribute to cutaneous immune processes

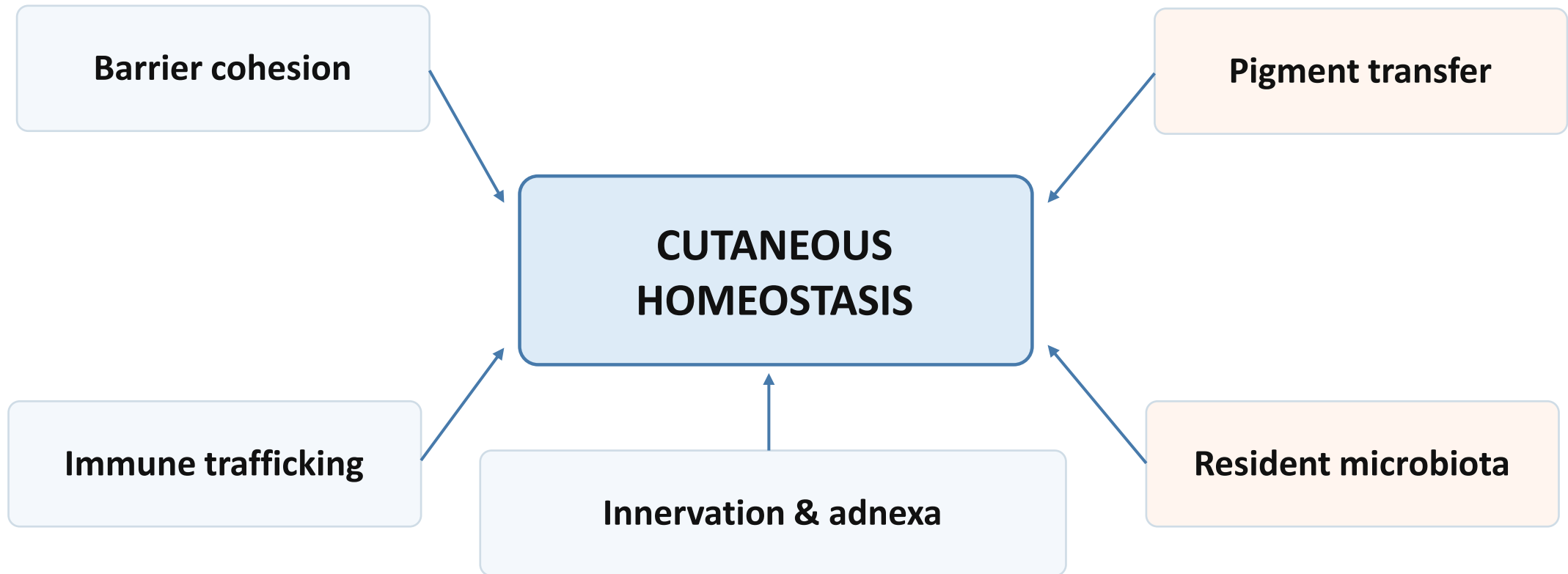
Dermal dendrocytes

Located in underlying dermis

Take part in dermal immune responses and repair

Skin homeostasis is a network property

Neither epithelial cells nor immune cells can explain skin function in isolation.



Disrupted homeostasis yields diverse disorders

Changes in cellular cooperation may manifest in several clinical domains.

Aging

Wrinkles and premature cutaneous aging

Appendage dysfunction

Hair loss

Barrier injury

Blisters

Inflammation

Rashes

Neoplasia

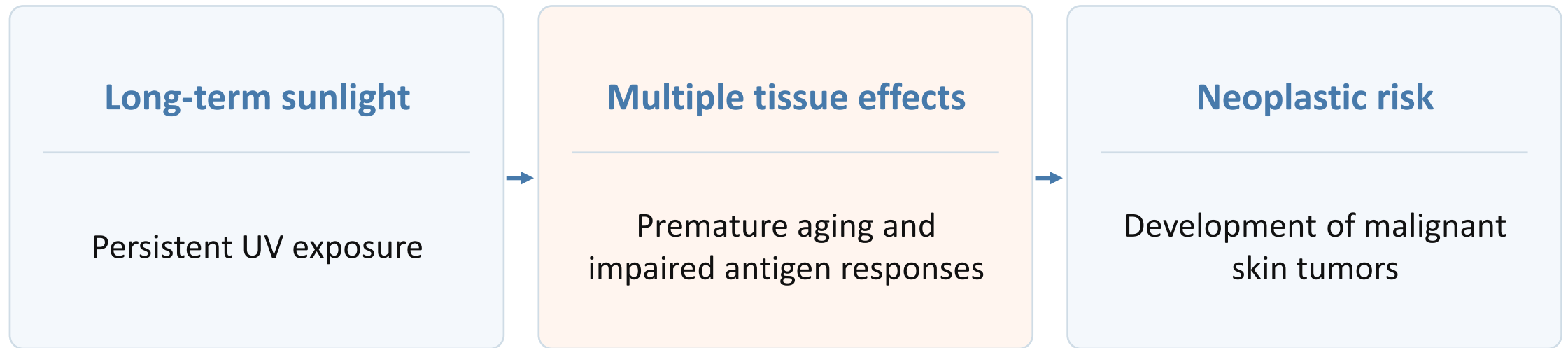
Cutaneous malignant tumors

Immune control

Disorders of immune regulation

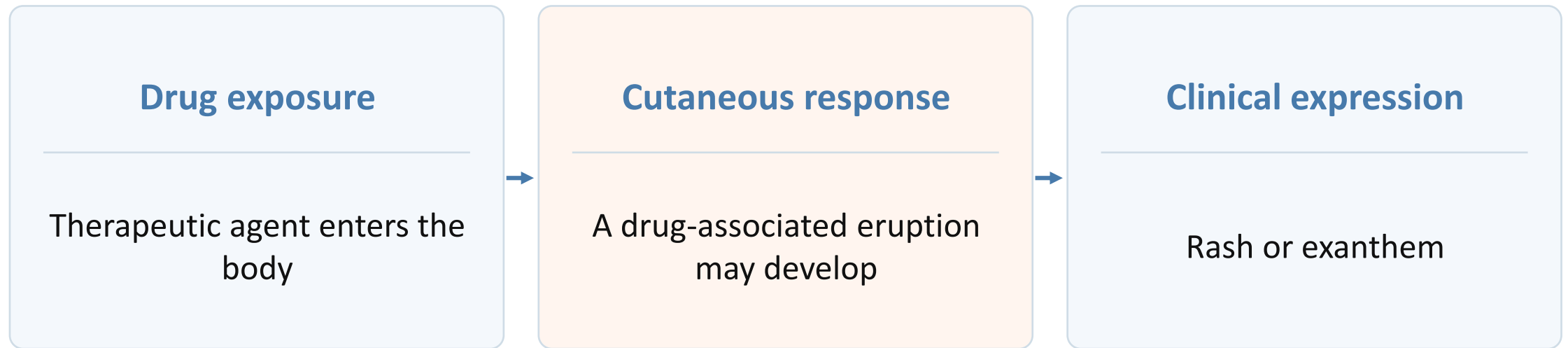
Chronic sun exposure perturbs several systems

Ultraviolet exposure has consequences beyond immediate surface damage.



Therapeutic drugs may provoke skin eruptions

A cutaneous eruption may arise from an agent ingested rather than from local exposure.



Cutaneous examination must account for medication exposure.

Systemic disease may be visible in skin

The skin can reveal pathology originating outside the integument.

Diabetes mellitus

A systemic metabolic disease with possible skin manifestations

Amyloidosis

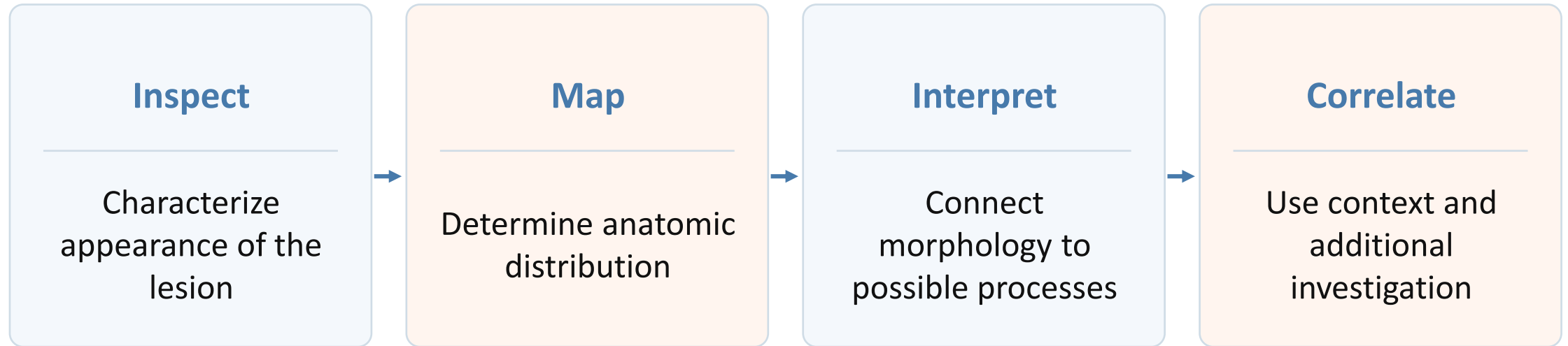
A systemic deposition disorder with possible skin findings

Lupus erythematosus

A systemic immune disorder with possible cutaneous involvement

Clinical examination begins with the lesion

The gross appearance and distribution of cutaneous findings inform diagnosis.



Macules, papules, and plaques are distinct

Dermatopathologic language distinguishes lesion topology, content, and tissue compartment.

Term	Gross morphology	Discriminator
Macule / patch	Circumscribed, flat color change	No elevation
Papule / nodule	Elevated lesion	Palpable mass
Plaque	Elevated, flat-topped lesion	Broad plateau-like surface

Vesicles, bullae, pustules, and wheals

Dermatopathologic language distinguishes lesion topology, content, and tissue compartment.

Term	Dominant feature	Implication for description
Vesicle / bulla	Raised, fluid-filled lesion	Describe blister morphology
Pustule	Localized collection of pus	Identify purulent content
Wheal	Transient, often itchy, elevated lesion	Associated with dermal edema

Scale, excoriation, and lichenification

Dermatopathologic language distinguishes lesion topology, content, and tissue compartment.

Term	Gross finding	Pathologic meaning
Scale	Dry, plate-like surface material	Disordered cornification
Excoriation	Raw linear epidermal defect	Traumatic scratching
Lichenification	Thickened rough surface	Typically repeated rubbing

Epidermal thickening: Precise terminology

Dermatopathologic language distinguishes lesion topology, content, and tissue compartment.

Microscopic term	Definition	Anatomic emphasis
Acanthosis	Diffuse epidermal hyperplasia	Viable epidermis
Hypergranulosis	Thickened granular layer	Stratum granulosum
Hyperkeratosis	Thickened cornified layer	Stratum corneum

Parakeratosis and dyskeratosis differ

Parakeratosis

Retained nuclei within the stratum corneum

Abnormal in much of skin; Normal at some mucosal surfaces

Dyskeratosis

Premature keratinization of individual cells

Occurs below the normal granular layer

Spongiosis, exocytosis, and ballooning

Dermatopathologic language distinguishes lesion topology, content, and tissue compartment.

Microscopic term	Definition	Compartment affected
Spongiosis	Intercellular edema	Epidermal spaces
Exocytosis	Inflammatory cells enter epidermis	Intraepidermal leukocytes
Ballooning	Intracellular edema of keratinocytes	Individual epithelial cells

Erosion and ulceration mark different depths

Erosion

Incomplete epidermal loss

Superficial defect with residual epidermis

Ulceration

Complete loss of epidermis

Underlying dermis or subcutis is exposed

Vacuolization, papillomatosis, and lentiginous

Dermatopathologic language distinguishes lesion topology, content, and tissue compartment.

Term	Source definition	Useful distinction
Vacuolization	Formation of vacuoles in or around cells	Often basal junctional region
Papillomatosis	Elevation by enlarged dermal papillae	Surface architecture
Lentiginous	Linear basal-layer melanocytic proliferation	Cell arrangement pattern

Apply the barrier concept to a blister

Why can a lesion arise when epidermal cell cohesion is disturbed?

Desmosomes normally connect keratinocytes into a cohesive epithelial sheet.

Weakening of adhesion permits separation within the epidermal architecture.

A fluid-filled lesion is described clinically as a vesicle or bulla.

Structure → cohesion → lesion morphology

Apply the immune circuit to an inflammatory rash

Why may a cutaneous antigen produce lymphocyte-rich inflammation?

Dendritic cells process antigens at the cutaneous interface.

Regional lymph-node presentation can stimulate T cells.

Skin-homing receptors and local chemokines promote return to dermis.

T-cell cytokines help determine microscopic and clinical features.

Antigen handling → T-cell trafficking → tissue response

Apply systemic thinking to a new eruption

Why should examination extend beyond the visible lesion?

The same rash morphology can reflect different upstream processes.

Ingested drugs can produce exanthems.

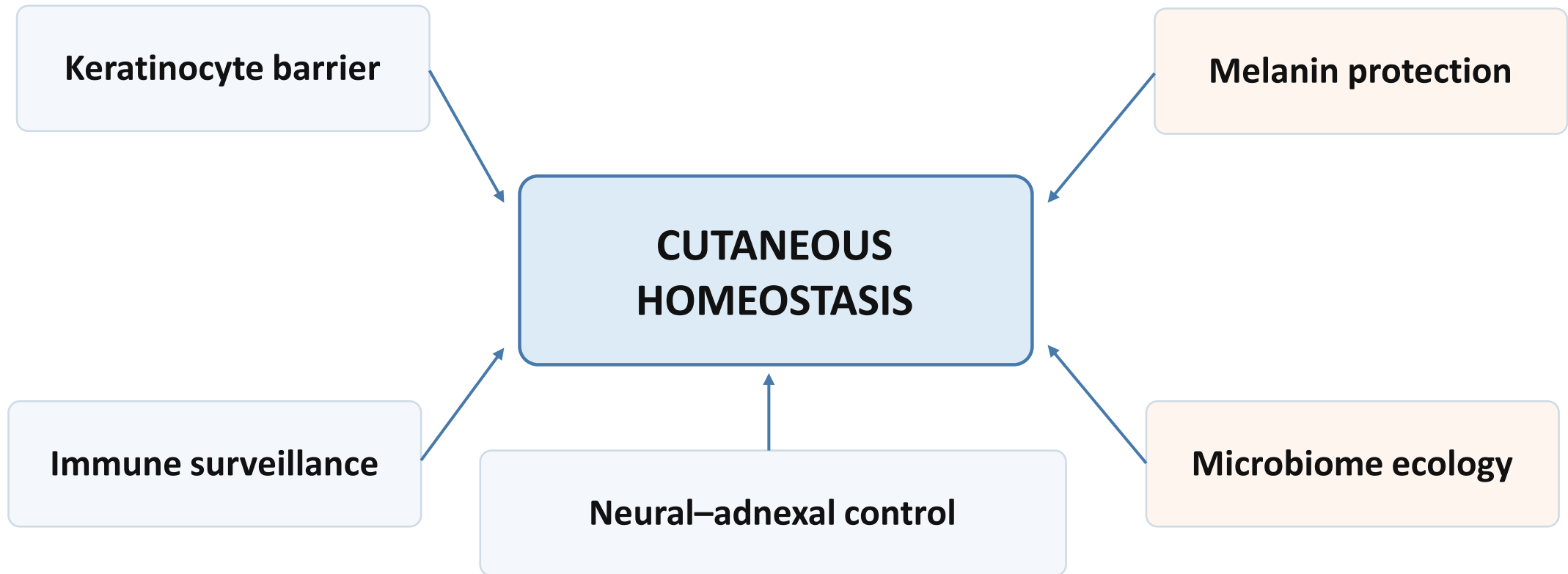
Systemic diseases can have important skin manifestations.

Appearance and distribution help formulate—rather than complete—a diagnosis.

Describe the lesion, then seek the systemic context

Integrated mechanism: The skin as a living interface

Disease becomes easier to understand when each process is assigned to its interacting cell populations.



Core clinicopathologic principles

Three principles connect the normal skin network to clinical pathology.

Structure predicts lesions

Cohesion and cornification explain physical integrity and some patterns of disruption

Signals predict inflammation

Immune-cell trafficking and cytokines explain tissue responses

Context predicts meaning

An eruption can reflect environmental exposure, medication, or systemic disease

Reasoning from skin function to disease

A focused clinicopathologic analysis connects the involved compartment to the observed lesion.

Locate the problem

Is epithelial cohesion, pigment transfer, immunity, innervation, or an appendage implicated?

Identify the mechanism

Relate a specific cell or signaling process to a structural or functional change

Describe the morphology

Use precise clinical and microscopic terminology instead of a nonspecific rash label

Integrate the context

Ask about sunlight, drugs, microbial exposure, and underlying systemic disease