

Integrated Stress Response

Cellular stress sensing • translational control • ER proteostasis

Molecular pathology

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Learning objectives

- Map diverse stressors to the four eIF2 α kinases.
- Explain how Ser51 phosphorylation reprograms translation.
- Describe ATF4-dependent adaptation and ISR resolution.
- Distinguish the ISR from ER unfolded protein response signaling.
- Interpret persistent stress signaling in major disease settings.

Cells continually balance synthesis and repair

Biosynthetic demand

Proteins must be synthesized, folded, trafficked, and degraded.

Energy availability

ATP and nutrient supply impose a limit on cellular production.

Quality control

Chaperones and degradation pathways manage misfolded proteins.

Stress adaptation

Translation and gene expression are reset when demand exceeds capacity.

A broad range of injuries can activate stress signaling

Metabolic stress

Hypoxia, ischemia, glucose or amino acid deprivation.

Pathogen-associated stress

Infection and abnormal viral RNA.

Proteostasis stress

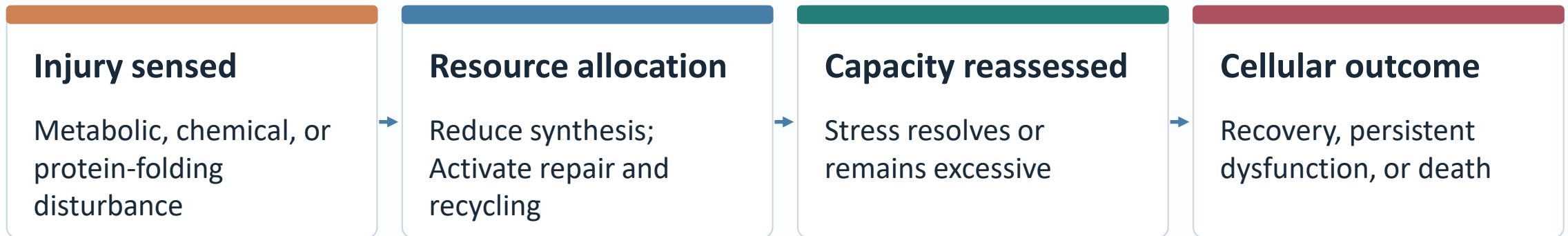
Misfolded proteins, impaired folding, and ER overload.

Additional injury

Membrane damage, altered redox state, and heme scarcity.

A cell must choose a response proportional to injury

Protective programs act before irreversible injury develops.



Cell fate depends on stress intensity, duration, and cellular context.

ISR, UPR, and autophagy: Related but distinct

ISR

An eIF2 α -centered translational response to many stressors.

UPR

ER-specific pathways that reduce folding load and increase ER capacity.

Autophagy

Lysosome-directed recycling of cytoplasmic material.

Crosstalk

Shared stress inputs and signaling nodes coordinate adaptation.

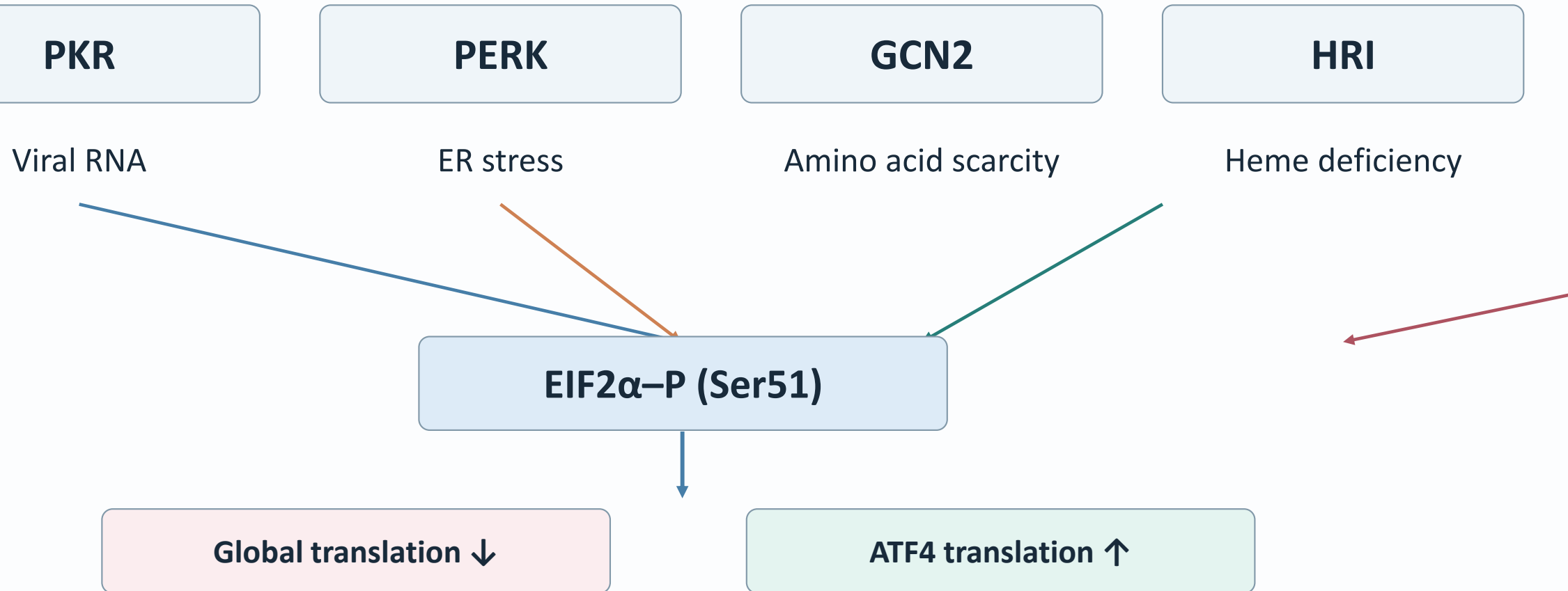
What is the integrated stress response?

A conserved signaling network that reprograms protein synthesis and gene expression during cellular stress.

Core event: Phosphorylation of eukaryotic initiation factor 2 α (eIF2 α).

Four upstream kinases, one convergence point

Different sensors converge on the same translational-control switch.



PKR links cytoplasmic RNA sensing to translation

Upstream setting

- Double-stranded RNA can arise during viral infection.
- Interferon signaling can increase PKR expression.
- Activated PKR phosphorylates eIF2 α .

Functional consequence

- Translation suppression limits production capacity during stress.
- ATF4-linked gene expression may be induced.
- PKR is not a virus-specific marker in every context.

PERK is an ER-membrane ISR kinase

Location and stimulus

- PERK spans the ER membrane.
- Its luminal sensor responds to disturbed ER proteostasis.
- ER stress activates the cytosolic kinase domain.

Mechanistic linkage

- PERK phosphorylates eIF2 α (Ser51).
- Protein influx into the ER is reduced by translation attenuation.
- PERK is the ISR branch of the unfolded protein response.

GCN2 detects inadequate amino acid availability

Nutritional signal

- Amino acid scarcity increases uncharged transfer RNA.
- GCN2 is an early sensor of nutrient limitation.
- Its regulatory region links tRNA status to kinase activation.

Adaptive logic

- Reduce protein production when building blocks are limited.
- Favor expression of stress-associated metabolic genes.
- Other stressors can recruit GCN2 in particular contexts.

HRI coordinates translation with heme availability

Canonical setting

- Heme-regulated inhibitor (HRI) is especially relevant in erythroid cells.
- Heme deficiency activates HRI signaling.
- HRI then phosphorylates eIF2 α .

Protective consequence

- Globin synthesis is restrained when heme is insufficient.
- This helps avoid excessive production of unpaired globin.
- HRI also responds to some other proteotoxic stresses.

The four ISR sensors at a glance

Kinase	Representative trigger	Key context
PKR	Double-stranded RNA	Infection-related stress
PERK	Misfolded ER proteins	Endoplasmic-reticulum proteostasis
GCN2	Amino acid scarcity	Nutrient sensing
HRI	Heme deficiency	Erythroid globin–heme coordination

Why four kinases rather than a single sensor?

Distinct upstream detectors

Different domains recognize different disturbances.

Common catalytic outcome

All phosphorylate the same Ser51 residue in eIF2 α .

Cooperative activity

More than one sensor may contribute to a complex insult.

Context-specific duration

Strength and timing shape adaptation versus injury.

The ISR integrates unrelated injuries

Example inputs can be different, but the downstream translational switch is shared.



A single phosphorylation readout cannot reveal which kinase was activated.

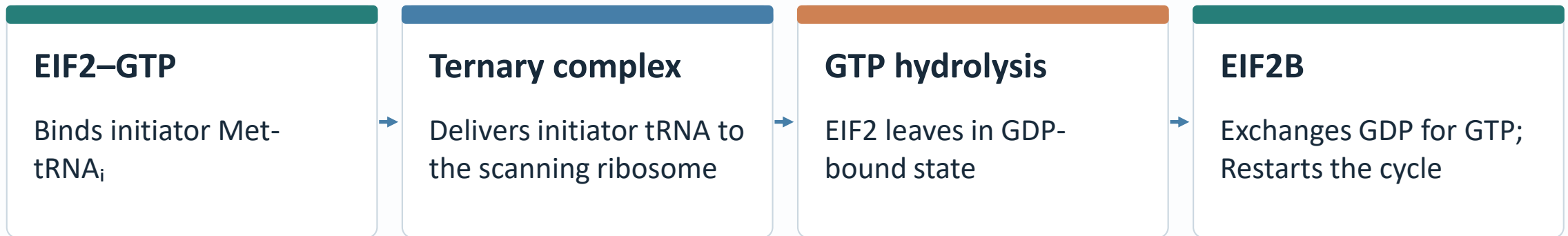
The biochemical core of the ISR

Phosphorylation of eIF2 α on serine 51 alters translation initiation.

EIF2 functions in initiation as a GTP-bound carrier of initiator methionyl-tRNA.

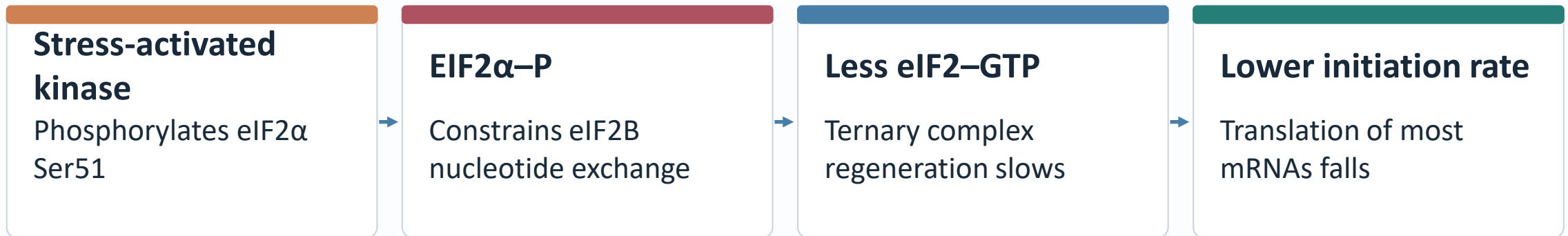
Translation initiation requires eIF2 recycling

EIF2 alternates between active GTP-bound and inactive GDP-bound states.



Stress interrupts a specific point of initiation

Ser51 phosphorylation changes how eIF2 interacts with its exchange factor.



Why inhibition of eIF2B matters

Normal operation

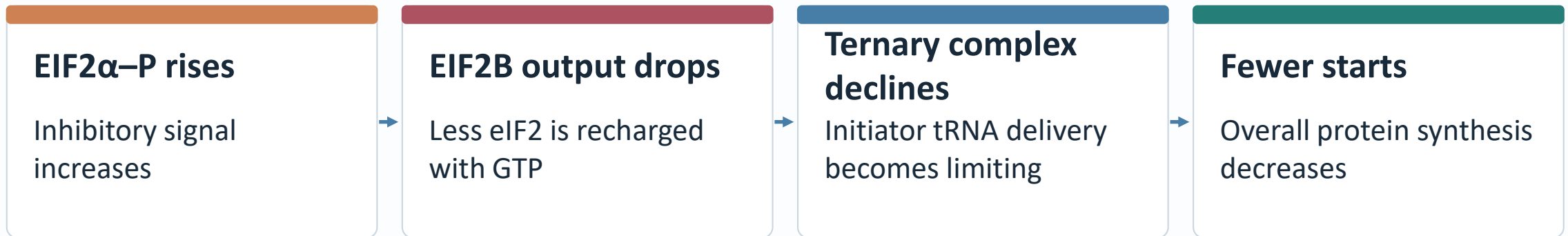
- EIF2B is the guanine-nucleotide exchange factor for eIF2.
- It regenerates GTP-bound eIF2 after initiation.
- Repeated cycles support ongoing protein synthesis.

During ISR activation

- Phosphorylated eIF2 α inhibits eIF2B activity.
- Less ternary complex is available to initiate translation.
- This is an initiation defect, not wholesale destruction of ribosomes.

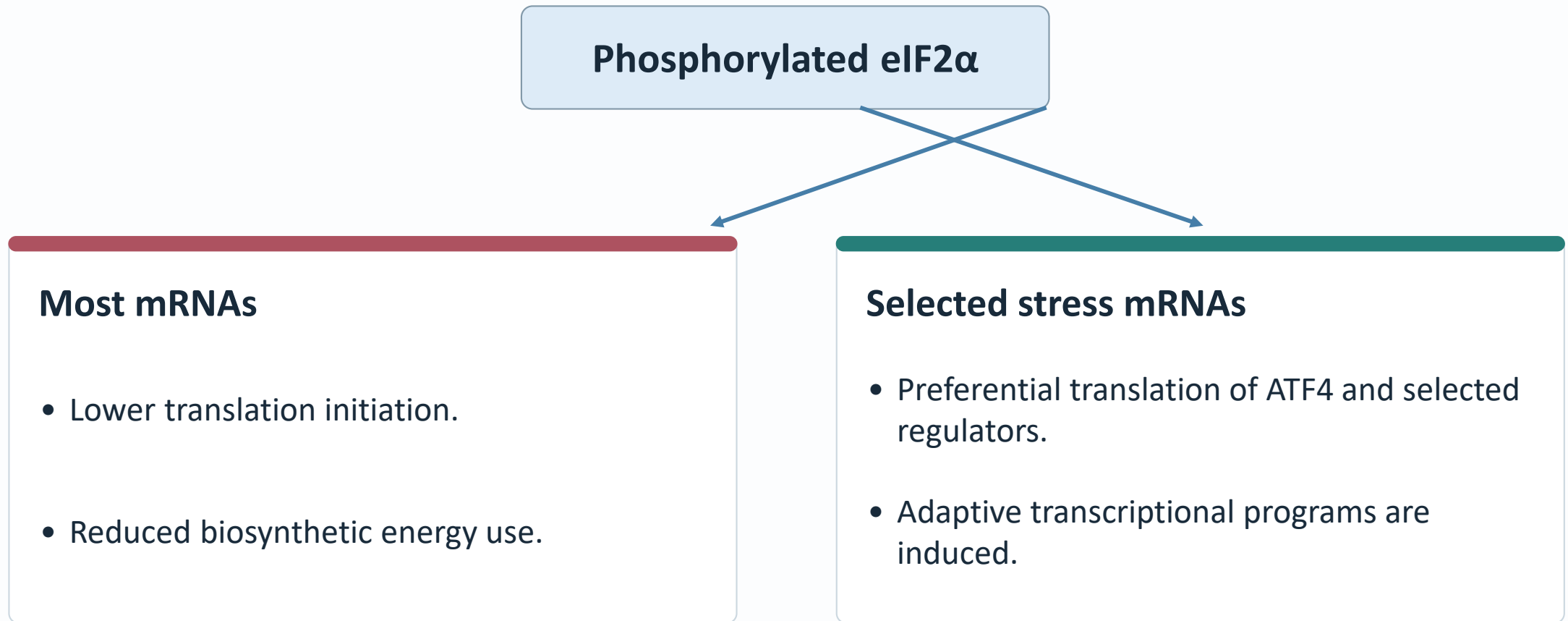
The ternary complex becomes rate limiting

EIF2–GTP–Met-tRNA_i is essential for productive translation initiation.



A single switch produces opposite translational effects

The apparent paradox is central to understanding the ISR.



Lower translation can be protective

Conserve ATP

Protein synthesis is energetically expensive.

Reduce folding load

Fewer newly synthesized proteins enter stressed compartments.

Limit damaged products

The cell avoids making proteins during resource shortage.

Create repair time

Quality control can catch up before synthesis resumes.

The pause in synthesis is not universal

Global is relative

Most—not literally all—mRNA translation is attenuated.

Selective exceptions

Some transcripts respond favorably to limited initiation complexes.

Time matters

Persistent inhibition can itself impair cell function.

Context matters

Different tissues tolerate different durations of synthesis arrest.

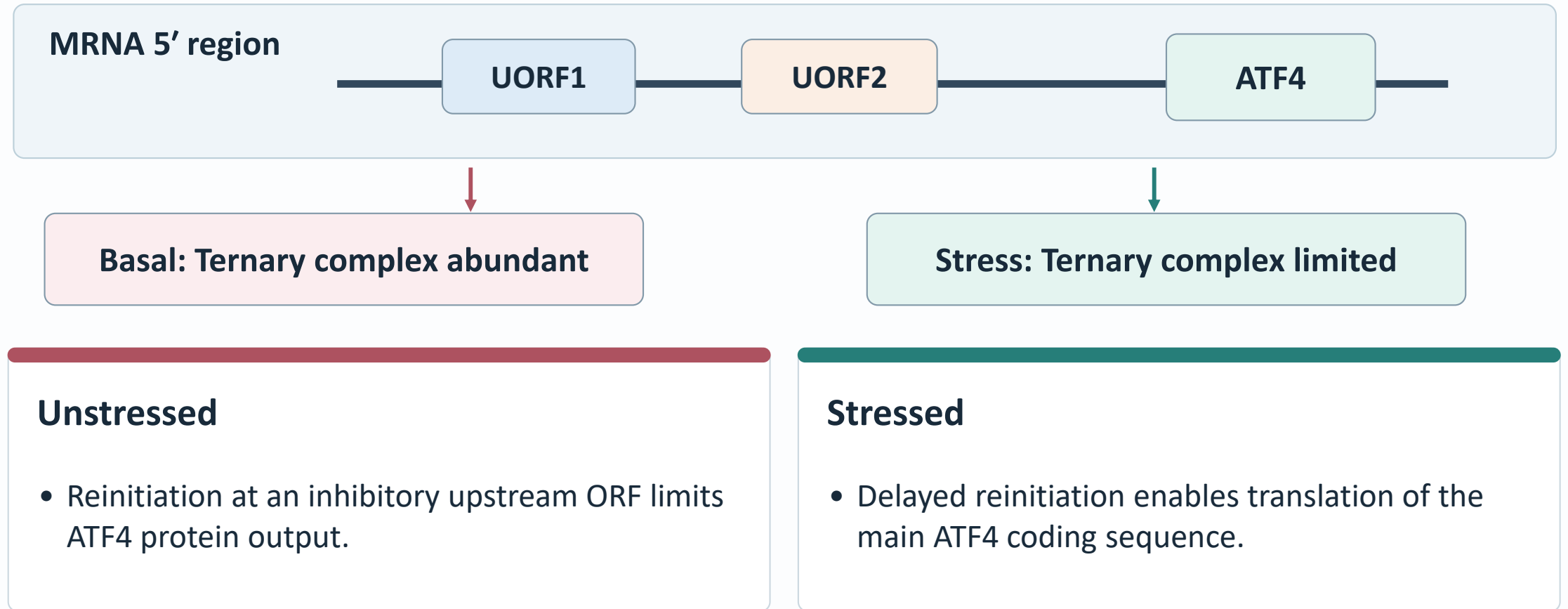
ATF4 is a major transcriptional effector

The ISR reduces translation of most proteins while favoring production of ATF4.

ATF4 then changes transcription of genes involved in stress adaptation.

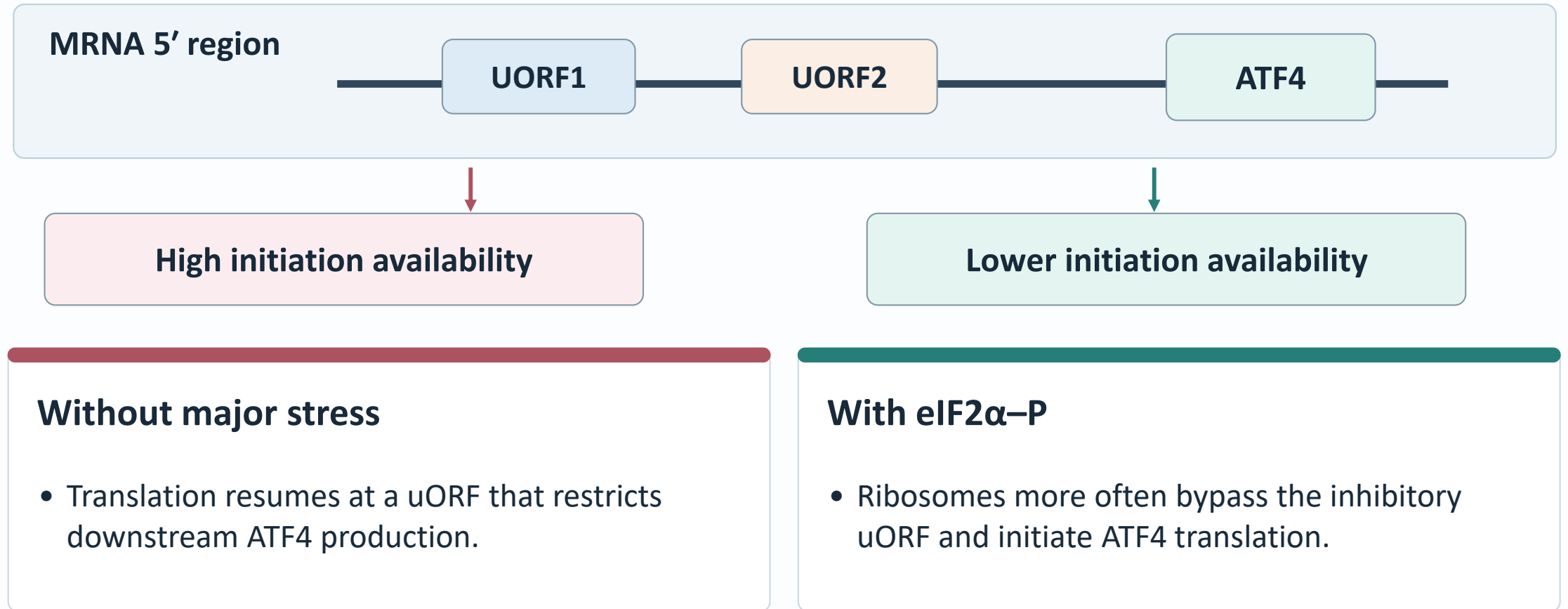
ATF4: Baseline translation control

Regulatory upstream open reading frames (uORFs) constrain ATF4 expression.



ATF4 preferential translation during ISR

A smaller pool of initiation complexes can paradoxically increase ATF4 translation.



ATF4 organizes a coordinated gene program

Amino acid homeostasis

Programs related to transport and nutrient metabolism.

Oxidative stress defense

Genes that support antioxidant responses.

Protein folding and repair

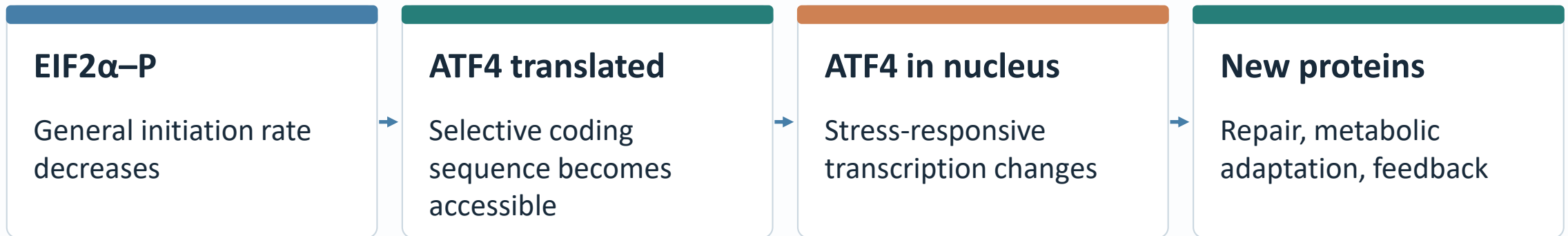
Components supporting cellular proteostasis.

Response remodeling

Regulators that help terminate or reshape the ISR.

ATF4 couples sensing to transcription

The output is not solely translation inhibition.



Amino acid programs support adaptation

Supply

Increase availability of amino-acid substrates when possible.

Metabolic routing

Reallocate resources under nutrient stress.

Synthesis restraint

Lower immediate demand for amino acids.

Recovery

Permit biosynthesis to resume if nutrients return.

Antioxidant defense is one ISR output

Stress context

- Hypoxia/reoxygenation and other insults perturb cellular redox balance.
- Accumulated reactive species challenge proteins and organelles.

Adaptation

- ATF4-responsive programs can contribute to antioxidant capacity.
- The exact program depends on the cellular context and additional transcription factors.

ISR signaling interfaces with protein quality control

Production side

- Translation attenuation reduces the quantity of newly synthesized proteins.
- This lowers immediate folding demand.

Repair and clearance side

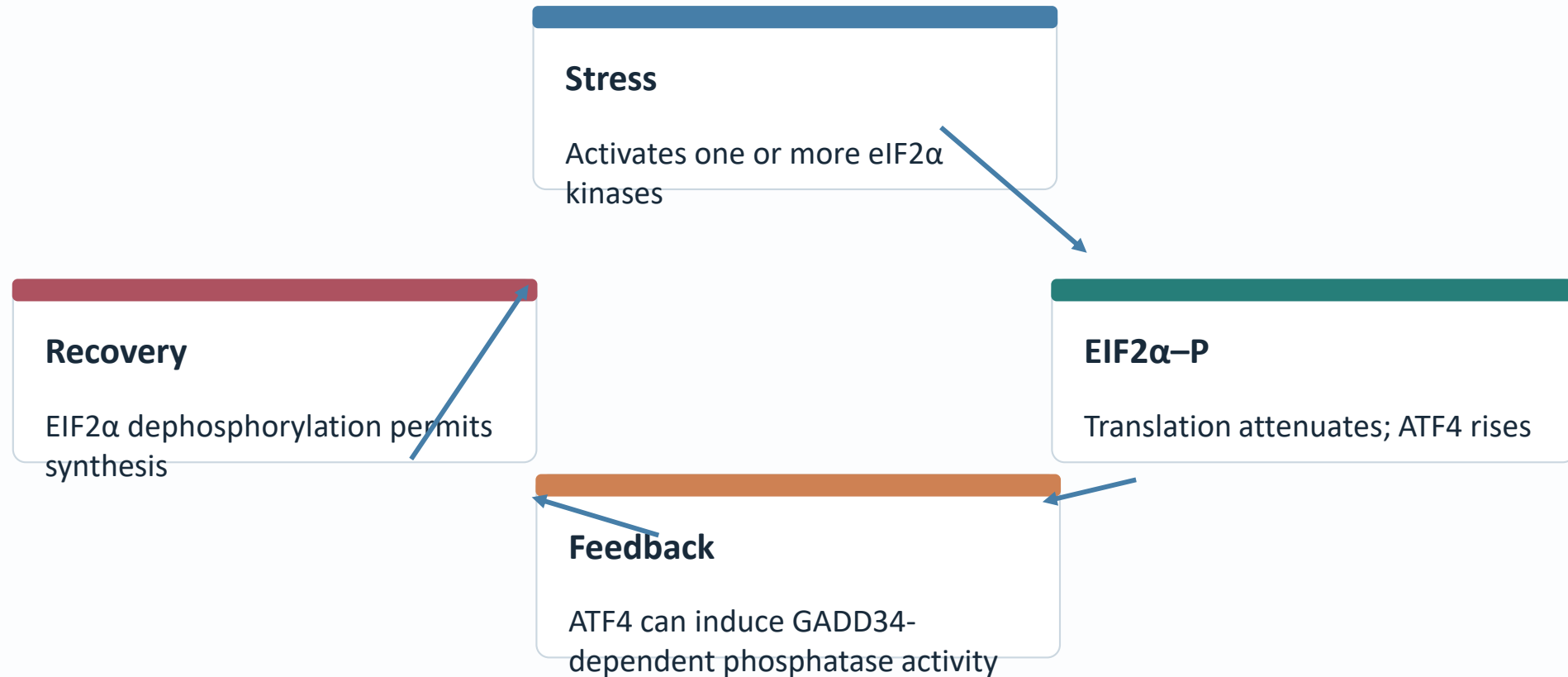
- ATF4 supports stress-response gene expression.
- ER quality control, proteasomes, and autophagy may cooperate with ISR.

Do not confuse transcription with translation

Process	ISR-associated event	Interpretive point
Translation	Most initiation rates decrease	Less protein from many pre-existing mRNAs
Selective translation	ATF4 protein increases	Selected mRNAs evade usual suppression
Transcription	ATF4 alters gene expression	New mRNA abundance may rise or fall
Recovery	EIF2 α phosphorylation resolves	Normal initiation can resume

The ISR contains a built-in recovery program

Adaptive responses must be reversible if homeostasis is restored.



GADD34 and CReP regulate dephosphorylation

Stress-inducible feedback

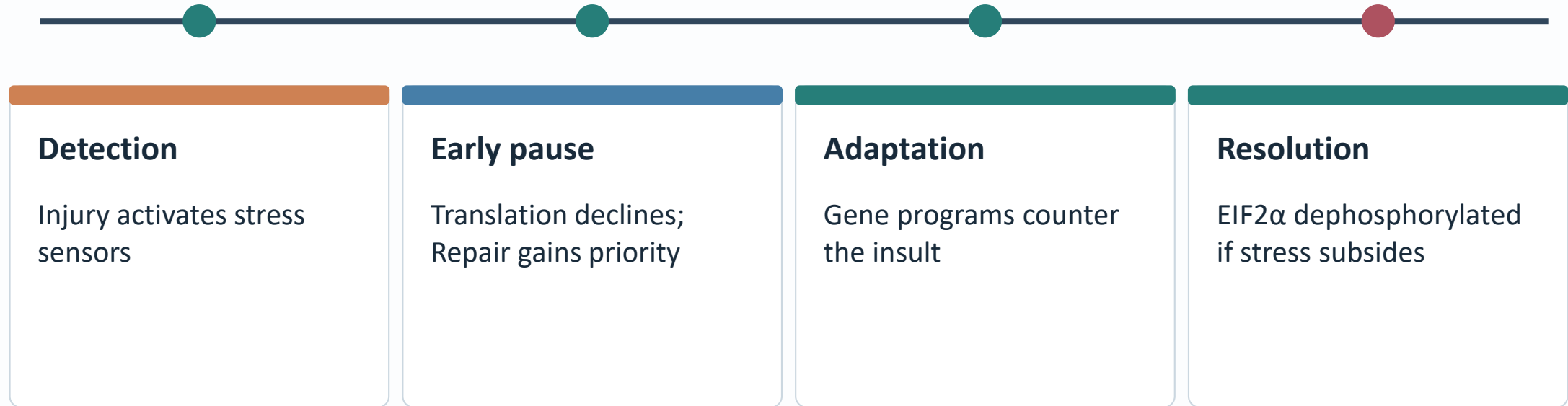
- ATF4-associated transcription can induce PPP1R15A / GADD34.
- GADD34 recruits phosphatase activity toward eIF2 α .

Constitutive restraint

- PPP1R15B / CReP contributes to baseline dephosphorylation.
- Both pathways oppose sustained eIF2 α phosphorylation.

Recovery is a dynamic sequence

A successful ISR changes over time rather than remaining permanently “on.”



When stress is not resolved, adaptation may fail

The same pathway may support survival or contribute to injury.

**Duration × intensity × cell
state**

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graph TD; A[Duration × intensity × cell state] --> B[Manageable stress]; A --> C[Persistent severe stress];
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Manageable stress

- Resource conservation and repair.
- Gradual restoration of protein synthesis.

Persistent severe stress

- Continued dysfunction and maladaptive signaling.
- Activation of apoptotic programs may occur.

Integrated signaling does not guarantee survival

Protective early phase

Translation restraint can buy time to repair injury.

Unresolved insult

Maintained protein misfolding or metabolic deprivation persists.

Maladaptive late phase

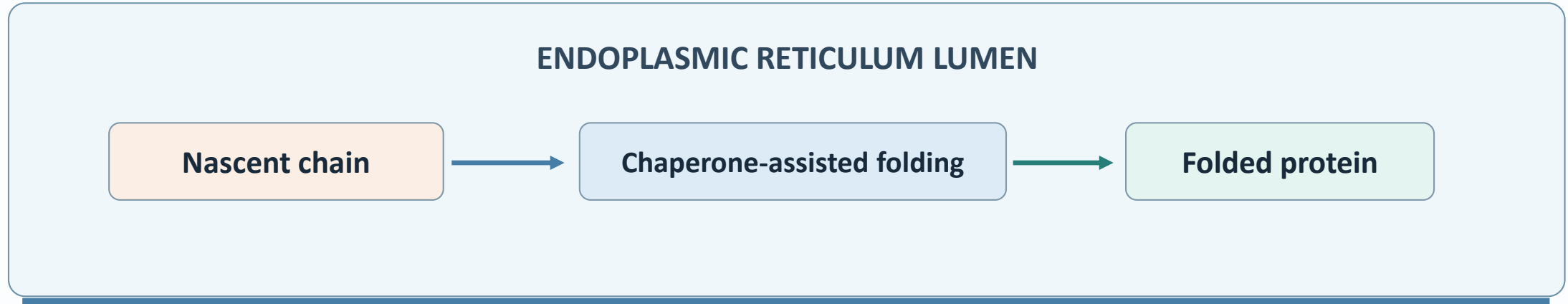
Stress transcription can engage proapoptotic effectors.

No universal threshold

Cell fate is not set by a single eIF2 α -P level.

Normal ER proteostasis is an active process

The ER is a synthesis, folding, and quality-control compartment.



CYTOSOL

Synthesis

Ribosomes produce secretory/membrane proteins.

Chaperones

Assist protein folding in ER lumen.

Quality control

Abnormal proteins are retained and cleared.

ER stress means folding demand exceeds capacity

Increased demand

High secretory protein load or altered protein synthesis.

Impaired folding

Mutations, aging, and altered ER redox/calcium state.

Compromised energy

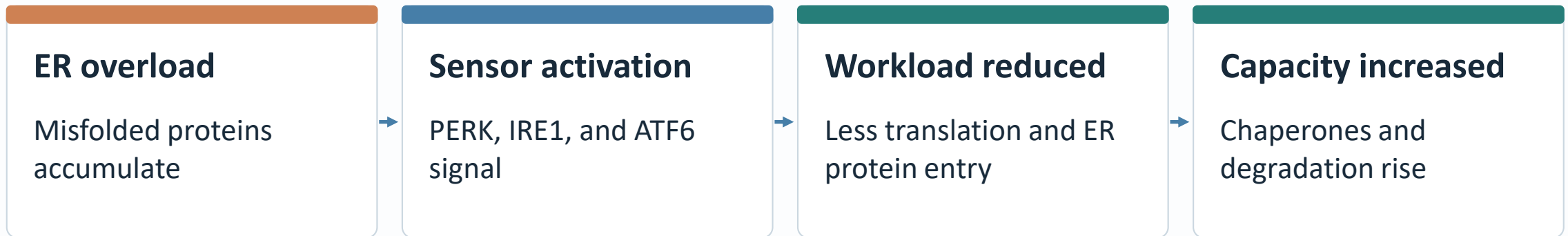
Hypoxia or ischemia limits ATP-dependent foldases.

Accumulated cargo

Unfolded/misfolded proteins strain the ER.

The unfolded protein response rebalances ER work

An adaptive UPR acts on both protein load and processing capacity.

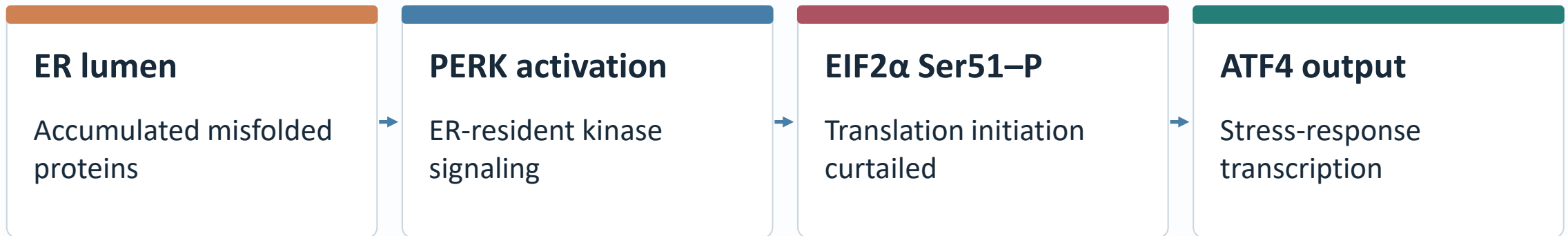


Three canonical arms of the mammalian UPR

Sensor	Main proximal output	Adaptive effect
PERK	EIF2 α phosphorylation	Reduce translation; Favor ATF4
IRE1	XBP1 mRNA splicing	Increase ER chaperones and ERAD
ATF6	Golgi cleavage; Nuclear ATF6(N)	Induce folding/quality-control genes

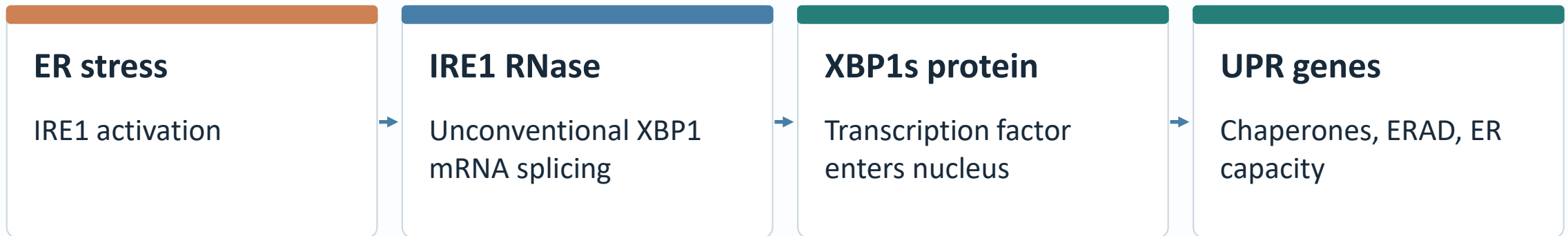
PERK is the direct bridge between UPR and ISR

PERK is both an ER stress sensor and an eIF2 α kinase.



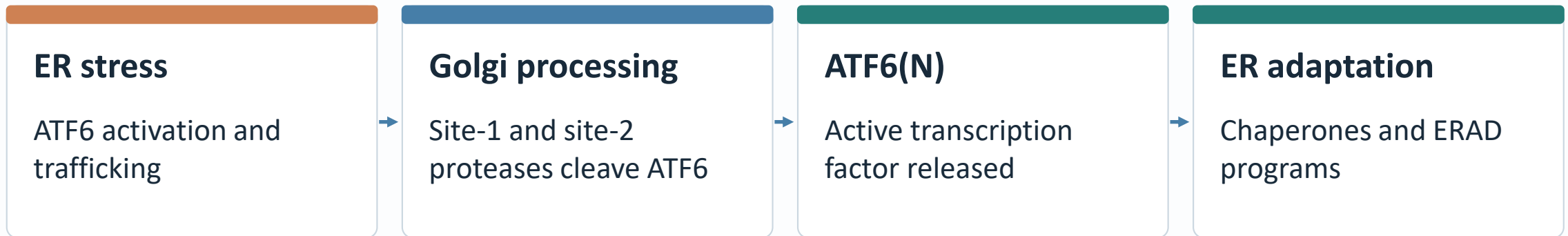
IRE1 promotes ER quality-control capacity

IRE1 has kinase and RNA-processing activities.



ATF6 signals through regulated proteolysis

An ER transmembrane precursor generates a nuclear transcription factor.



ER chaperones increase folding capacity

Normal role

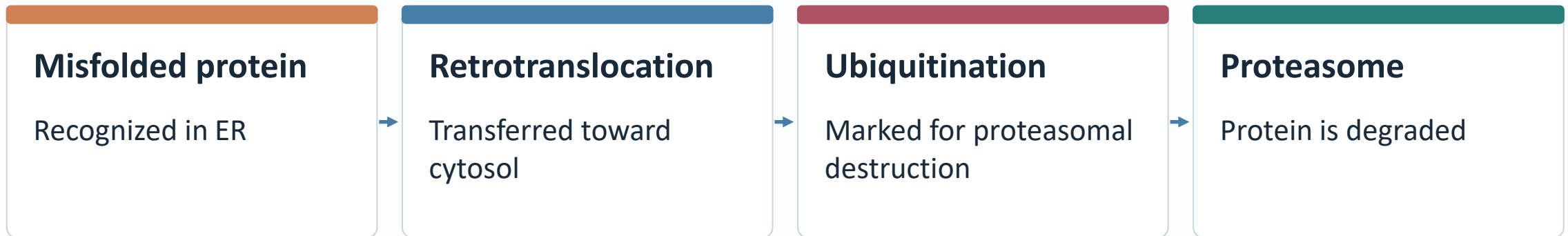
- Assist maturation of nascent ER proteins.
- Reduce inappropriate aggregation.
- Support folding of secreted/membrane proteins.

During the UPR

- Transcriptional programs increase folding support.
- This helps processing catch up with production.
- Persistent overload can exceed this adaptation.

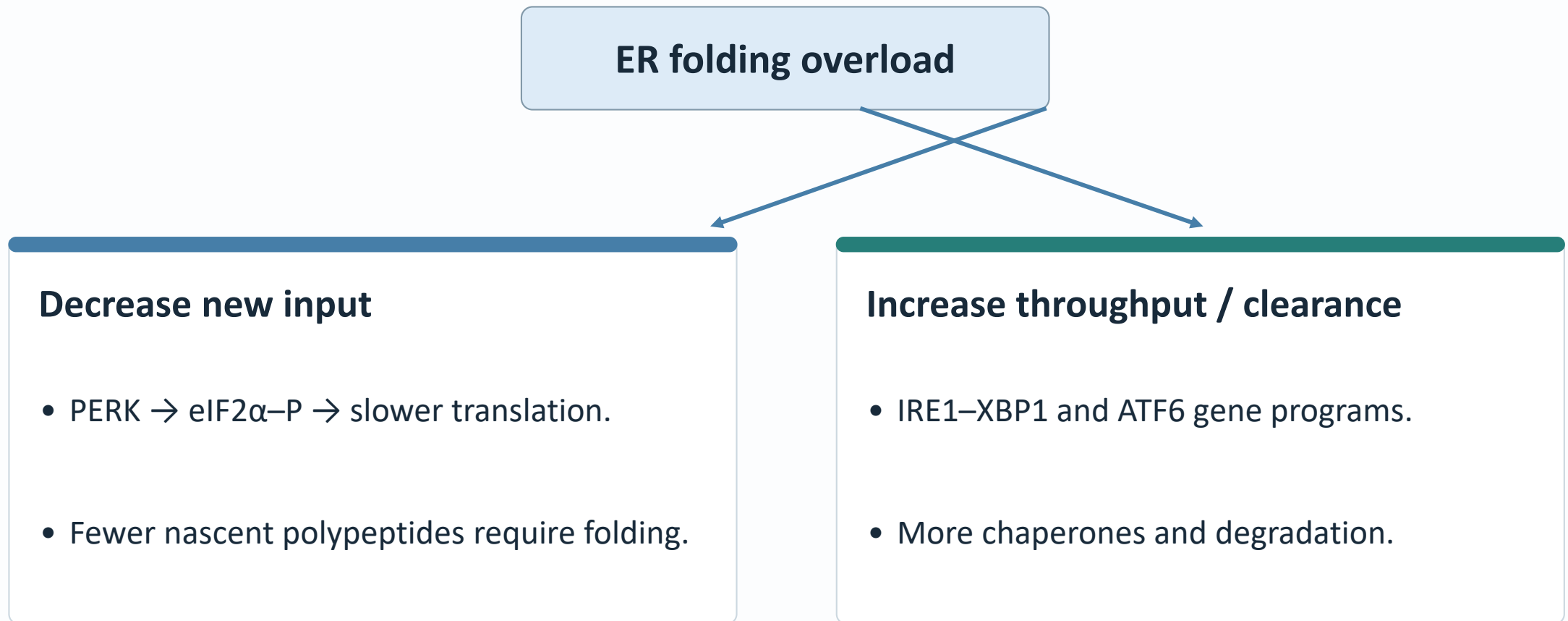
ER-associated degradation removes failed products

ERAD prevents irreparably abnormal proteins from accumulating.



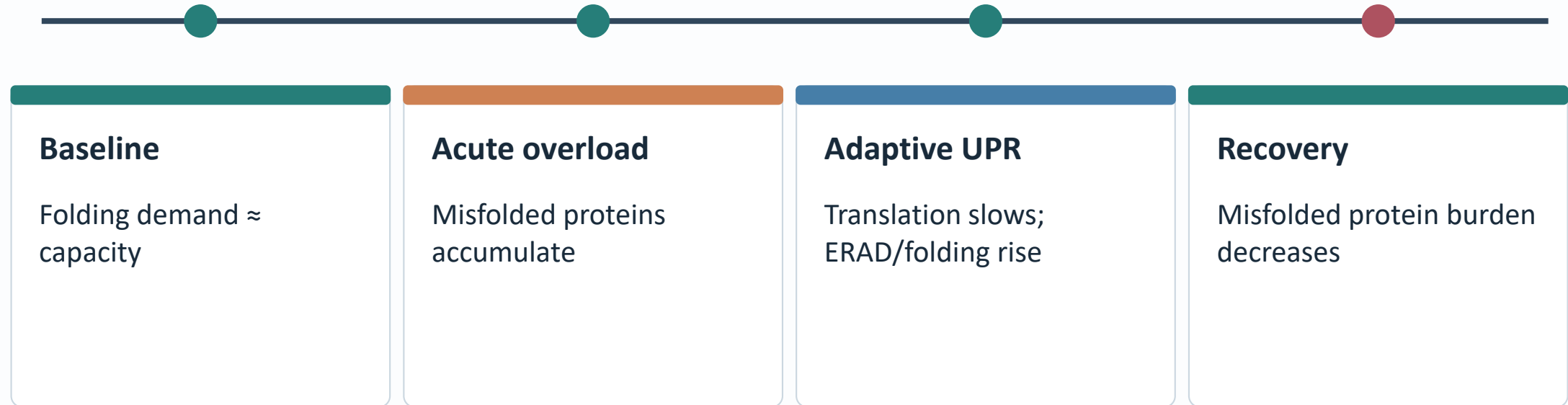
ER proteostasis can be restored by two levers

Homeostasis requires bringing demand back below processing capacity.



A successful UPR prevents escalation

Conceptual sequence: Stress handling versus terminal injury.



Terminal ER stress can activate apoptosis

If protective measures cannot resolve severe injury, death pathways may dominate.

Persistent folding imbalance

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graph TD; A[Persistent folding imbalance] --> B[Adaptation effective]; A --> C[Adaptation insufficient];
```

Adaptation effective

- Protein quality recovers.
- Proteotoxic stress declines.

Adaptation insufficient

- Proapoptotic signaling, including BH3/caspase pathways.
- Mitochondrial apoptosis may follow.

ISR versus UPR: Precise distinctions

Feature	ISR	UPR
Primary domain	Many stress inputs	ER proteostasis stress
Core sensors	Four eIF2α kinases	PERK, IRE1, ATF6
Central effect	EIF2α–P / selective translation	Protein folding load and capacity
Overlap	PERK and ATF4 branch	PERK drives part of ISR
Possible outcome	Recovery or dysfunction	Recovery or ER-stress apoptosis

Autophagy is a partner, not a synonym for ISR

ISR

Modulates translation through eIF2 α and transcription via ATF4.

UPR

Reduces ER load and increases quality-control capacity.

Autophagy

Sequesters and degrades selected cytoplasmic cargo via lysosomes.

Integrated protection

Stress pathways coordinate energy conservation and protein turnover.

Ischemia can recruit multiple ISR mechanisms

Cellular insult

- Reduced oxygen and glucose challenge ATP production.
- ATP-dependent protein folding becomes less efficient.
- Oxidative and organellar stress may accompany reperfusion.

Predicted adaptation

- Translation attenuation reduces energy demand.
- ATF4 programs may support cellular survival.
- Magnitude and persistence of ischemia determine overall injury.

Infection can generate translational stress

Initiating factors

- Double-stranded RNA may activate PKR.
- High viral protein production can burden ER folding.
- Host immunity contributes additional cell stress.

Integrated cellular response

- PKR and/or PERK can phosphorylate eIF2 α .
- Translation attenuation changes host protein synthesis.
- Viral strategies can modulate or evade these pathways.

Nutrient starvation changes both supply and demand

Nutrient limitation

- Amino acid shortages alter charged tRNA availability.
- GCN2 can sense the resulting scarcity.
- Sustained deprivation impairs normal growth and repair.

Rebalancing response

- EIF2 α -P restrains protein synthesis.
- ATF4 may mobilize nutrient-response transcription.
- Recovery requires sufficient restoration of substrates.

Secretory-cell stress illustrates clinical relevance

High-demand setting

- Insulin-resistant states can increase insulin secretory demand.
- Plasma cell neoplasms can produce very large protein loads.
- Misfolded polypeptides may exceed ER capacity.

What may follow

- UPR attempts to expand folding/degradation capacity.
- PERK links ER stress to ISR.
- Failed adaptation can contribute to dysfunction or cell death.

Neurodegenerative disease and proteostasis

Pathologic context

- Several neurodegenerative disorders involve protein misfolding or aggregation.
- Chronic proteostasis disruption may activate stress pathways.

Interpretive caution

- A persistent ISR or UPR may be adaptive or harmful by context.
- Association does not prove a pathway is the initiating cause.
- Cell type and disease stage modify the effects.

Cancer cells also experience proteotoxic stress

Stress environment

- High proliferative demand and altered metabolism raise biosynthetic strain.
- Hypoxia and nutrient shortage can coexist in tumors.
- ISR/UPR activation has been associated with cancer.

Biologic implications

- Stress adaptation can support survival in hostile conditions.
- Excessive or manipulated ISR signaling may instead compromise viability.
- Tumor-specific interpretation is required.

Inflammatory and autoimmune disease associations

Why signaling may matter

- Infection, immune activation, and increased protein secretion stress cells.
- ISR and UPR changes have been linked to immune-mediated disease.

What can be concluded

- The pathway may modify cellular responses during inflammation.
- Direction and causality differ among cell types and disorders.
- A generic ISR marker is not a disease-specific diagnostic test.

Interpreting common experimental readouts

Readout	What it supports	What it does not establish
Phospho-eIF2α (Ser51)	Activation of an eIF2 α kinase pathway	Identity of upstream kinase
ATF4 protein increase	Stress-associated selective translation	Benefit or harm without context
CHOP increase	Stress-associated transcriptional response	Inevitable apoptosis
Global translation assay	Net protein synthesis change	Which stress sensor caused it

Common mechanistic interpretation errors

Confusing ISR and UPR

UPR is ER-focused; ISR accepts diverse inputs.

Equating phosphorylation with death

EIF2 α -P often supports early adaptation.

Treating all mRNAs identically

ATF4 illustrates selective translation.

Ignoring the time axis

Transient and chronic responses can have different effects.

Case 1: A stressed secretory cell

A highly secretory cell accumulates abnormal proteins within its ER while protein output remains elevated.

Observed cellular context

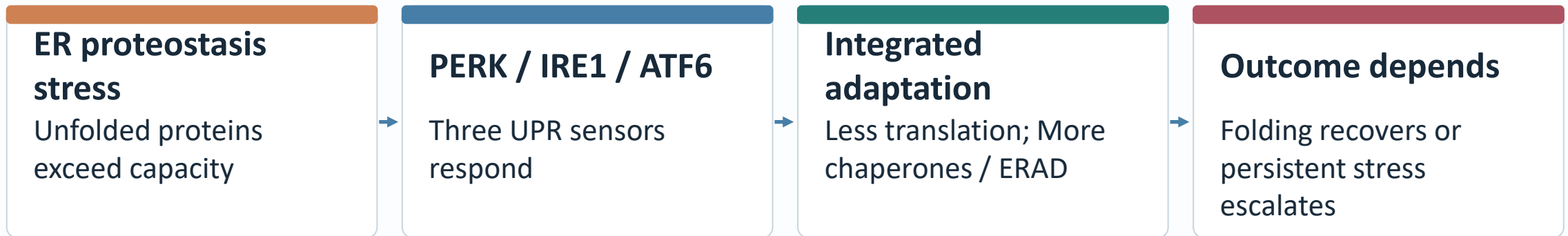
- Misfolded ER proteins accumulate.
- Protein folding demand exceeds processing capacity.
- ER-resident sensors are plausible responders.

Interpretation task

- Predict the earliest protective changes in protein synthesis and quality control.
- Which UPR arm directly phosphorylates eIF2 α ?

Case 1: Mechanistic interpretation

ER overload can activate several complementary branches.



The UPR is initially adaptive; Its failure may initiate apoptosis.

Case 2: A virally infected cell

An infected cell develops abundant double-stranded viral RNA and a measurable rise in eIF2 α Ser51 phosphorylation.

Observed cellular context

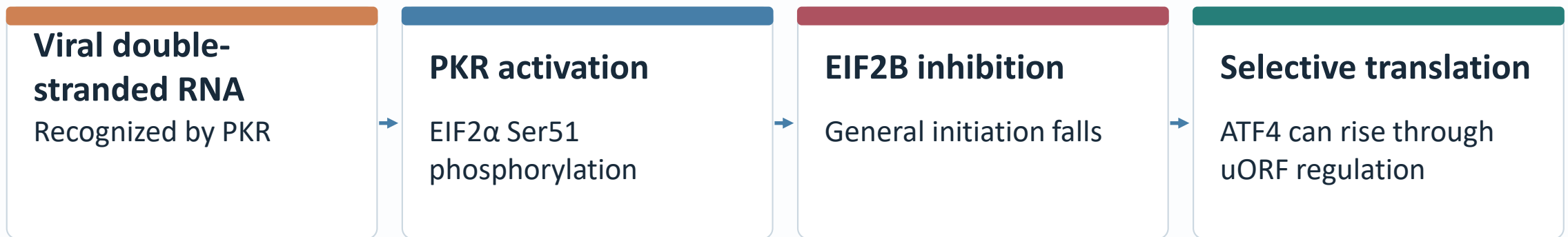
- A viral RNA-associated stress input is present.
- eIF2 α Ser51 is phosphorylated.
- Protein synthesis is reduced in a cell-based assay.

Interpretation task

- Identify the likely sensing kinase and explain why ATF4 may still increase.
- Does phospho-eIF2 α alone prove this kinase caused the signal?

Case 2: Mechanistic interpretation

PKR is a plausible, but not automatically exclusive, stress sensor.



Attributing causality requires sensor-specific perturbation or corroboration.

Clinical reasoning checkpoint

Why can a translation-inhibitory phosphorylation event increase a stress-response transcription factor?

Answer: Selective translation of transcripts such as ATF4 through uORF-dependent regulation.

Core mechanistic summary

Input

Four kinases respond to distinct cellular stresses.

Switch

All converge on eIF2 α phosphorylation at Ser51.

Output

Most translation decreases; ATF4 translation and adaptive transcription rise.

Fate

Homeostasis may recover; Unresolved stress can contribute to dysfunction/death.

Selected sources and further reading

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