

Growth factors and receptors

From controlled regeneration to angiogenesis, fibrosis, and cancer

A mechanism-based pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

Orientation

Explain

Connect ligand binding to receptor activation and altered gene expression.

Compare

Identify major growth-factor families, receptors and key actions.

Apply

Relate VEGF, TGF- β and other factors to tissue injury and repair.

Interpret

Distinguish controlled regeneration from pathologic pathway activation.

Growth factors: More than mitogens

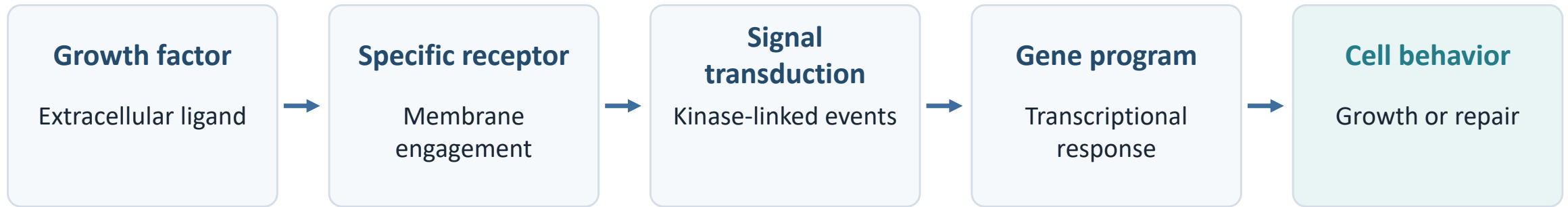
Conceptual foundations

Extracellular signals that alter cellular behavior

Cell survival, proliferation, migration, differentiation and biosynthesis are regulated in a context-dependent manner.

From ligand to cellular response

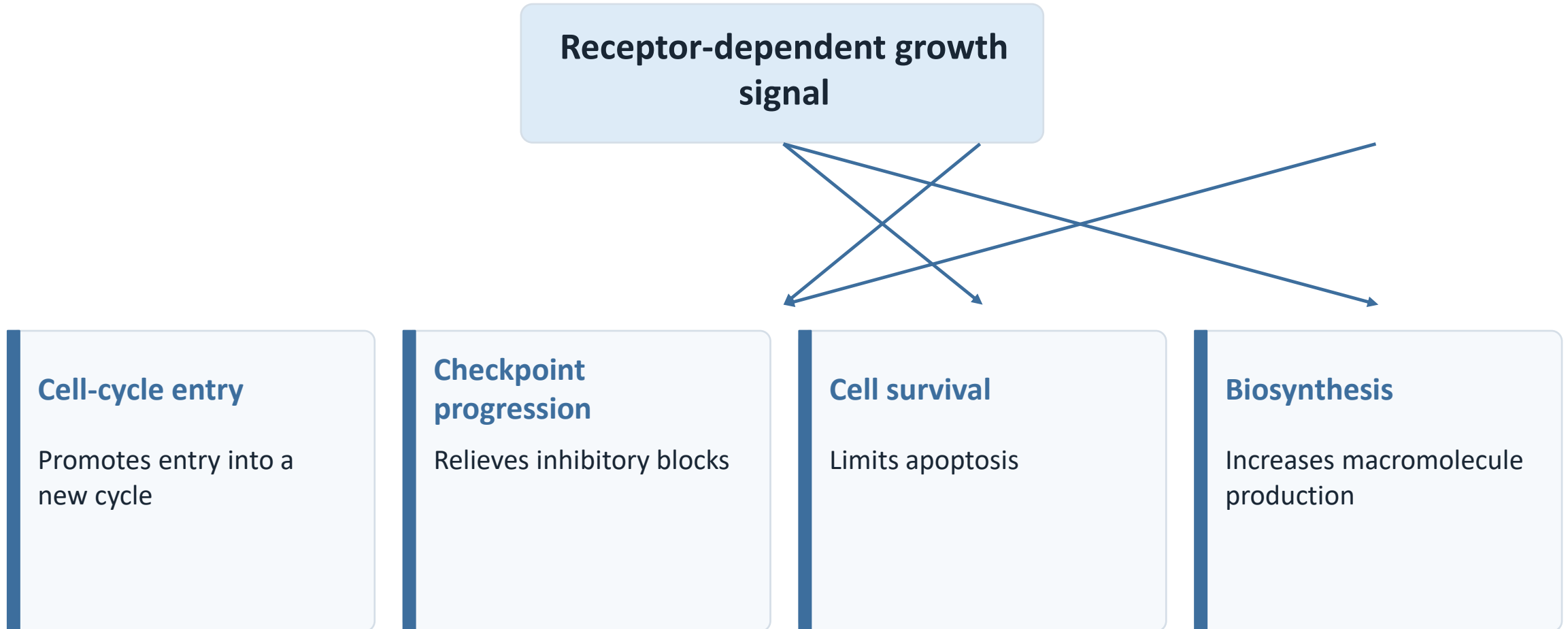
Conceptual foundations



The signal is converted into a change in protein activity and gene expression.

How growth factors support cell division

Conceptual foundations



Growth factors regulate nongrowth functions

Conceptual foundations

Migration

Cell movement during tissue repair

Differentiation

Changes in tissue pattern or cell fate

Synthetic capacity

Production of proteins and matrix

Survival

Maintenance of viable cells

Chemotaxis

Recruitment toward injury-associated cues

Morphogenesis

Organized tissue development

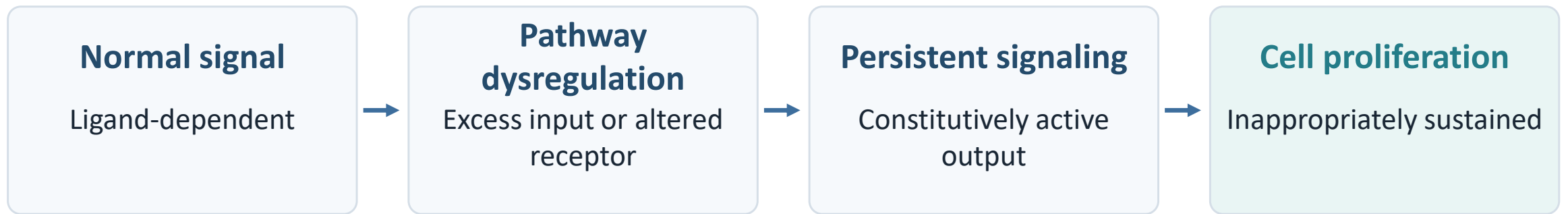
Homeostasis versus injury response

Conceptual foundations

Setting	Biologic problem	Growth-factor role
Steady state	Routine cell turnover	Regulate normal cellular proliferation
Acute injury	Damaged cells need replacement	Coordinate replacement and repair
Healing tissue	Cells must move and synthesize matrix	Support migration and matrix production

When growth signals escape control

Conceptual foundations



Growth-factor pathway genes may behave as oncogenes after activating alterations.

Receptor kinase classes

Conceptual foundations

Receptor class	Representative factors	Catalytic output
Receptor tyrosine kinase	EGF, HGF, PDGF, VEGF, FGF	Tyrosine phosphorylation
Serine/threonine kinase receptor	TGF- β	Smad pathway activation

The growth-factor landscape

Conceptual foundations

EGF / TGF- α

Epithelial proliferation and migration

HGF / MET

Hepatocyte response and cell motility

PDGF

Cell recruitment and mesenchymal proliferation

VEGF

Blood vessels and permeability

FGF

Development, repair and angiogenesis

TGF- β

Matrix accumulation and inflammation control

EGF and TGF- α share an overlapping receptor system

EGF and ERBB family

Ligands

Epidermal growth factor (EGF) and transforming growth factor- α (TGF- α) belong to the EGF family.

Biologic relationship

They bind overlapping receptor sets and share many activities.

Do not confuse TGF- α (EGF-family ligand) with TGF- β (a distinct kinase-receptor family).

Sources and target cells of EGF-family ligands

EGF and ERBB family

Ligand	Representative sources	Responsive targets
EGF	Macrophages, epithelial/other cells	Hepatocytes, fibroblasts, epithelia
TGF- α	Macrophages, keratinocytes, other cells	Hepatocytes and epithelial cells

The ERBB receptor family

EGF and ERBB family

Four family members

EGF receptor family includes four related ERBB membrane receptors

EGFR

Also called EGFR1 or ERBB1

ERBB2

Also termed HER2

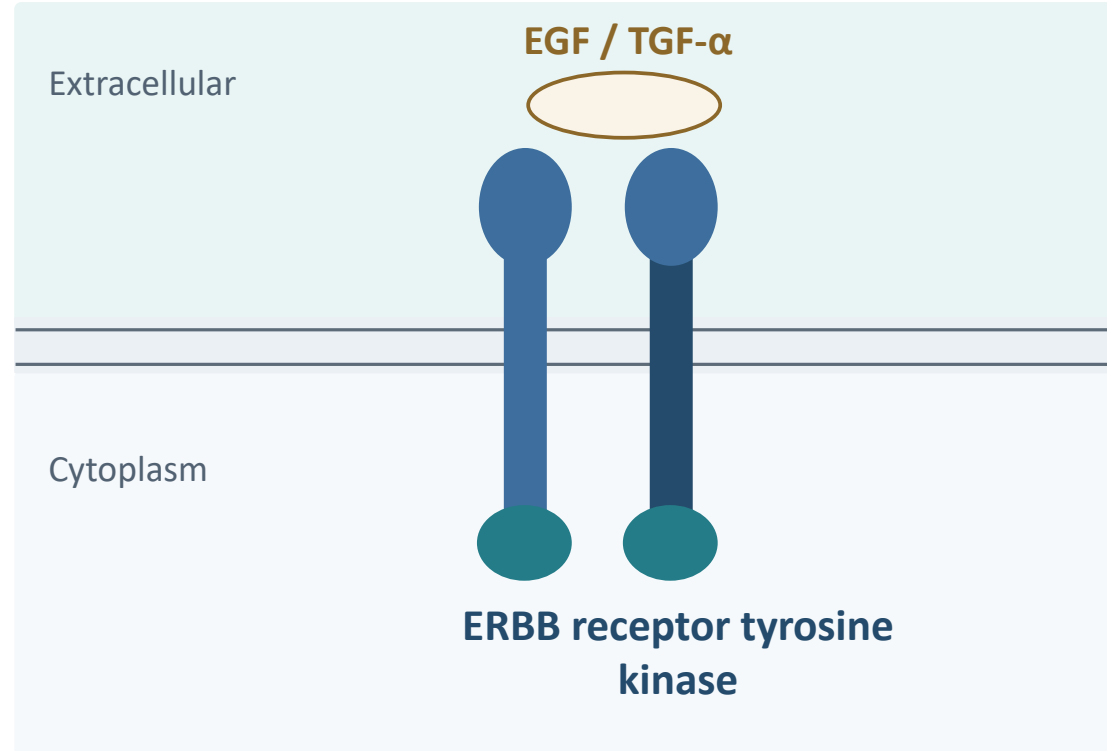
Receptor dysfunction

Amplification, mutation or overexpression in neoplasia

Ligand engagement of an EGF-family receptor

EGF and ERBB family

- Ligand binds a specific extracellular receptor domain.
- Intracellular kinase signaling transmits the response.
- The resulting program varies by target cell.



EGF-family activities in repair

EGF and ERBB family

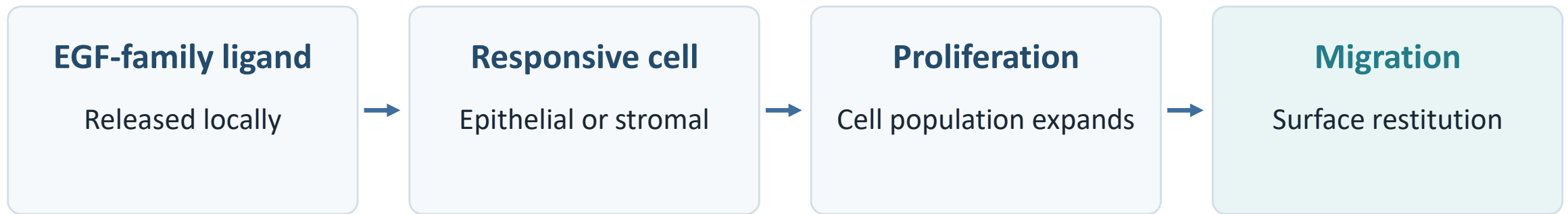


Table 1.1 also describes EGF-associated granulation-tissue formation.

EGFR alterations in human cancers

EGF and ERBB family

Type of dysregulation

Mutation and/or receptor amplification

Cancer contexts

Lung, head and neck, breast and brain tumors are examples.

Effect

Growth-regulatory signaling can become excessive.

Interpretation

Alteration type and tumor context determine whether targeting is relevant.

ERBB2 (HER2) and breast carcinoma

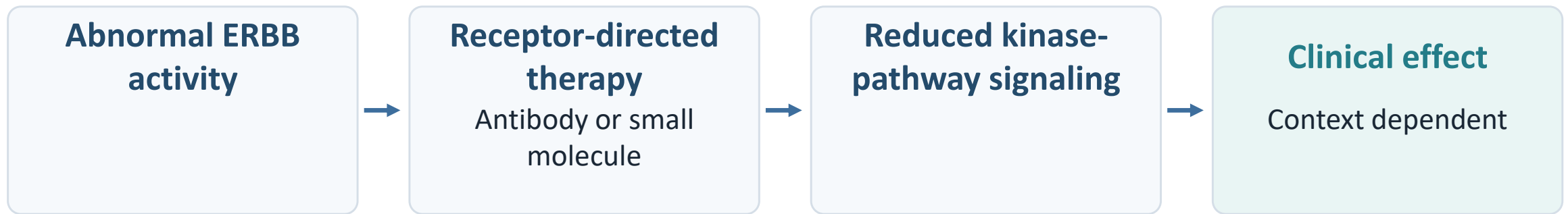
EGF and ERBB family

HER2 overexpression is present in a subset of breast cancers

The receptor itself is a potential molecular target. This is a receptor-level example of oncogenic growth-factor signaling.

Targeting abnormal ERBB signaling

EGF and ERBB family



Clinical effectiveness of receptor-directed agents in selected cancers; No universal response is implied.

HGF: Growth factor and scatter factor

HGF and MET

Hepatocyte growth factor promotes growth and cell movement

The name “scatter factor” reflects its ability to promote migration; It also participates in embryonic morphogenesis.

Where HGF is produced

HGF and MET

Fibroblasts

Stromal source in many tissues

Other mesenchymal cells

Additional local HGF producers

Endothelial cells

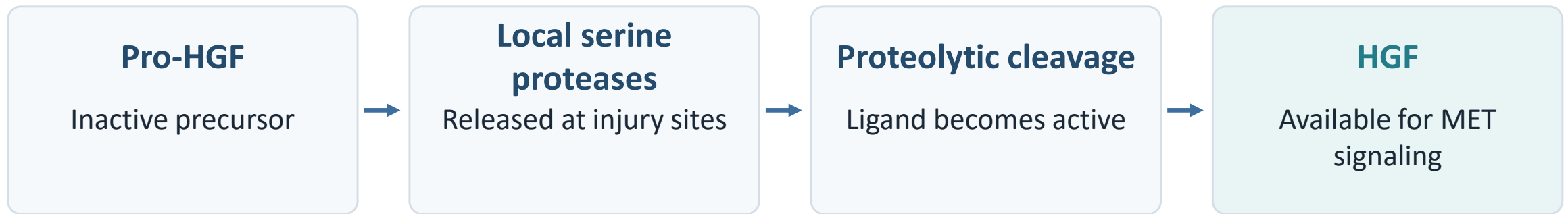
Contribute to paracrine signaling

Nonhepatocyte liver cells

Support hepatocyte responses within the liver

HGF activation is injury-linked

HGF and MET

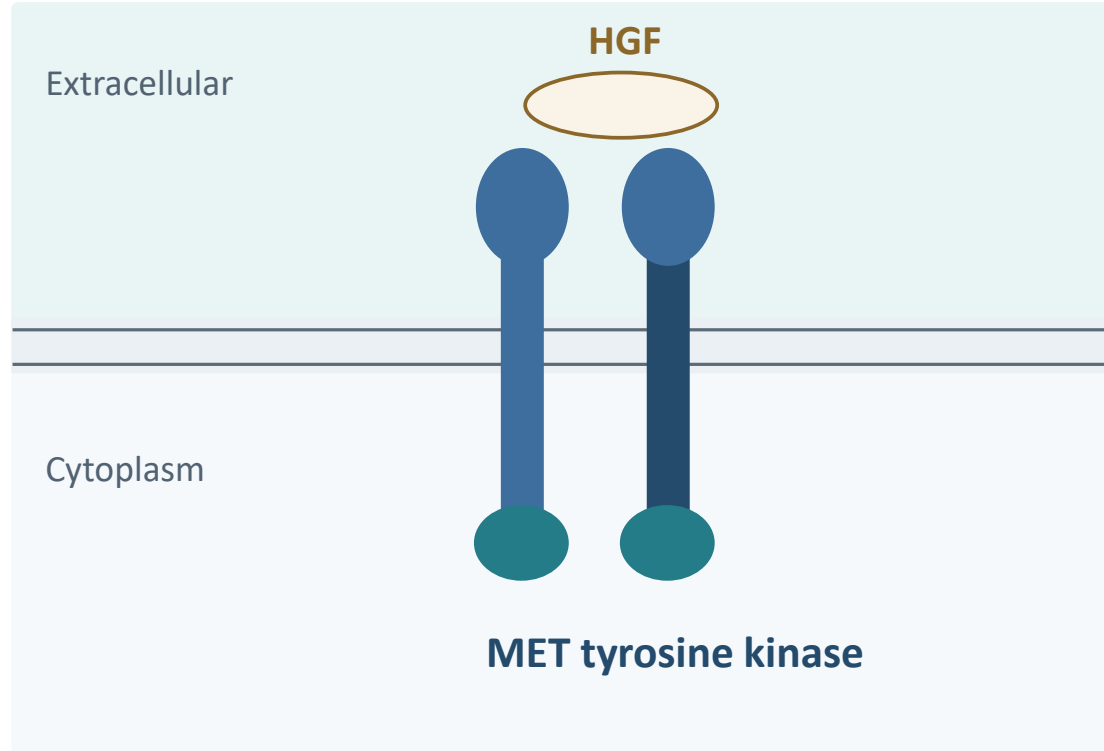


Proteolytic processing couples growth-factor availability to the injury milieu.

MET is the HGF receptor

HGF and MET

- MET is a cell-surface receptor with intrinsic tyrosine kinase activity.
- Ligand-dependent signaling alters growth and movement programs.
- Altered MET expression or sequence can contribute to malignancy.



HGF-responsive epithelial tissues

HGF and MET

Liver

Hepatocytes and biliary epithelium

Lung

Respiratory epithelium

Kidney

Renal epithelial compartments

Breast

Mammary epithelium

Skin

Cutaneous epithelium

Other epithelia

Broader epithelial response

HGF is simultaneously mitogenic and motogenic

HGF and MET

HGF–MET signaling

```
graph TD; A[HGF–MET signaling] --> B[Proliferation]; A --> C[Migration]; A --> D[Survival]; A --> E[Morphogenesis];
```

Proliferation

Expansion of responsive cells

Migration

Cell motility / scatter response

Survival

Protection of hepatocytes

Morphogenesis

Developmental tissue patterning

MET dysregulation in cancer

HGF and MET

Alterations

Overexpression or mutation of MET

Tumor examples

Renal and papillary thyroid carcinomas; Some lung carcinomas

Biologic significance

Receptor signaling can support inappropriate growth

Therapeutic relevance

Selected lung tumors with MET alterations may be treated using MET-directed drugs

PDGF is a family of two-chain ligands

PDGF and recruitment

Platelet-derived growth factors consist of paired polypeptide chains

Different PDGF isoforms have distinct activation requirements, but their signaling is mediated through PDGF receptors.

PDGF isoforms differ in activation

PDGF and recruitment

PDGF isoforms	Activation requirement	Concept
PDGF-AA, -AB, -BB	Directly biologically active	Available without the specified proteolytic maturation
PDGF-CC and -DD	Proteolytic cleavage required	Extracellular processing permits activation

PDGF is not produced by platelets alone

PDGF and recruitment

Activated platelets

Granule storage and release

Activated macrophages

Inflammation-associated synthesis

Endothelial cells

Vascular source

Smooth muscle cells

Vascular wall source

Tumor cells

May produce PDGF

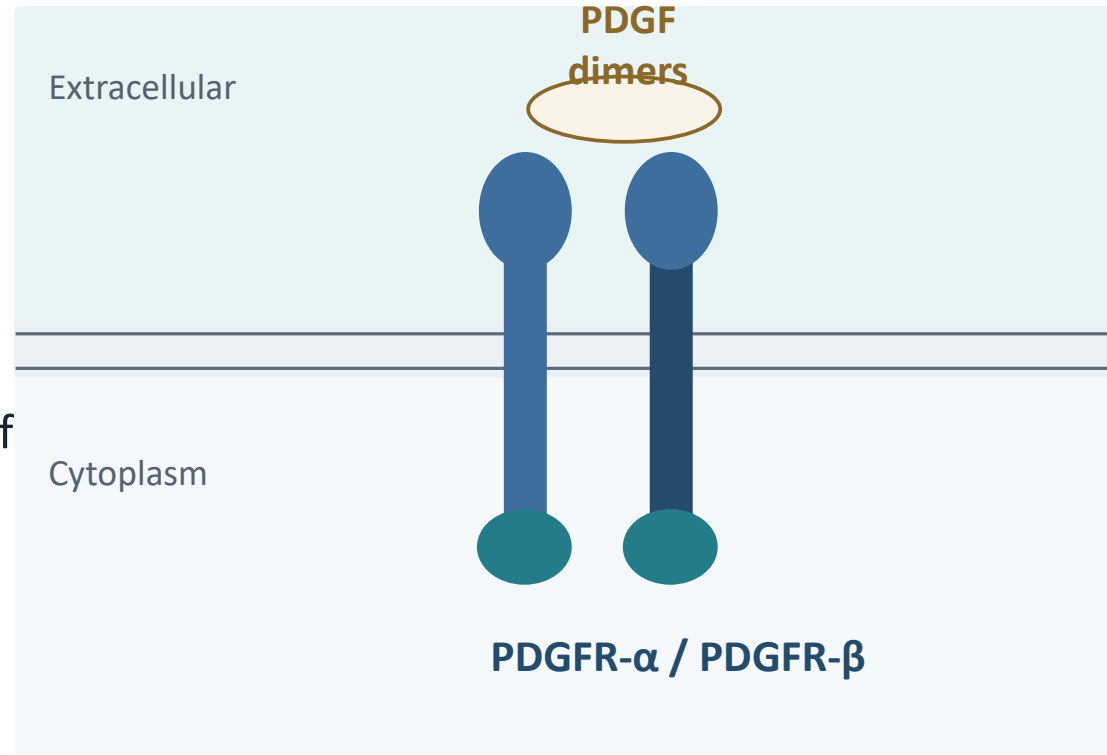
Other tissues

PDGF production is widely distributed

Two related PDGF receptor types

PDGF and recruitment

- PDGFR- α and PDGFR- β are intrinsic receptor tyrosine kinases.
- PDGF ligand isoforms bind members of the receptor system.
- These signals are central to local cell recruitment and proliferation.



PDGF recruits and expands repair cells

PDGF and recruitment

PDGF receptor activation

```
graph TD; A[PDGF receptor activation] --> B[Chemotaxis]; A --> C[Fibroblast growth]; A --> D[Smooth muscle growth]; A --> E[Endothelial effects];
```

Chemotaxis

Moves cells toward injury

Fibroblast growth

Expands stromal cells

Smooth muscle growth

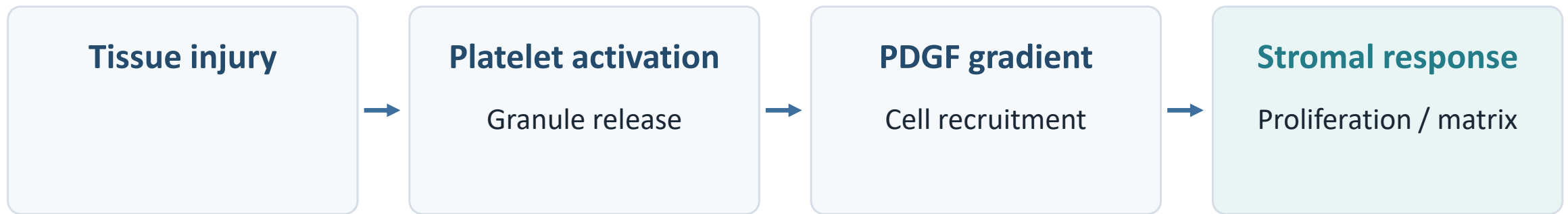
Expands vascular wall cells

Endothelial effects

Supports vascular repair cells

PDGF in an injury-response sequence

PDGF and recruitment



PDGF couples early local injury signals to fibroblast and vascular-cell responses.

VEGF is a family, not a single molecule

VEGF and angiogenesis

VEGF-A

Major angiogenic VEGF after injury and in tumors

VEGF-B

Embryonic vessel-development role

PlGF

Placental growth factor; Vessel development

VEGF-C

Angiogenesis and lymphangiogenesis

VEGF-D

Angiogenesis and lymphangiogenesis

Structure

VEGF family members are dimeric proteins

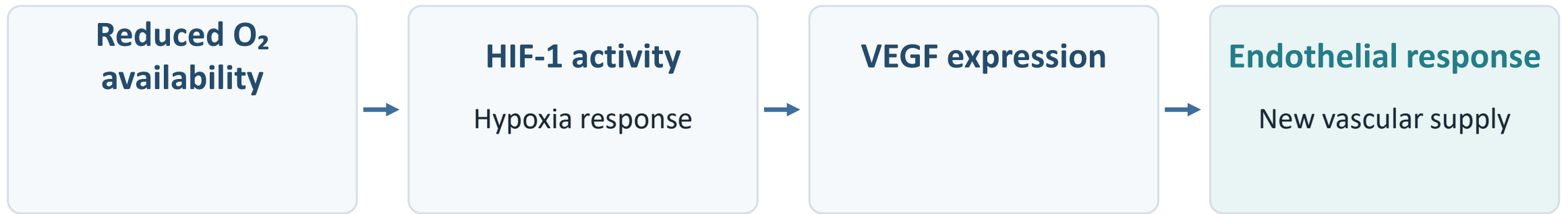
Functional distinctions across VEGF ligands

VEGF and angiogenesis

Family component	Emphasis	Principal context
VEGF-A	Angiogenesis	Injury and tumors
VEGF-B / PlGF	Vessel development	Embryogenesis
VEGF-C / VEGF-D	Blood and lymphatic vessel formation	Angiogenesis + lymphangiogenesis

Hypoxia is a major stimulus for VEGF

VEGF and angiogenesis



The hypoxia–HIF-1–VEGF axis links inadequate oxygenation to angiogenic signaling.

HIF-1 couples oxygen sensing to transcription

VEGF and angiogenesis

Hypoxic tissue → HIF-1
activation

```
graph TD; A[Hypoxic tissue → HIF-1 activation] --> B[Transcriptional effect  
Higher VEGF expression]; A --> C[Paracrine signaling  
VEGF reaches endothelium]; A --> D[Vascular response  
Proliferation and migration];
```

Transcriptional effect

Higher VEGF expression

Paracrine signaling

VEGF reaches endothelium

Vascular response

Proliferation and migration

VEGF production also rises with injury mediators

VEGF and angiogenesis

Hypoxia

Dominant regulator

PDGF

Can increase VEGF production
at injury sites

TGF- α

Another injury-associated
VEGF inducer

The VEGF receptor family

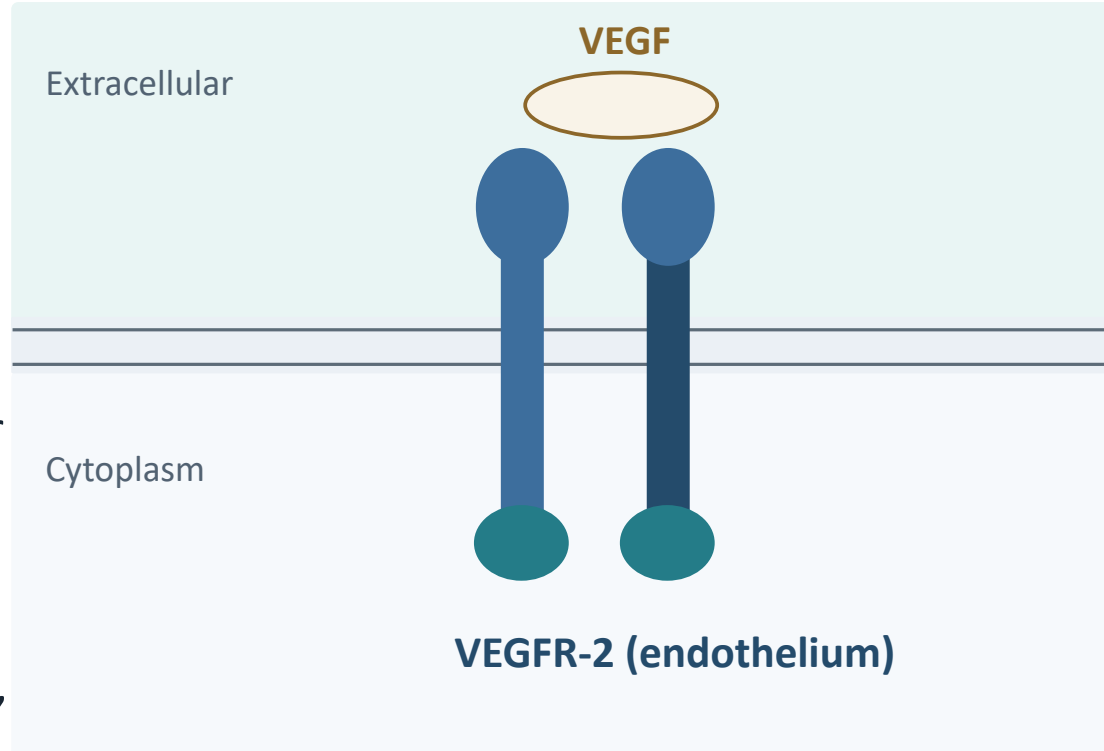
VEGF and angiogenesis

Receptor	Biochemical type	Importance
VEGFR-1	Tyrosine kinase	Part of VEGF receptor network
VEGFR-2	Tyrosine kinase	Major receptor for endothelial angiogenic responses
VEGFR-3	Tyrosine kinase	Part of VEGF signaling, including lymphatic responses

VEGFR-2 drives the canonical angiogenic response

VEGF and angiogenesis

- VEGFR-2 is highly expressed by endothelial cells.
- It is the most important VEGF receptor for angiogenesis.
- Downstream effects include migration, proliferation and lumen formation.



Angiogenesis involves coordinated cellular behaviors

VEGF and angiogenesis

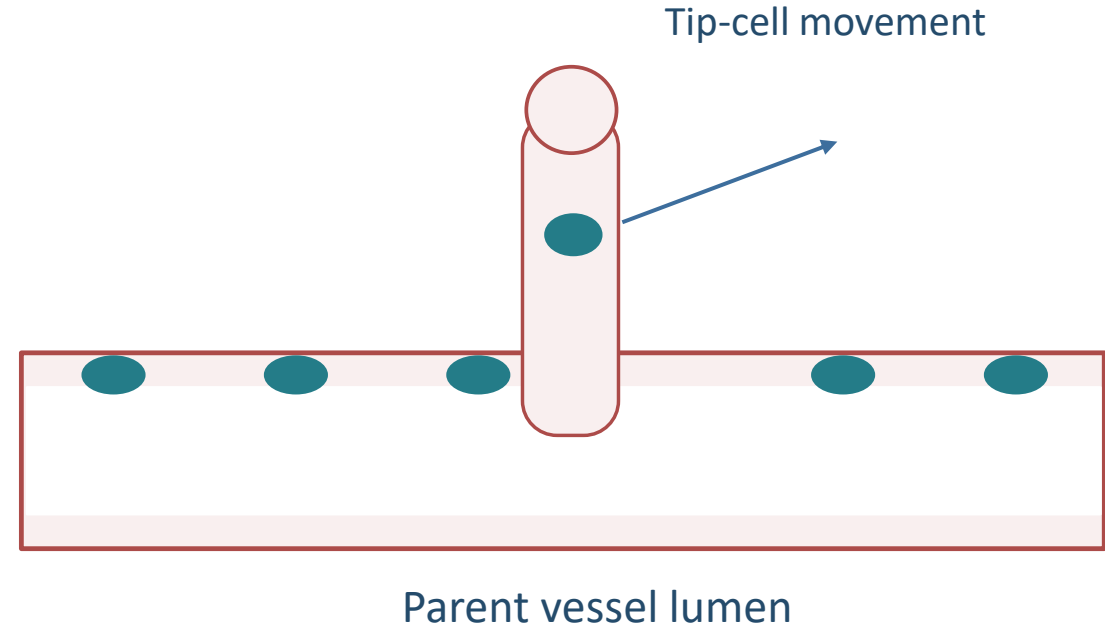


A patent capillary requires more than endothelial proliferation alone.

Capillary sprouting: An original schematic

VEGF and angiogenesis

- Endothelial cells leave the existing vessel wall to form a sprout.
- Migration and proliferation support extension.
- Lumen formation is a central later step.



Schematic

VEGF changes vascular permeability

VEGF and angiogenesis

VEGF signal at blood vessels

```
graph TD; A[VEGF signal at blood vessels] --> B[Angiogenesis  
New vessel formation]; A --> C[Permeability  
Increased vascular leakage]; A --> D[Vasodilation  
Change in vessel caliber];
```

Angiogenesis

New vessel formation

Permeability

Increased vascular leakage

Vasodilation

Change in vessel caliber

VEGF also maintains resting endothelium

VEGF and angiogenesis

Kidney

Podocyte-associated local VEGF signaling

Eye

Retinal pigment epithelium as local source

CNS

Choroid plexus-associated expression

Tumor angiogenesis uses a normal repair program

VEGF and angiogenesis



An otherwise adaptive angiogenic response can be co-opted by neoplasia.

VEGF-directed therapy in oncology

VEGF and angiogenesis

Rationale

Some tumors rely on angiogenesis for continued growth and spread.

Therapeutic approach

Blocking VEGF can suppress vascular support;
Selected renal and colorectal cancers.

Biologic rationale is not equivalent to clinical effectiveness in every tumor.

VEGF-driven ocular vascular disease

VEGF and angiogenesis

Wet age-related macular degeneration

Pathologic neovascularization and leakage

Diabetic macular edema

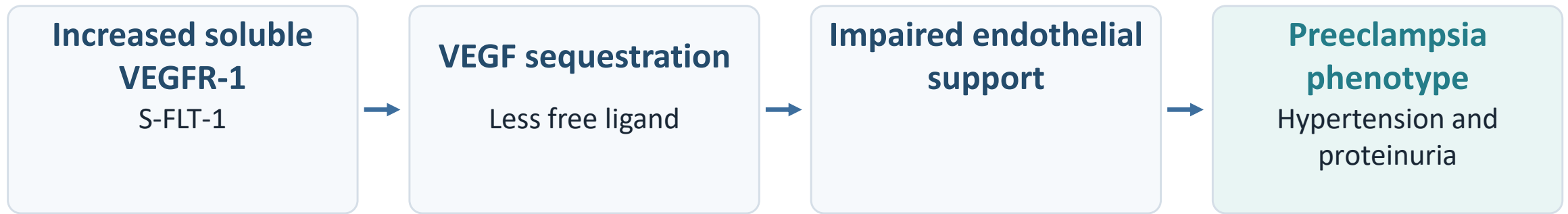
Leakage-associated retinal edema

Retinopathy of prematurity

Abnormal angiogenesis in the developing retina

Excess soluble VEGFR-1 and preeclampsia

VEGF and angiogenesis



The text describes elevated maternal s-FLT-1 as a possible pathogenic mechanism.

FGF is a broad ligand family

FGF and matrix storage

More than 20 fibroblast growth factors are described

FGFs regulate development and tissue repair; Individual family members have different target-cell profiles.

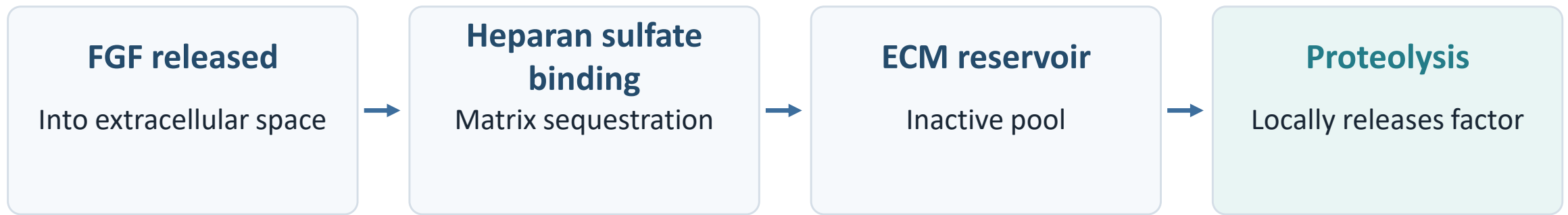
FGF-1, FGF-2 and FGF-7

FGF and matrix storage

Factor	Alternative name	Instructional role
FGF-1	Acidic FGF	Well-characterized family member
FGF-2	Basic FGF	Angiogenic and repair-associated activities
FGF-7	Keratinocyte growth factor (KGF)	Keratinocyte migration, proliferation and differentiation

Heparan sulfate stores released FGFs in the ECM

FGF and matrix storage



ECM binding creates spatial and temporal control of FGF availability.

Injury can mobilize matrix-bound FGF

FGF and matrix storage

Before injury

FGF is retained through association with heparan sulfate in the extracellular matrix.

At a wound site

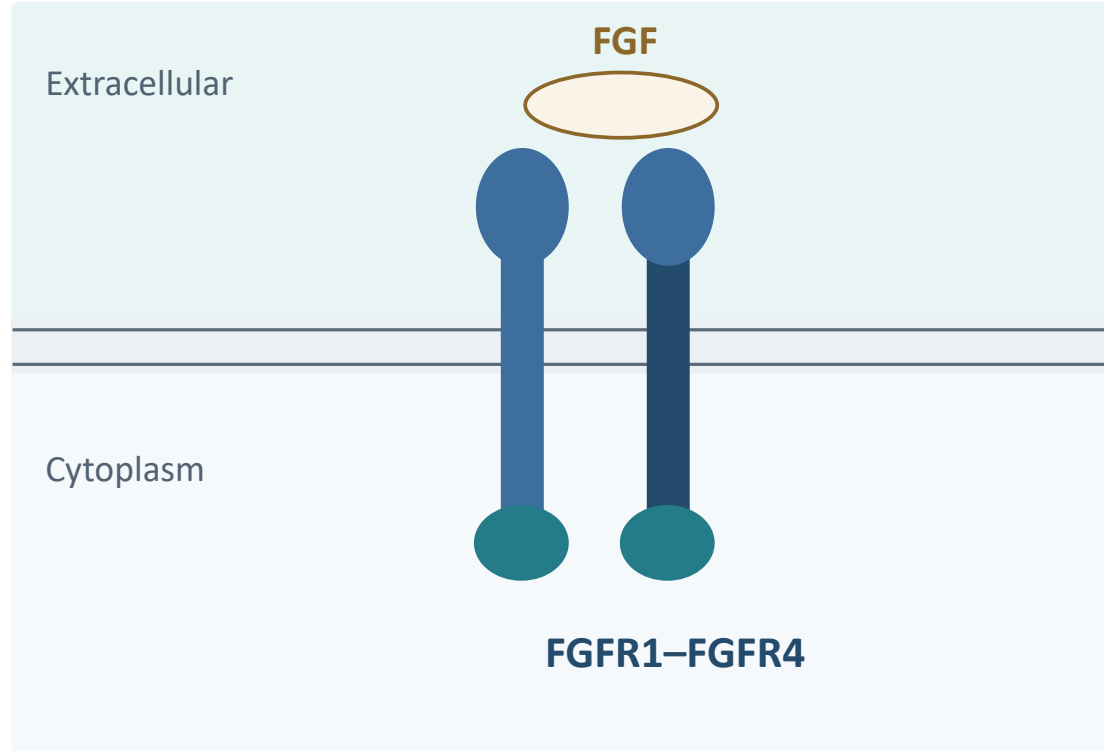
Proteolytic activity can release stored factor to participate in healing.

The matrix functions as a growth-factor reservoir, not only as structural support.

FGF signals through four receptor kinases

FGF and matrix storage

- FGFR1 through FGFR4 have intrinsic tyrosine kinase activity.
- Receptor activation contributes to tissue development and healing.
- The precise cellular effect depends on ligand and tissue context.



FGF-2 and angiogenesis

FGF and matrix storage



FGF-2 has the cellular activities needed to support angiogenesis.

FGF-7 targets keratinocyte repair

FGF and matrix storage

FGF-7 / KGF from fibroblasts

```
graph TD; A[FGF-7 / KGF from fibroblasts] --> B[Migration<br/>Keratinocyte movement]; A --> C[Proliferation<br/>Epithelial expansion]; A --> D[Differentiation<br/>Maturation of epithelial cells];
```

Migration

Keratinocyte movement

Proliferation

Epithelial expansion

Differentiation

Maturation of epithelial cells

TGF- β belongs to a distinct superfamily

TGF- β and fibrosis

TGF- β 1, β 2, β 3

Three TGF- β isoforms; β 1 is most widespread

Related families

BMPs, activins and inhibins are included in the broader group.

Principal signals

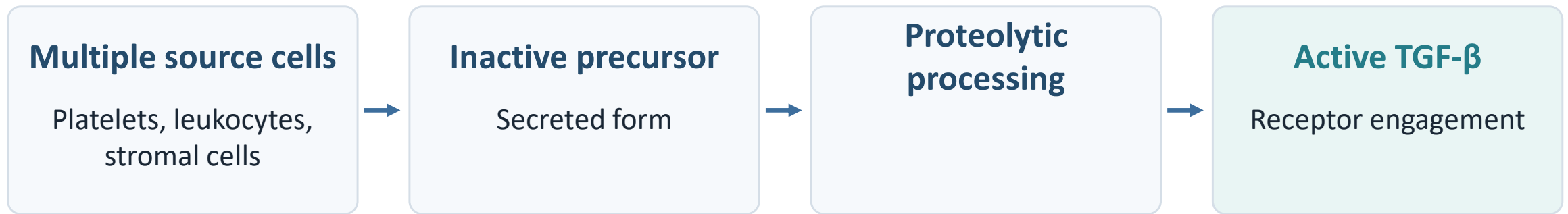
Extracellular matrix synthesis and immune regulation

Critical distinction

TGF- β uses serine/threonine kinase receptors, unlike the RTK examples.

TGF- β is widely produced and locally activated

TGF- β and fibrosis



Many cells can supply TGF- β , including endothelial and epithelial cells.

Type I and type II TGF-β receptors

TGF-β and fibrosis

Feature	TGF-β receptor system	Most other families here
Kinase activity	Serine / threonine	Tyrosine
Canonical effectors	Smad transcription regulators	RTK-associated signaling pathways
Functional emphasis	Matrix accumulation, immune regulation	Growth, motility or angiogenesis

Smad signaling connects receptor to nucleus

TGF- β and fibrosis



Activated Smad complexes cooperate with DNA-binding partners to regulate target genes.

TGF- β effects depend on cellular context

TGF- β and fibrosis

Same ligand: TGF- β

```
graph TD; A[Same ligand: TGF-β] --> B[Fibroblast context]; A --> C[Immune context]; A --> D[Tissue context];
```

Fibroblast context

Matrix synthesis and scar formation

Immune context

Suppressed inflammatory activity

Tissue context

Effects modified by concurrent signaling

TGF- β favors extracellular matrix accumulation

TGF- β and fibrosis

TGF- β signaling

```
graph TD; A[TGF-β signaling] --> B[Collagen  
Increased synthesis]; A --> C[Fibronectin  
Increased synthesis]; A --> D[Proteoglycans  
Increased synthesis];
```

Collagen

Increased synthesis

Fibronectin

Increased synthesis

Proteoglycans

Increased synthesis

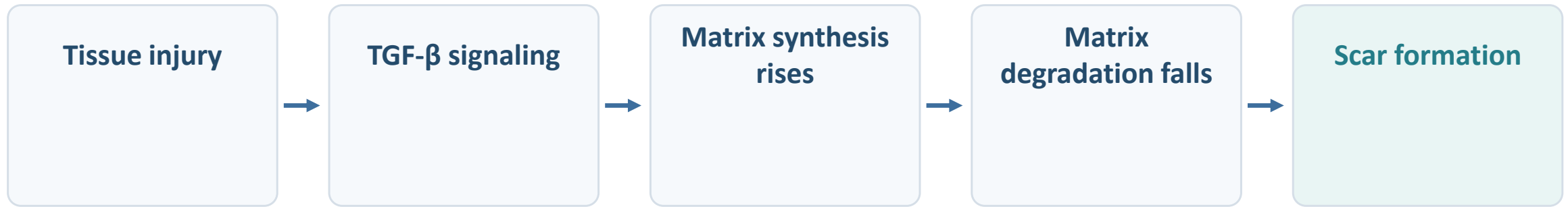
MMP and TIMP regulation favors retention

TGF-β and fibrosis

Component	TGF-β effect	Net matrix consequence
Matrix metalloproteinases (MMPs)	Reduced matrix-degrading activity	Less extracellular-matrix breakdown
Tissue inhibitors of MMPs (TIMPs)	Increased inhibitory activity	Further protection from degradation
Collagen production	Increased synthesis	Greater matrix accumulation

Scar formation is a controlled use of TGF- β

TGF- β and fibrosis



Matrix deposition is physiologic in repair but harmful when persistent or excessive.

Persistent TGF- β activity can drive fibrosis

TGF- β and fibrosis

Lung

Fibrotic remodeling reduces functional parenchyma

Liver

Persistent matrix deposition disrupts organ architecture

Kidney

Progressive fibrosis impairs renal function

Intestine

Chronic inflammation can cause fibrotic tissue remodeling

TGF- β limits inflammatory responses

TGF- β and fibrosis

**TGF- β anti-inflammatory
signal**

```
graph TD; A[TGF-β anti-inflammatory signal] --> B[Lymphocytes]; A --> C[Other leukocytes]; A --> D[Inflammation];
```

Lymphocytes

Reduced proliferation

Other leukocytes

Reduced activation / activity

Inflammation

Limitation and termination of
response

Loss of TGF- β restraint permits inflammation

TGF- β and fibrosis

Physiologic regulation

TGF- β helps dampen leukocyte-driven inflammation after injury.

Deficient signaling

Widespread persistent inflammation in animals lacking TGF- β .

Anti-inflammatory and profibrotic effects can coexist within the same tissue.

Growth-factor receptors: Comparative map

Integration

Growth factor	Principal receptor	Signature response
EGF / TGF- α	EGFR family (ERBB)	Epithelial cell growth
HGF	MET	Epithelial growth and motility
PDGF	PDGFR- α / β	Chemotaxis; Stromal proliferation
VEGF	VEGFR-1 / 2 / 3	Angiogenesis; Permeability
FGF	FGFR1–4	Repair; Angiogenesis
TGF- β	TGF- β RI / RII	Fibrosis; Immunoregulation

Repair requires distinct, overlapping signals

Integration

Cell replacement

EGF, TGF- α and HGF support proliferation

Stromal recruitment

PDGF directs and expands repair cells

New vessels

VEGF and FGF-2 support angiogenesis

Epithelial restitution

EGF-family signals and FGF-7 aid surface repair

Matrix deposition

TGF- β drives ECM synthesis and retention

Inflammation resolution

TGF- β restrains inflammatory activity

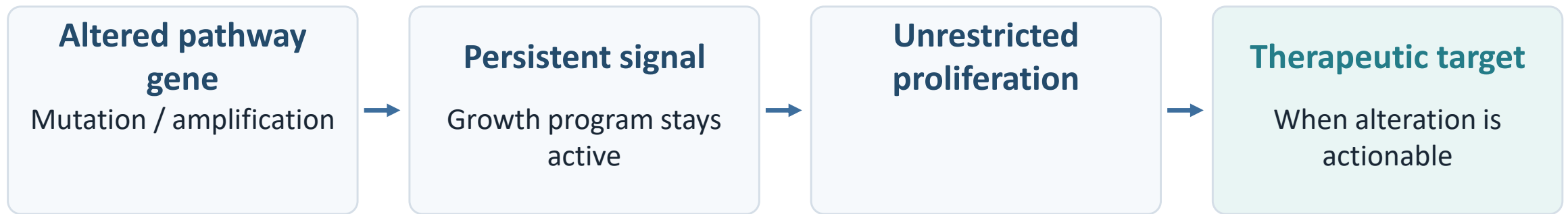
Angiogenesis and fibrosis are not synonyms

Integration

Repair component	Predominant signal	Pathologic excess
Vessel sprouting	VEGF; Also FGF-2	Tumor vascularization or pathologic ocular vessels
Fibroblast recruitment	PDGF	Excess stromal-cell activity
Matrix accumulation	TGF- β	Organ fibrosis and impaired function

The oncogenic problem can be receptor-level

Integration



EGFR, HER2 and MET illustrate clinically relevant pathway dysregulation.

Clinical application: Altered MET signaling

Application

A lung carcinoma is found to harbor an activating alteration in the MET signaling system.

Question

What is the receptor-level therapeutic rationale?

Teaching answer

MET is an HGF-responsive receptor tyrosine kinase. Selected MET-altered cancers may be susceptible to MET-directed inhibition; Eligibility depends on the actual alteration.

Clinical application: Vascular-endothelial dysfunction

Application

A pregnant patient develops hypertension and proteinuria. Increased circulating soluble VEGFR-1 is proposed as a contributing factor.

Question

How can soluble VEGFR-1 contribute?

Teaching answer

Soluble VEGFR-1 can sequester free VEGF, reducing signaling that helps maintain normal endothelial function; This is one proposed mechanism of preeclampsia.

Four high-yield pathway associations

Synthesis

1

EGFR / HER2

Proliferative signaling and cancer-associated receptor abnormalities

2

HGF / MET

Epithelial motility and oncogenic kinase signaling

3

VEGF / VEGFR-2

Endothelial sprouting, permeability and angiogenesis

4

TGF- β / Smads

Matrix production, fibrosis and immunoregulation

Knowledge check: Identify the signal

Synthesis

Clinical or experimental observation	Likely pathway
Abnormal endothelial sprouting after hypoxia	HIF-1 → VEGF → VEGFR-2
Fibroblast chemotaxis at wound margin	PDGF → PDGFR
Matrix deposition with decreased degradation	TGF-β → Smads / MMP–TIMP effects
Motogenic response in epithelial cells	HGF → MET

Principal reference and content boundaries

Reference

1 Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 1, “Growth Factors and Receptors,” pp. 18–20.

2 Context

The preceding “Signal Transduction Pathways” section (pp. 16–17) supplies receptor-kinase background.

3 Visual source

Diagrams are originally authored schematic PowerPoint objects, not reproduced textbook figures.

4 Clinical scope

Therapeutic examples are mechanistic teaching context from the supplied source, not treatment protocols.