

Ultraviolet Rays

Radiation carcinogenesis, DNA repair and cutaneous neoplasia

Mechanisms → mutation signatures → skin cancer pathology

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives: Interpret UV-associated carcinogenesis

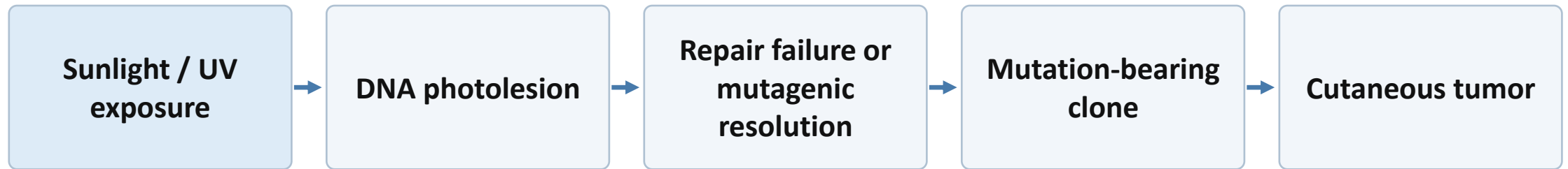
- Differentiate UV wavelength ranges and explain why exposure varies with pigmentation.
- Trace UVB photolesions through nucleotide excision repair and mutagenesis.
- Use xeroderma pigmentosum and mutation signatures as causal evidence.
- Connect exposure and molecular events to actinic keratosis, SCC, BCC and melanoma.

Ultraviolet light as a physical carcinogen

- Solar UV is radiant energy capable of generating mutagenic DNA lesions.
- Its most important pathology consequences concern cutaneous cancers.
- Carcinogenic action links environmental exposure to cellular genomic instability.
- The outcome reflects the interaction of exposure, pigment protection and repair.

An exposure is not a tumor: Transformation requires selected cellular alterations.

The causal chain: Exposure to cutaneous malignancy



- UV damage initiates an opportunity for mutations.
- Selection and subsequent alterations are required for neoplasia.

Radiant energy: UV versus ionizing radiation

Dimension	Ultraviolet light	Ionizing radiation
Principal lesion discussed	Pyrimidine dimers	DNA strand breaks and DNA cross-linkage
Main cancer context	Sun-exposed skin	Several tissues, sometimes after long latency
Inherited repair illustration	Xeroderma pigmentosum / NER	Other DNA damage-response defects
Teaching distinction	Photochemical adjacent-base lesion	More varied direct and indirect DNA injury

Solar ultraviolet bands and the ozone filter

Wavelength ranges stated

UVC 200–280 nm	UVB 280–320 nm	UVA 320–400 nm
--------------------------	--------------------------	--------------------------

UVC: Described as filtered by stratospheric ozone

UVB: Emphasized as the main direct DNA-damaging solar band

Wavelength labels are categories, not a quantitative solar spectrum.

Solar UV: Three defined wavelength groups

UVC

200–280 nm. Potently mutagenic in principle; Naturally screened by the ozone layer.

UVB

280–320 nm. Directly linked by Robbins to cutaneous carcinogenesis through pyrimidine dimers.

UVA

320–400 nm. Defined in the source spectrum; The focused passage does not detail UVA mechanisms.

Do not interpret the limited treatment of UVA as evidence that it is harmless.

The atmosphere modifies biologically relevant exposure

- The ozone layer intercepts solar UVC before it reaches the skin.
- UVB reaches the skin and can produce carcinogenic photochemical DNA injury.
- The wavelength distribution reaching tissue matters more than mutagenicity in isolation.
- Hence environmental filtering modifies the exposure that cells actually experience.

Three determinants of UV cancer risk

Radiation

UV wavelength influences the kind and biological relevance of DNA damage.

Exposure

Intensity and duration alter the burden of incident photons reaching skin.

Host phenotype

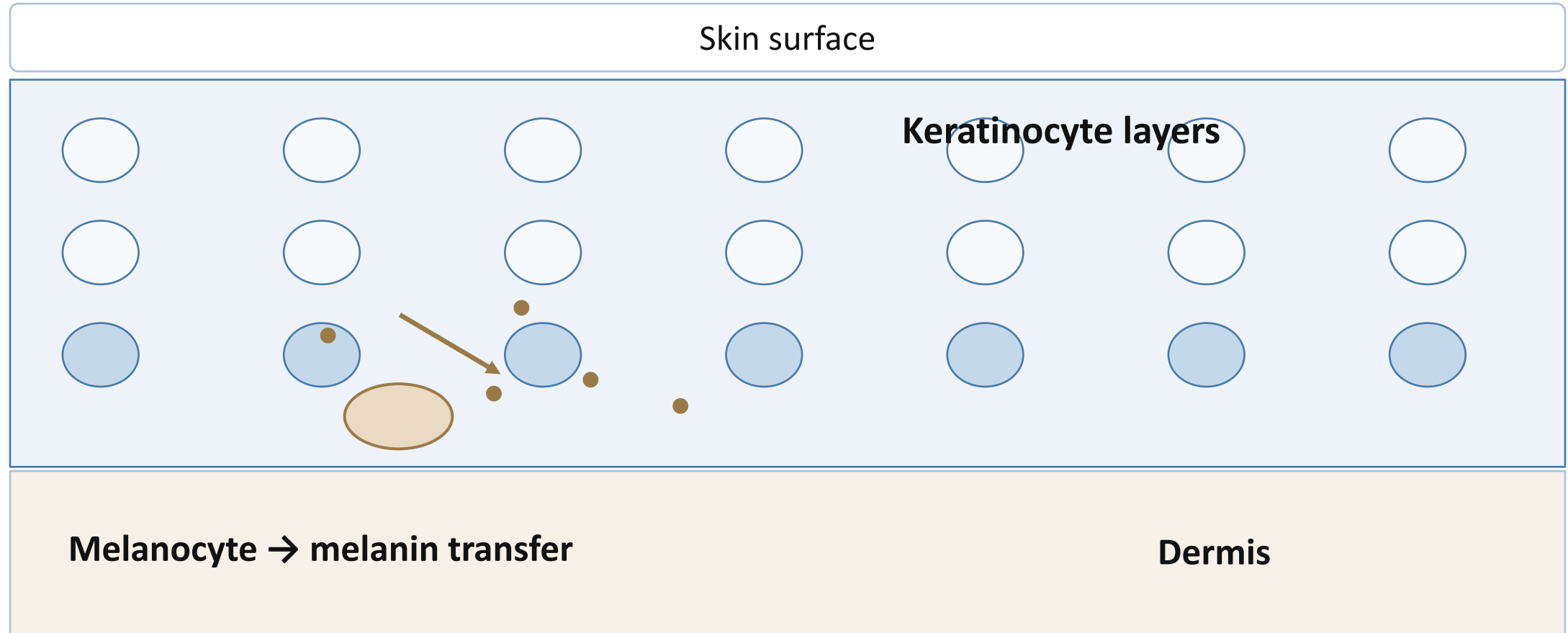
Melanin quantity and the capacity to respond to UV lesions modify biological injury.

Risk is multifactorial; The source does not give a numerical risk equation.

Why pigmentation changes UV vulnerability

- Melanin absorbs incident UV energy and attenuates injury to cellular DNA.
- Epidermal melanocytes synthesize melanin and transfer it to keratinocytes.
- Skin pigmentation therefore changes effective DNA exposure at a given sunlight intensity.
- Pigmentation is protective, not absolute immunity from skin cancers.

Epidermal cells explain the major UV-associated tumors



Schematic: Keratinocytes give rise to SCC/BCC; Melanocytes give rise to melanoma.

Fair skin and poor tanning are clinically relevant

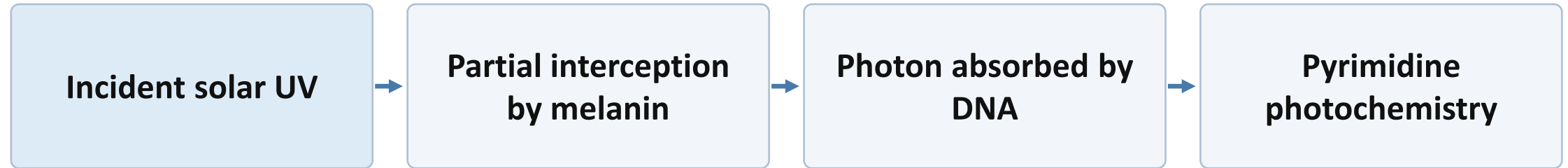
- Robbins singles out fair skin that burns readily and does not tan.
- Limited melanin shielding helps explain higher susceptibility to UV injury.
- Strong sunlight exposure compounds the vulnerability of lightly pigmented skin.
- A high-risk phenotype describes susceptibility; It is not diagnostic of malignancy.

Do not infer that darkly pigmented patients cannot develop melanoma or SCC.

Geography and exposure intensity interact

- Queensland, Australia, as a high-sunlight exposure setting.
- Fair skin plus strong sunlight is a particularly high-risk combination.
- Location is an exposure modifier rather than a biological mutation.
- Mechanistic interpretation must distinguish environmental dose from host sensitivity.

How sunlight reaches the genomic target



- Melanin reduces exposure but does not eliminate the potential for DNA injury.
- Direct DNA absorption can generate a characteristic photoproduct.

The endpoint is mutation, not simply sunburn

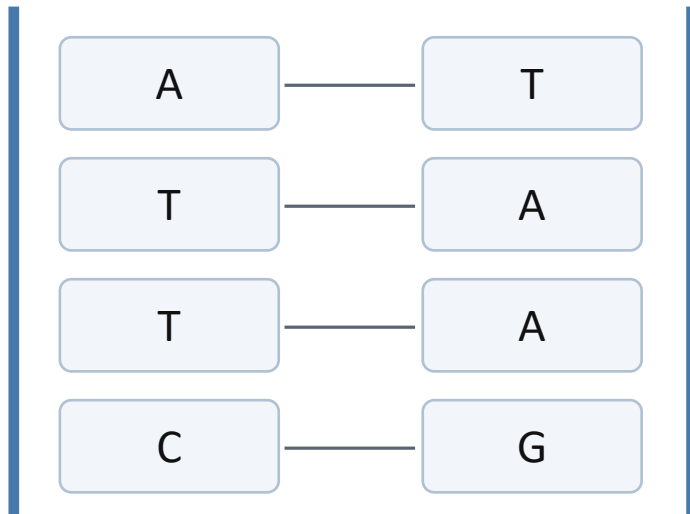
- Acute visible injury and long-term oncogenic changes are distinct outcomes.
- A DNA lesion may be repaired accurately without permanent sequence change.
- If an unrepaired lesion is bypassed or resolved inaccurately, mutations may result.
- A mutagenic event matters for cancer when it affects a surviving, proliferating lineage.

Keratinocytes and melanocytes define different tumors

- Keratinocytes form the epidermal epithelial barrier and its proliferating layers.
- Melanocytes reside within the epidermis and produce photoprotective melanin.
- Squamous and basal cell carcinomas arise from epithelial lineages.
- Melanoma is a malignant neoplasm of melanocytic lineage.

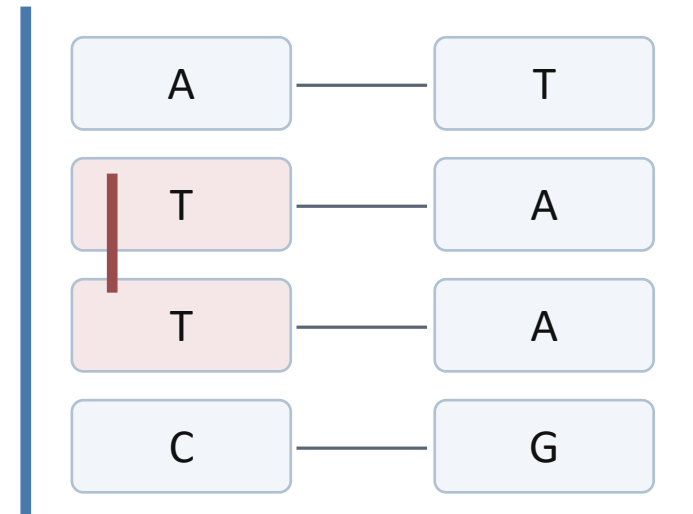
Adjacent pyrimidines form a UV-induced photolesion

Before photochemical injury



Normal base pairing

After UVB photon absorption



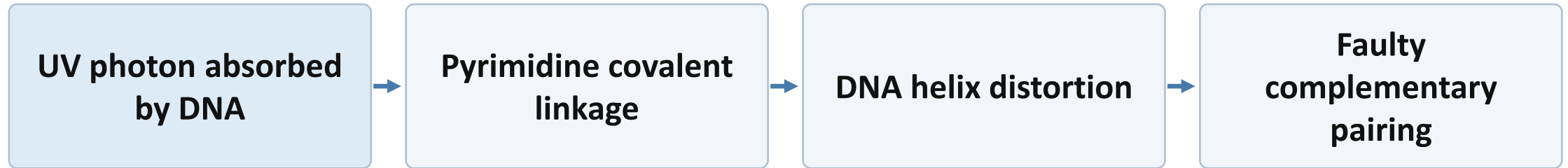
Covalent linkage

Conceptual illustration: Two adjacent pyrimidines on one strand become covalently linked.

Why adjacent thymidines are especially important

- Pyrimidines in the same DNA strand can become covalently linked after UV exposure.
- The textbook particularly emphasizes neighboring thymidine residues.
- The lesion is a chemical change in DNA—not a protein cross-link or chromosome break.
- A dimer spans neighboring bases and disrupts the geometry of double-stranded DNA.

A photon-to-lesion mechanism



- UVB carcinogenesis begins at the molecular scale.
- The abnormal structure is a substrate for cellular DNA-repair systems.

Helix distortion has replicative consequences

- A covalently linked pyrimidine pair distorts the normal double helix.
- The damaged bases cannot pair properly with the opposite strand.
- Persistent lesions interfere with faithful copying of genetic information.
- Accurate repair before propagation protects sequence integrity.

Nucleotide excision repair as genome protection

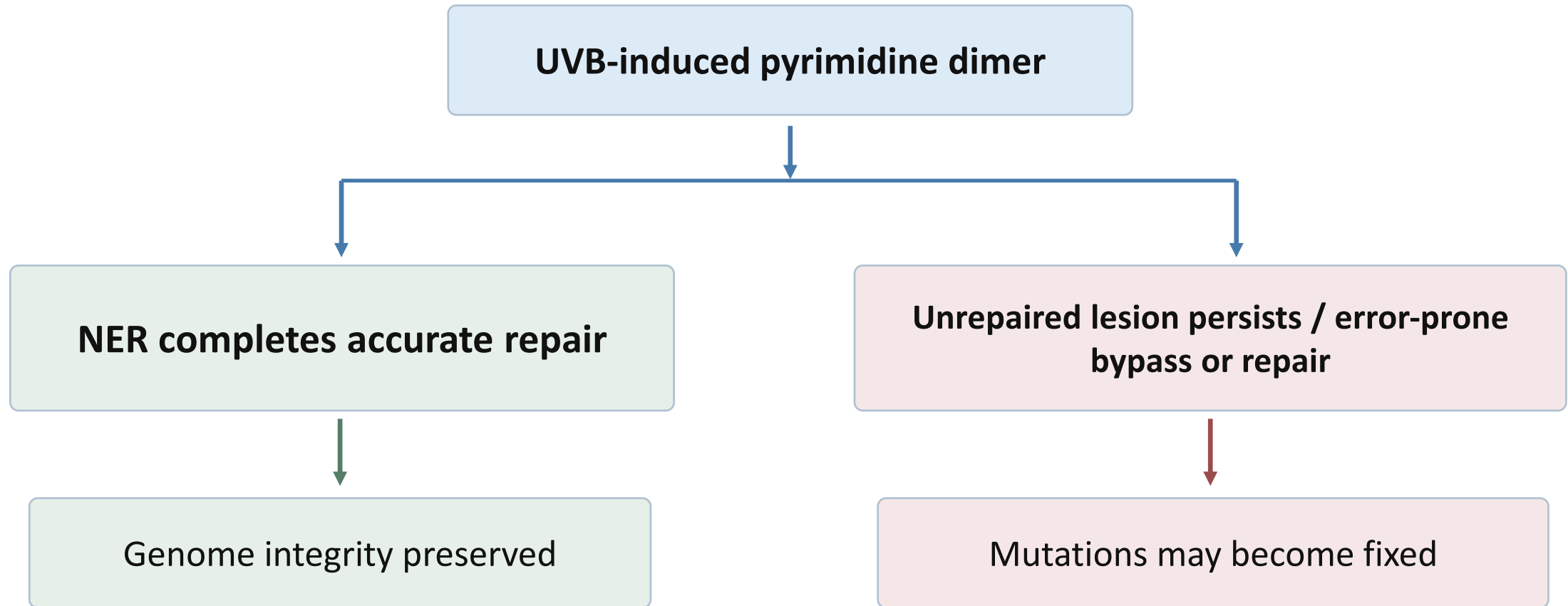


- Simplified conceptual sequence, not a full biochemical protein inventory.
- A repair network involving at least 30 proteins.

NER is a multicomponent repair mechanism

- The UV passage identifies nucleotide excision repair (NER) as the dimer repair pathway.
- Repair requires the coordinated functions of 30 or more proteins.
- Pathway integrity matters because DNA synthesis must resume from accurate sequence.
- An inherited defect in one required component can markedly increase cancer susceptibility.

Repair capacity determines whether DNA injury persists



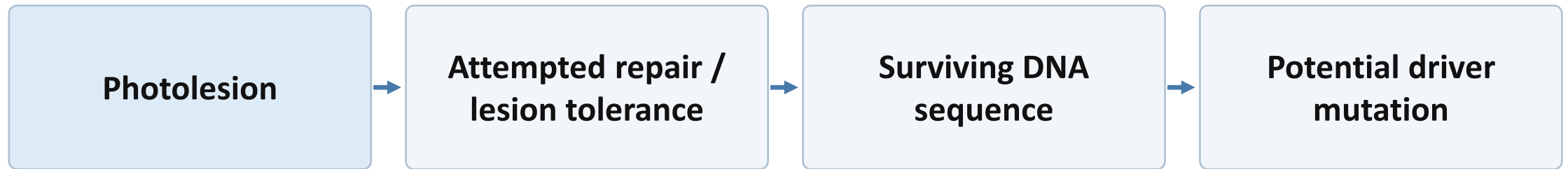
Repair saturation with excessive exposure; The exact threshold is not supplied.

Excessive UV exposure may overwhelm repair

- That high solar exposure can exceed NER repair capacity.
- Some lesions may then persist or be resolved through more error-prone processes.
- Cell survival in this setting can come at the price of new DNA mutations.
- The passage does not supply a numerical NER saturation threshold.

Repair saturation is framed as a hypothesis by the source, not an established dose cut-off.

Cell survival and mutagenesis are not equivalent



- Survival does not imply fidelity: Inaccurate resolution can fix a mutation.
- A driver mutation alone need not produce a fully malignant phenotype.

Repair outcomes after UV photodamage

Accurate resolution

Original sequence restored;
No fixed mutation from that lesion.

Mutagenic resolution

An incorrect base substitution may be inherited by daughter cells.

Persistent lesion

Replication and cell viability may be compromised unless the lesion is managed.

These are mechanistic teaching outcomes, not measured proportions.

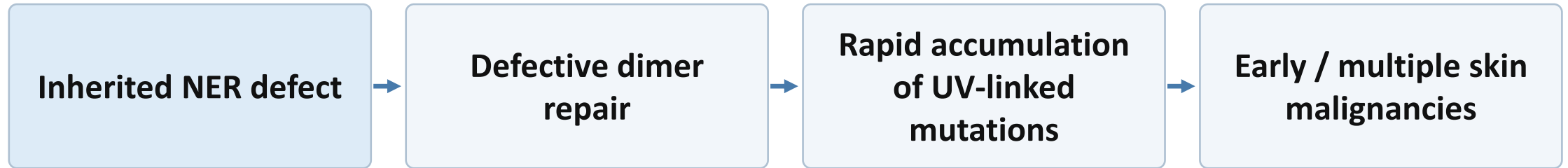
Why repair genes function as cancer-susceptibility genes

- Genome maintenance suppresses the accumulation of oncogenic lesions.
- When repair fails, the same exposure can produce more permanent mutations.
- Inherited defective repair amplifies susceptibility to environmentally induced cancers.
- This is an example of genomic instability enabling malignant transformation.

Xeroderma pigmentosum: The genetic experiment

- Xeroderma pigmentosum (XP) results from inherited loss of NER function.
- The disorder produces profound susceptibility to UV-exposed skin cancers.
- Both cutaneous squamous cell and basal cell carcinomas are emphasized in Chapter 7.
- XP illustrates that DNA repair—not exposure alone—governs cancer vulnerability.

Xeroderma pigmentosum: Gene to phenotype



- Inherited repair deficiency magnifies the carcinogenic consequences of sunlight.
- The link is mechanistic and epidemiologic, not a morphology-only association.

XP and the meaning of repair-pathway specificity

- XP highlights defects in nucleotide excision repair.
- The key unrepaired lesions are UV-induced pyrimidine dimers.
- This contrasts with mismatch repair syndromes, which accumulate replication errors.
- Different repair failures create different genomic vulnerabilities and cancer patterns.

Mismatch-repair contrast comes from adjacent Ch 7 “DNA Mismatch Repair Factors.”

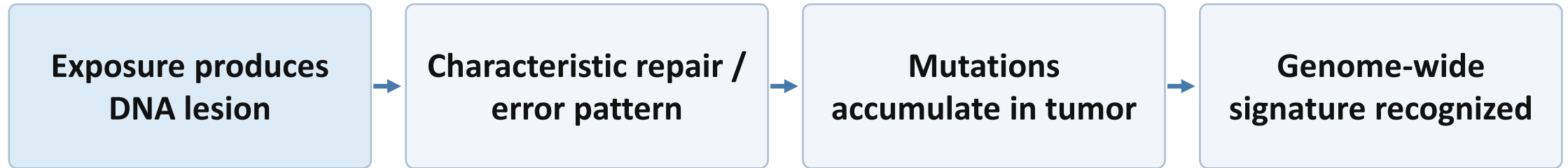
XP links constitutional risk to somatic mutations

- The repair defect is present as an inherited cellular susceptibility.
- UV-induced mutations then arise somatically in exposed skin cells.
- Tumor formation reflects the later acquisition and selection of oncogenic changes.
- A germline repair defect should not be confused with a tumor-specific driver mutation.

Genome sequencing can reveal the cause of mutation

- Mutagens can leave reproducible patterns of base substitution in tumor genomes.
- A UV signature associated with faulty resolution of pyrimidine dimers.
- The signature provides molecular evidence implicating the damaging exposure.
- A signature is mechanistic evidence, not proof of when any one exposure occurred.

Using mutation signatures as causal evidence



- Concordance between molecular damage and observed substitutions strengthens causal inference.
- Mutation signatures complement clinical and epidemiologic observations.

Melanoma genomics resolved a key controversy

- Sun-exposed melanomas contain numerous mutations bearing a UV-associated signature.
- This pattern supports a causal role for UV-induced DNA injury in many melanomas.
- This evidence with earlier controversy about melanoma etiology.
- The inference is strongest for melanomas arising in sun-exposed skin.

A mutational signature is not the same as a driver

- The UV signature describes the process that generated mutations.
- A driver mutation confers a selective advantage on the neoplastic lineage.
- A skin tumor can contain many passenger substitutions alongside causal driver lesions.
- Do not equate high mutational burden with one specific molecular pathway.

Actinic keratosis: A visible precursor in sun-damaged skin

- Actinic keratoses typically arise on chronically sun-exposed cutaneous surfaces.
- They are especially frequent in lightly pigmented individuals.
- Lesions may exhibit progressive epithelial dysplasia toward cutaneous SCC.
- They may also remain stable or regress rather than necessarily progress.

Actinic keratosis: Clinicopathologic correlation

Clinical appearance

Rough or sandpaper-like keratotic lesions; Usually small, often face or dorsal hands.

Microscopic atypia

Atypia typically affects lower epidermal layers; Hyperkeratosis and parakeratosis are common.

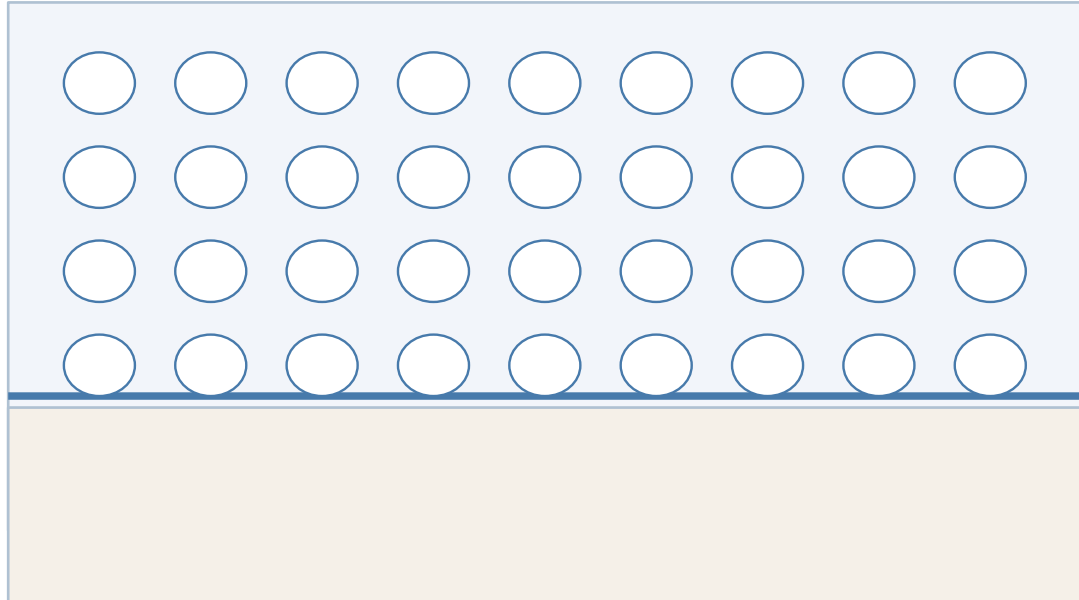
Adjacent sun damage

Dermal solar elastosis reflects chronically sun-damaged connective tissue.

A clinical impression is insufficient for histologic grading of atypia.

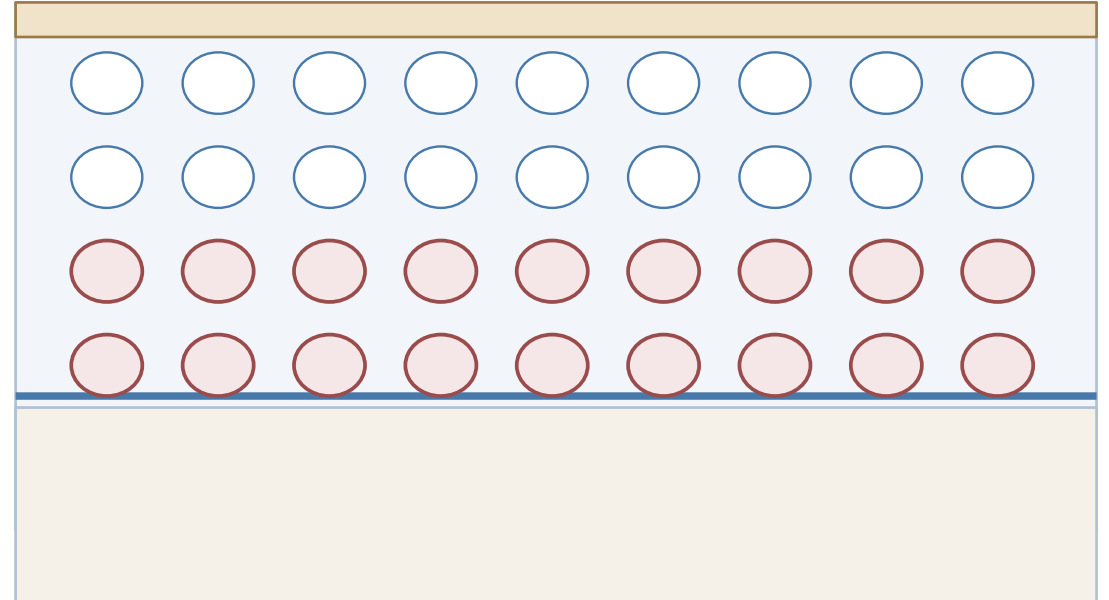
Actinic keratosis: Atypia starts in lower epidermis

Reference epidermis



Basement membrane

Illustrated abnormality



Dermis

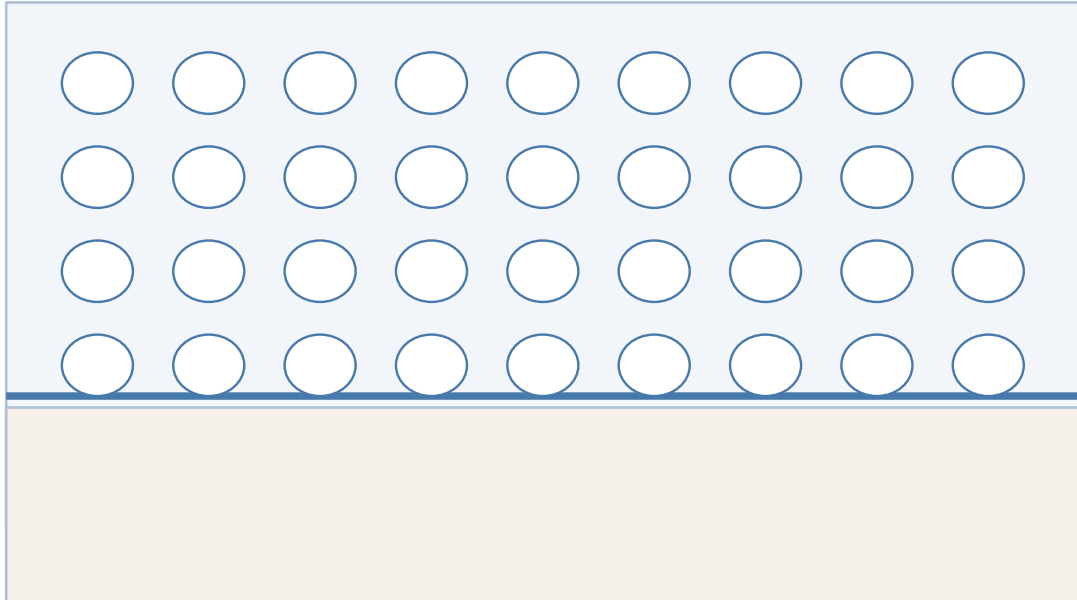
Schematic: Lower-layer atypia with an intact basement membrane.

Solar elastosis records cumulative dermal damage

- UV-exposed skin can show thickened abnormal elastic material in superficial dermis.
- Blue-gray elastotic fibers beneath actinic keratoses.
- This finding supports chronic photodamage of the surrounding tissue.
- Solar elastosis is a contextual feature, not an independent diagnosis of carcinoma.

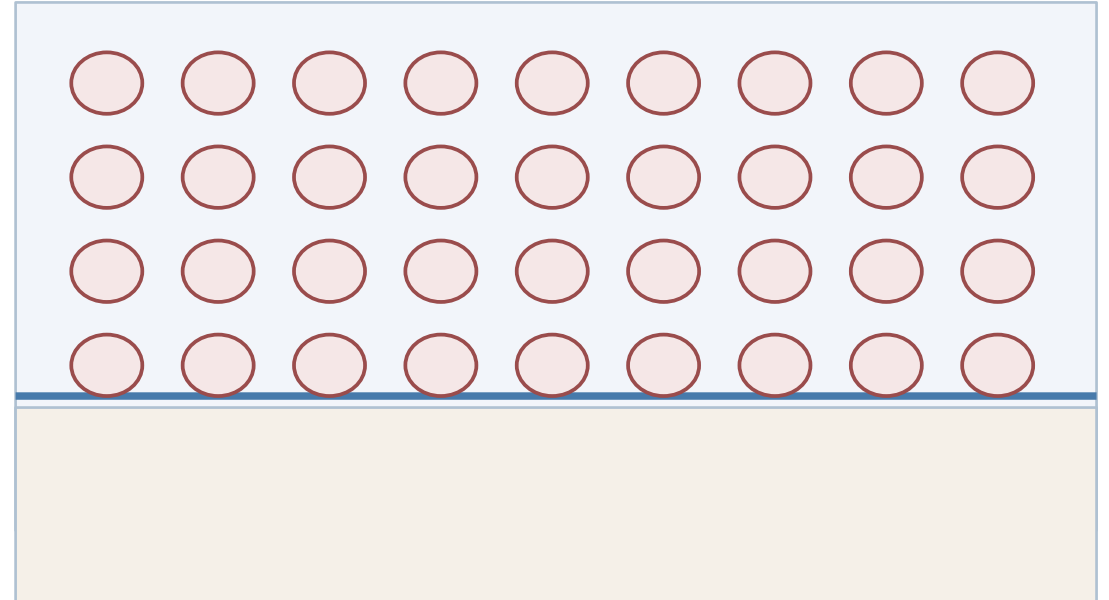
SCC in situ: Atypia throughout the epidermis

Reference epidermis



Basement membrane

Illustrated abnormality

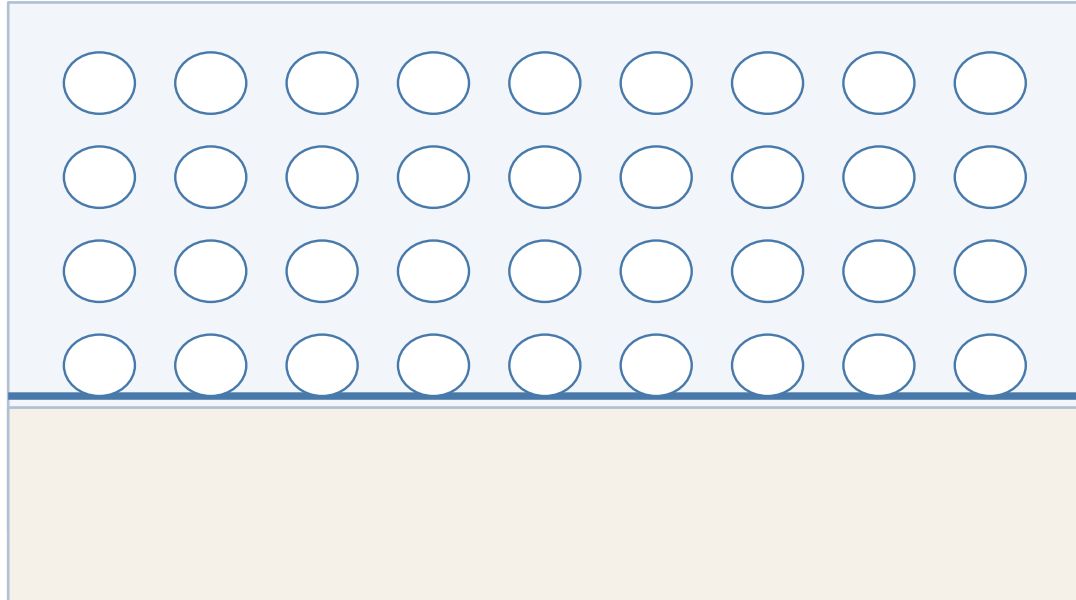


Dermis

Schematic: Full-thickness atypia without basement membrane breach.

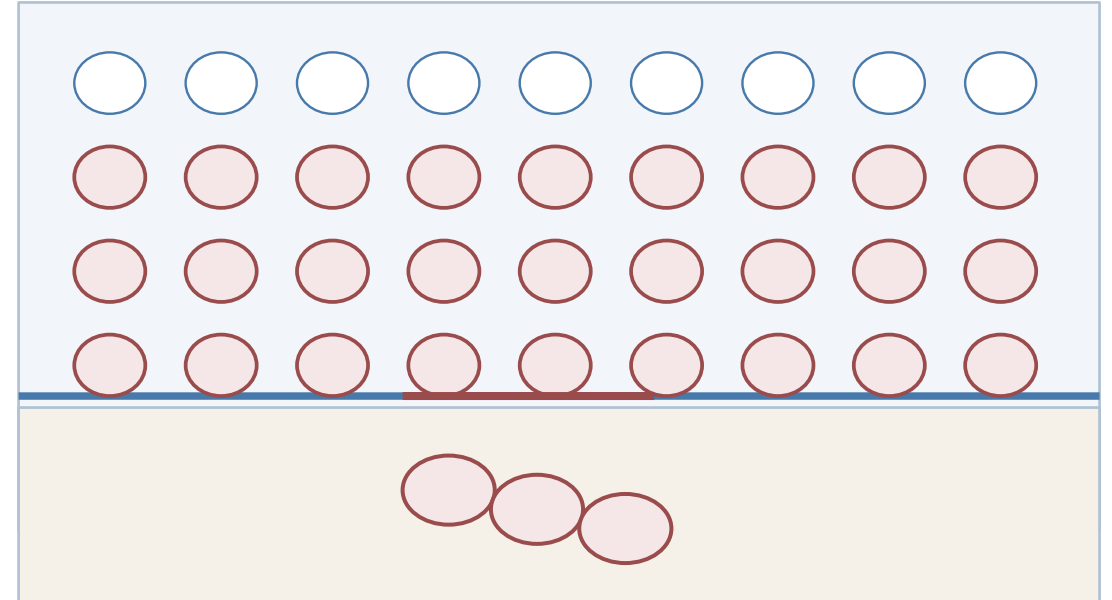
Invasive SCC: Atypical cells traverse the basement membrane

Reference epidermis



Basement membrane

Illustrated abnormality



Dermis

Schematic: Dermal tumor groups indicate stromal invasion; Not an H&E image.

TP53 mutations connect photodamage to early SCC

- Chapter 25 describes TP53 mutations in actinic keratoses.
- UV-associated substitutions occur at sites of pyrimidine dimer damage.
- Early p53 dysfunction reduces a key genomic integrity safeguard.
- Further driver alterations are required during progression to invasive carcinoma.

From UV damage to cutaneous SCC



- An illustrative progression model, not an obligatory route for every tumor.
- The basement membrane separates in situ disease from invasion.

Cutaneous SCC has multiple etiologic contexts

- Lifetime sun exposure is a dominant epidemiologic determinant.
- Immunosuppression following transplantation or chemotherapy increases risk.
- Old burns, chronic ulcers and chemical carcinogens are additional associations.
- The presence of SCC is not by itself proof of UV as the sole cause.

Cutaneous SCC: A multistep driver process

- Loss of p53 activity is an important early molecular event.
- Additional changes increasing RAS signaling may promote proliferation.
- Reduced Notch signaling is another contributor.
- Each alteration acts within a mutation-bearing epithelial clone.

SCC morphology must establish invasion

- In situ disease: Atypical keratinocytes involve epidermal thickness.
- Invasion: Atypical squamous nests or tongues extend into dermis.
- Keratinization varies with the degree of tumor differentiation.
- Poorly differentiated tumors may require keratin immunostains to verify lineage.

Why UV-associated SCC is clinically consequential

- Most cutaneous SCC can be recognized and treated locally.
- Unlike BCC, SCC has a meaningful capacity for nodal spread.
- Advanced disease can be locally destructive or metastatic.
- Morphologic diagnosis informs both clinical management and prognosis.

Basal cell carcinoma: UV-associated but molecularly distinct

- BCC often develops at sun-exposed sites in lightly pigmented older adults.
- Its principal oncogenic pathway involves excessive Hedgehog signaling.
- Most BCCs are locally aggressive, slow growing and rarely metastatic.
- The UV connection operates through acquired mutations rather than a unique UV-specific morphology.

Basal cell carcinoma: Oncogenic Hedgehog signaling

Regulated signaling

PTCH suppresses SMO



No ligand → pathway off



GLI activity restrained

PTCH loss of function

PTCH inhibition lost



SMO signaling permitted



GLI-driven tumor cell growth

UV-signature substitutions in a subset of sporadic PTCH mutations.

UV signatures are detected in PTCH mutations

- PTCH is a tumor suppressor restraining Smoothed-dependent signaling.
- Loss-of-function PTCH changes occur frequently in sporadic BCC.
- UV-associated C→T transitions in a subset of PTCH mutations.
- The UV signature supplies direct molecular support for the exposure–BCC link.

BCC morphology: Recognition points

- Clinically, lesions may be pearly papules with telangiectatic vessels.
- Microscopy shows basaloid nests, often with peripheral palisading.
- Stromal retraction clefts may border tumor islands.
- The morphology differs from keratinizing invasive cutaneous SCC.

Cutaneous SCC versus BCC: Practical differences

Dimension	Cutaneous SCC	Basal cell carcinoma
Major lineage	Squamous keratinocyte differentiation	Basaloid epithelial neoplasm
Useful histology	Atypical squamous cells, keratinization	Basaloid nests, palisading, stromal clefts
Characteristic driver context	TP53, RAS/Notch alterations	PTCH/SMO/GLI Hedgehog pathway
Metastatic behavior	Potential for regional/distant spread	Metastasis extremely rare

Melanoma: UV injury in a different cell lineage

- Melanoma arises from melanocytes rather than keratinocytes.
- Sun-exposed cutaneous melanomas show high UV-signature mutational burdens.
- Low melanin production increases UV vulnerability in some genetic backgrounds.
- Familial predisposition and other factors also influence melanoma development.

The sunlight–melanoma link is not uniform

- Melanomas can occur on sites with little or no UV exposure.
- Melanoma also occurs in individuals with more highly pigmented skin.
- Intermittent severe sunburns may be important, but exposure patterns are complex.
- Avoid assuming that every melanoma arose through a solar UV pathway.

Melanoma drivers are separable from UV damage

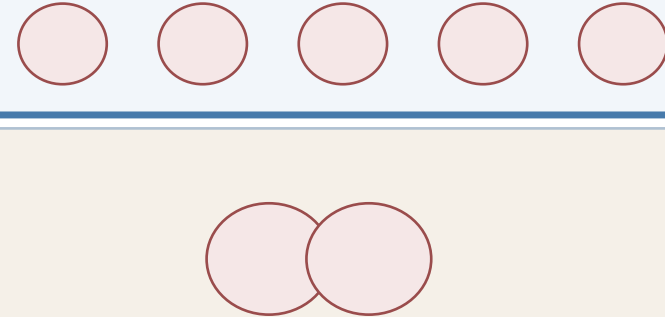
- Cell-cycle lesions (e.g., CDKN2A dysfunction) support proliferation.
- BRAF/RAS pathway activation supplies progrowth signals in many tumors.
- Telomerase activation supports replicative persistence.
- A UV signature describes damage history; These alterations describe selection.

Melanoma progression: Radial versus vertical growth

Radial growth phase



Vertical growth phase



Schematic, not specimen: Downward dermal invasion defines the vertical component.

Recognizing melanoma in a pathology context

- Clinical suspicion may arise from irregular shape, color variation or changing lesions.
- Microscopic assessment determines architecture, atypia and invasion.
- Radial growth describes lateral spread; Vertical growth includes dermal invasion.
- The UV causal pathway must not be confused with pathologic stage.

Three major skin cancers linked to solar UV

Feature	SCC	BCC	Melanoma
Cell lineage	Squamous epithelial	Basaloid epithelial	Melanocytic
UV-related molecular evidence	TP53 photodamage changes	PTCH UV-type substitutions	Genome-wide UV signatures
Key teaching morphology	Keratinization / invasion	Palisading / retraction	Atypical melanocytes / invasion
Clinical concern	Nodal or distant metastasis	Primarily local destruction	Potential for aggressive spread

Cumulative injury versus varied melanoma exposure

- Lifetime sun exposure closely correlates with SCC and BCC incidence.
- In melanoma, the relationship with sunlight is more heterogeneous.
- The UV signature demonstrates a mechanism even when individual exposure histories vary.
- Exposure pattern, cell lineage and tumor genotype should be considered separately.

UV-induced injury can coexist with immune effects

- Chapter 25 notes chronic sunlight may blunt cutaneous immune responsiveness.
- Reduced immune elimination of damaged cells a possible contributor to SCC.
- Immunosuppression is independently associated with an elevated cutaneous SCC risk.
- These immunologic associations supplement the direct DNA-damage mechanism.

Source indicates immune effects as partly uncertain rather than a complete pathway.

The UV mutational signature has wider skin pathology relevance

- Many sun-exposed SCCs and melanomas contain extensive DNA substitutions.
- A subset of sporadic BCC driver mutations carry UV-type base substitutions.
- Robbins also describes UV-signature–driven Merkel carcinomas without viral causation.
- Distinct neoplastic lineages can share the same initiating environmental mutagen.

Interpret the type of evidence correctly

Observation	Supported inference	What it does not prove
High UV-associated mutations	Prior UV-like DNA damaging process	Exact lifetime dose or age at exposure
XP with multiple skin cancers	NER protects against UV mutagenesis	All sporadic cancers have germline NER defects
Actinic keratosis with TP53 mutation	Early molecular damage in precursor	Inevitable evolution to invasive SCC
Melanoma on unexposed site	UV is not universally necessary	UV is unimportant in exposed melanomas

Applied case: Extreme repair susceptibility

Clinical vignette

A young person has many keratinocytic malignancies in sunlight-exposed skin and a documented inherited nucleotide excision repair defect.

Which molecular lesion is not being repaired effectively?

Reasoning: UV-induced pyrimidine dimers. The inherited defect defines xeroderma pigmentosum and greatly increases UV-related skin cancer risk.

Applied case: Grading epidermal dysplasia

Clinical vignette

A keratotic lesion arises on a chronically sun-exposed forearm. Histology shows atypical keratinocytes concentrated in the basal epidermis with an intact basement membrane.

What precursor pattern fits, and what would signal progression?

Reasoning: Actinic keratosis is compatible with lower-layer atypia. Full-thickness atypia indicates SCC in situ; Dermal invasion establishes invasive SCC.

Applied case: Linking tumor genotype to exposure

Clinical vignette

A cutaneous malignancy arising on a sun-exposed site has an exceptionally high burden of substitutions bearing the characteristic UV-repair signature.

Does this prove a particular single sunburn caused the cancer?

Reasoning: No. It strongly implicates the UV-like mutagenic mechanism but cannot reconstruct the dose or time of an individual exposure.

Applied case: Distinguish the principal epithelial cancers

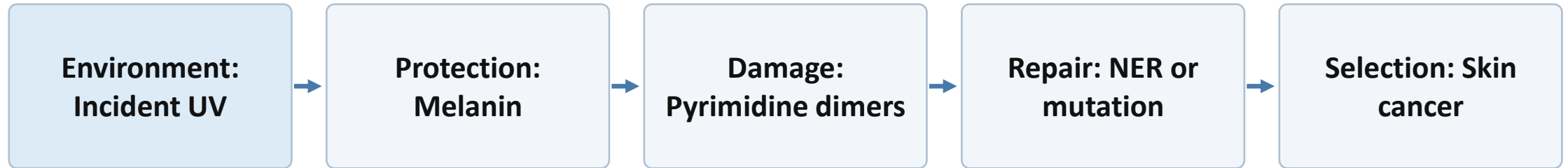
Clinical vignette

A slow-growing pearly facial papule shows dermal islands of basaloid cells with peripheral palisading and stromal clefting.

Which cutaneous cancer is favored, and what pathway is characteristic?

Reasoning: Basal cell carcinoma. Constitutive Hedgehog signaling—commonly through PTCH loss—is central to its oncogenic biology.

Integrated carcinogenesis model



- Different steps explain why similar exposure does not lead to identical outcomes.
- The final cancer phenotype depends on the affected lineage and drivers.

Core pathology conclusions

- UVB produces covalent pyrimidine dimers that disrupt DNA pairing.
- NER normally repairs these lesions; Deficient repair amplifies mutational risk.
- Genomic UV signatures substantiate the UV contribution to cutaneous melanoma.
- SCC, BCC and melanoma differ in lineage, driver pathways and morphology.

Clinical interpretation and limitations

- Photodamage, repair susceptibility and sun exposure act together—not in isolation.
- Histology establishes the lesion type; Mutation signature supports mechanism.
- Sun-damage—associated tumors are not necessarily caused exclusively by UV.
- No quantitative risk prediction, diagnostic cutoff or treatment guideline is inferred here.

Sources and selected Robbins cross-references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 7: Radiation Carcinogenesis; Ultraviolet Rays, p. 289.
- Chapter 7: Nucleotide Excision Repair Factors, pp. 281–282.
- Chapter 25: The Skin—melanocytes, melanoma, actinic keratosis, cutaneous SCC and BCC, pp. 1028–1043.
- Only original editable teaching schematics are included; no extracted textbook photos or histology figures are reproduced.