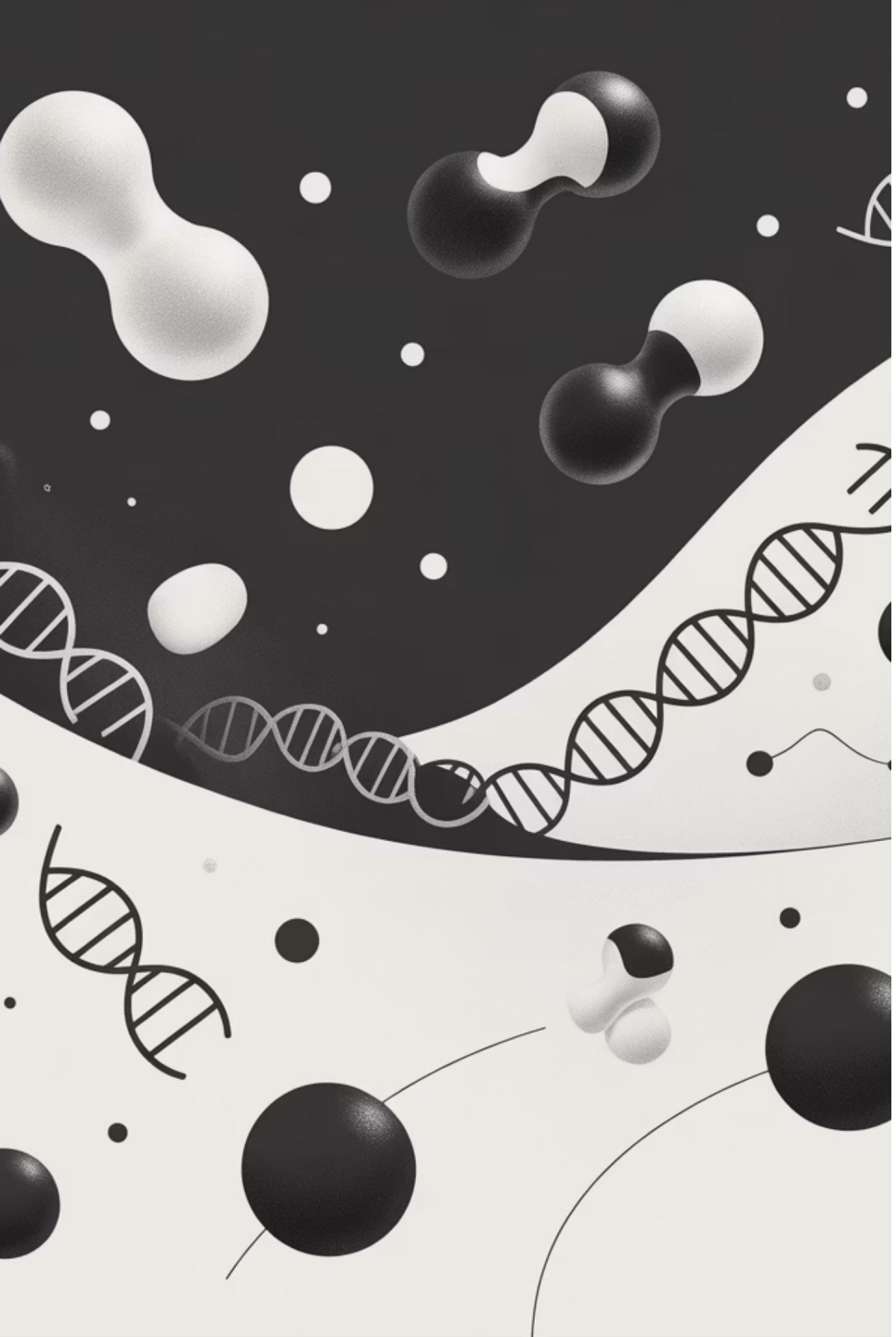


Top 3 Peptides used in Podiatry

Regenerative Medicine Certification Course
for Podiatric Physicians
February 2026

Presented by: Joanne Balkaran, DPM, MS, CWS, FACFAS, FAMIFAS, FAMOS

In Medicine

What do we study?

- **Diseases**
- Etiologies
- Triggers
- Risk Factors
- Procedures
- Drug treatment
- Complications

- **Goal:**

Prescribed treatment / protocol / surgery will erase or arrest the disease progression.

What if we focus on the cell & its function?

Focus on preserving health

Understand the body's capacity to heal

The inherent drive for Homeostasis!

Goal

To avoid the downside of aging that triggers disease

As we age ; there is decrease in signaling agents after 30

Focus on Aging and Diseases
Loss of cellular efficiency
Cell damage - senescence

W. Seeds. Peptide Protocols Volume 1, 2020

What are Peptides ?

- Endogenous signaling tools that restore homeostasis
- 50-100 amino acids connected by a peptide bond
- Synthesized by ribosomes via mRNA, exist in all cells
- Over 7000 naturally occurring peptides in the body
- 60 FDA approved peptide medicine
  140 in therapeutic treatments
  > 500 in preclinical development

Can re-create these signaling agents in the body

- Insulin – 51 amino acid peptide
- Glucagon
- Oxytocin
- Gonadrotrophin releasing hormone
- Vasopressin
- Somatostatin
- Glutathione

Peptides

- Aid in signaling
- Target cellular function, signaling pathways and root cause
- Immune modulators
- Have a short ½ life in the body
- They signal- work – exit
- Give the cells what they need to function efficiently
- Support metabolic flexibility
- Modulate inflammatory response

- **Metabolism**
- **Immunity**
- **Inflammation**

Key Actions of Peptides

Interact between:

- hormones
- neurotransmitters
- growth factors
- ion channel control
- ligands
- anti-infective properties

of the cell function

Function as therapeutics - homeostasis	Offset cellular senescence	Amerliorate tissue, bone, muscle healing and function
Support immune response after injury and during repair	Regain neuromuscular functioning	Preserve collagen / extracellular matrix
Minimize soft tissue, kidney, cardiac , liver and pulmonary fibrosis	Treat anxiety, depression and improve cognition and memory	Improve recovery from training (change landscape for athletes)

False Image

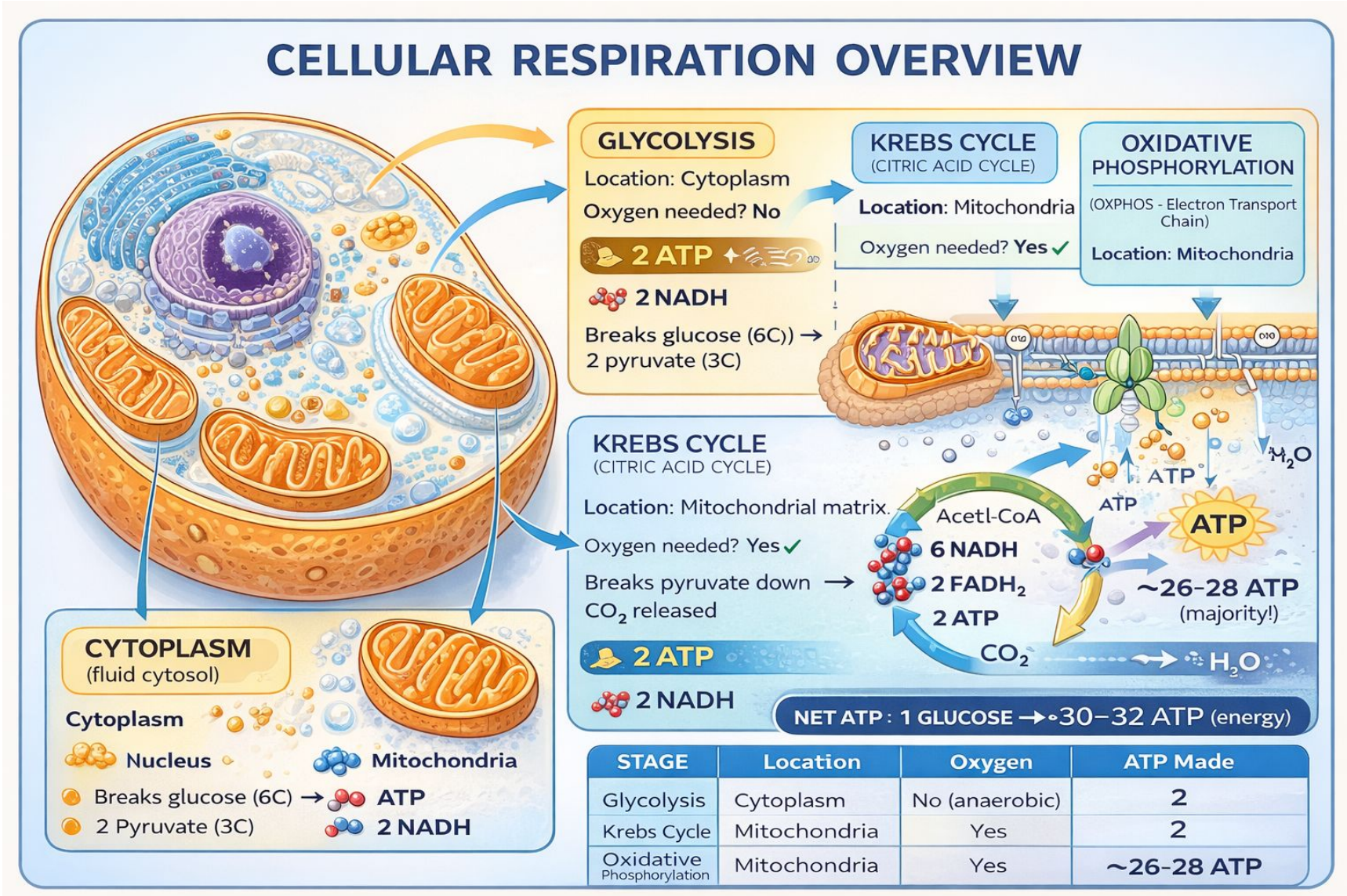
Adaptation
Mitochondria biogenesis

Stress

Cellular dysfunction

Epigenetic changes

Peptides restore homeostasis →



STAGE	Location	Oxygen	ATP Made
Glycolysis	Cytoplasm	No (anaerobic)	2
Krebs Cycle	Mitochondria	Yes	2
Oxidative Phosphorylation	Mitochondria	Yes	~26-28 ATP

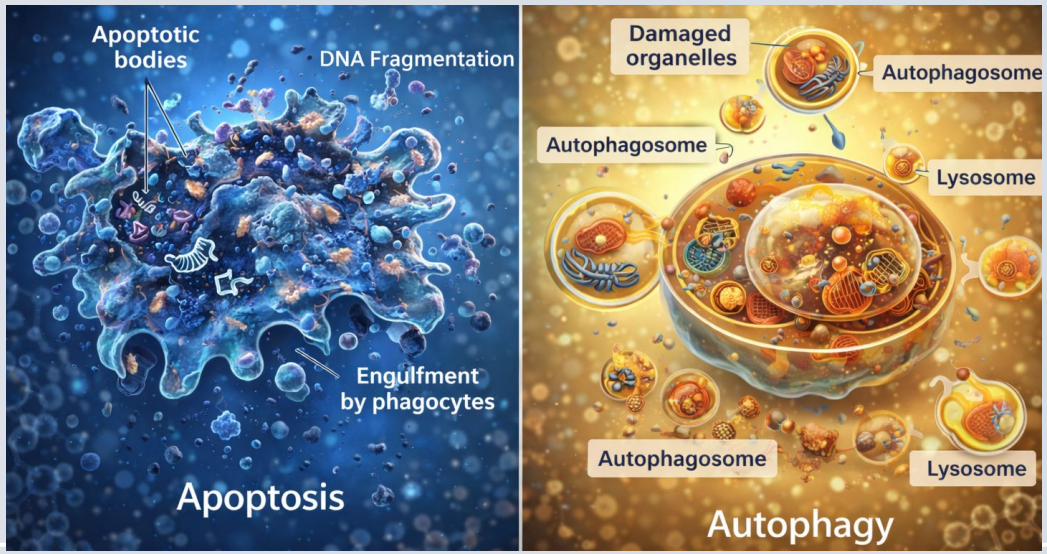
Cell Intelligence

To understand peptides – cell cycle, mechanisms for protecting itself and making decisions and its motivations
Cells – preprogrammed to grow, replicate & divide

Self-check system

- If a cell divides and unlikely to survive –undergoes – APOPTOSIS (cell suicide)
- AUTOPHAGY – signals the innate immune system cells to clean up debris from cell disintegration

- **As We Age** – lose capacity for adaptation, decrease proliferation, decrease cell efficiency and can begin to make signaling mistakes
    - Loss of metabolic flexibility
    - Less ability to handle stress
    - Affect the self-check system



Epigenetics

Bridge between the environment (positive vs negative stress – gene expression and cell behavior

In response to environmental factors, gene may change their messaging and up / down regulate

When genes begin to adapt to stressors – function differently – cell phenotype changes

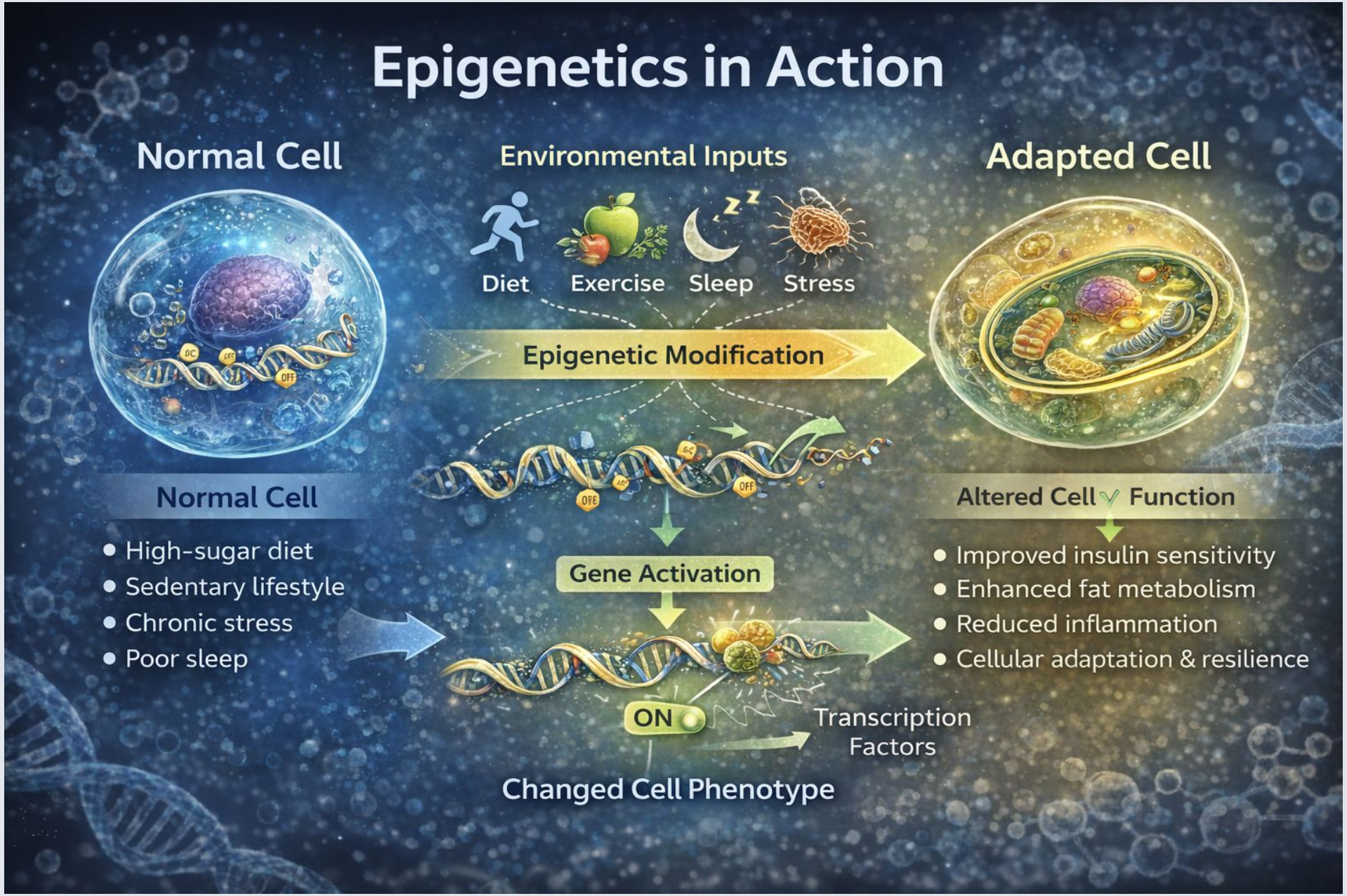
Example: food or exercise – can change the way genes transcribe proteins or enzymes

Capacity to handle stress – bacterial/ viral / smoking / trauma/ cancer/lifestyle

Create inter or extracellular changes that disrupts cell functioning

When the cell is under insult – relies on the self check system (apoptosis/ autophagy) to move forward and improve

Mitochondria also undergoes MITOPHAGY – clean up ‘bad mitochondria’ or debris harmful to its environment


Epigenetics in Action
Normal Cell
Environmental Inputs
Adapted Cell
Diet
Exercise
Sleep
Stress
Epigenetic Modification
Normal Cell
Altered Cell Function
High-sugar diet
Sedentary lifestyle
Chronic stress
Poor sleep
Gene Activation
Improved insulin sensitivity
Enhanced fat metabolism
Reduced inflammation
Cellular adaptation & resilience
ON
Transcription Factors
Changed Cell Phenotype

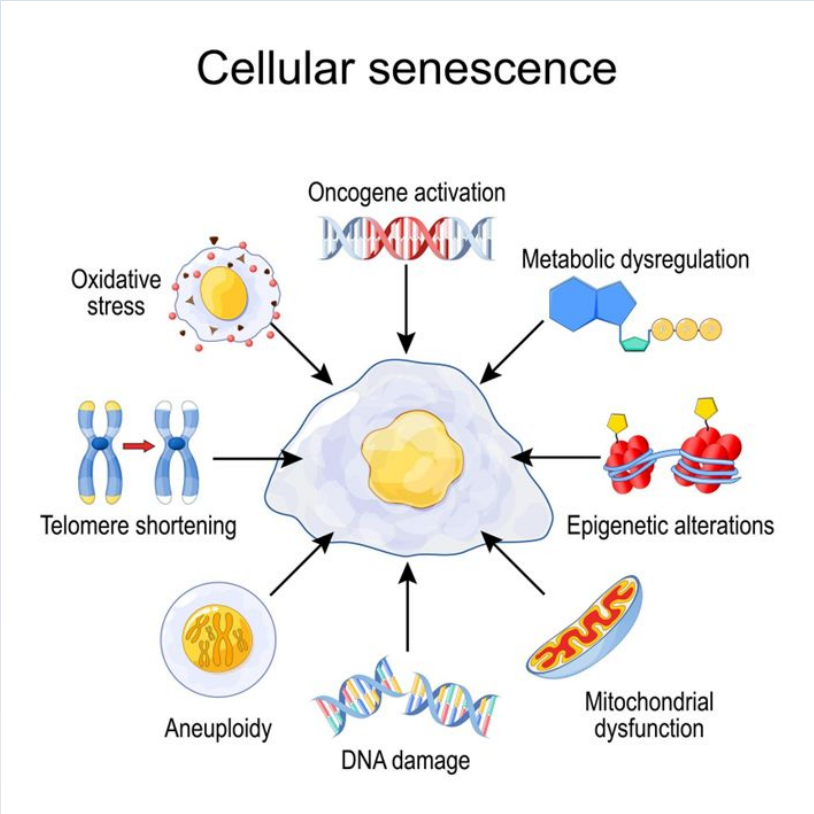
Cell Senescence

- Discovered in 1960s – Hayflick and Moorehead
- Shortening of telomeres with each cell division
- Telomere erosion

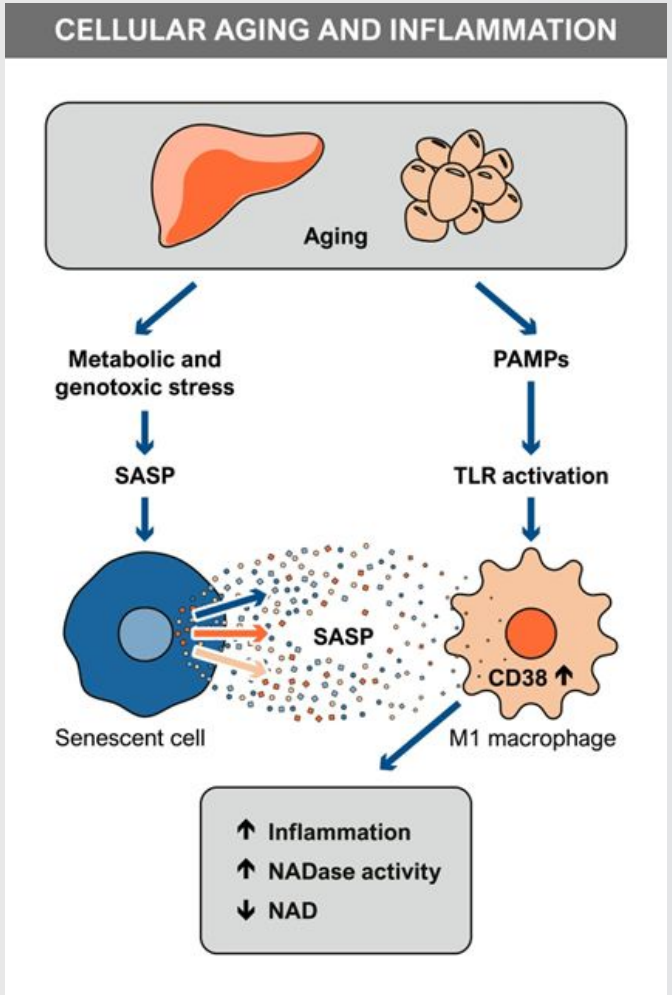
When the processes of the self-check system can no longer keep up with the stressors – cells are post mitotic and stop dividing → cell senescence

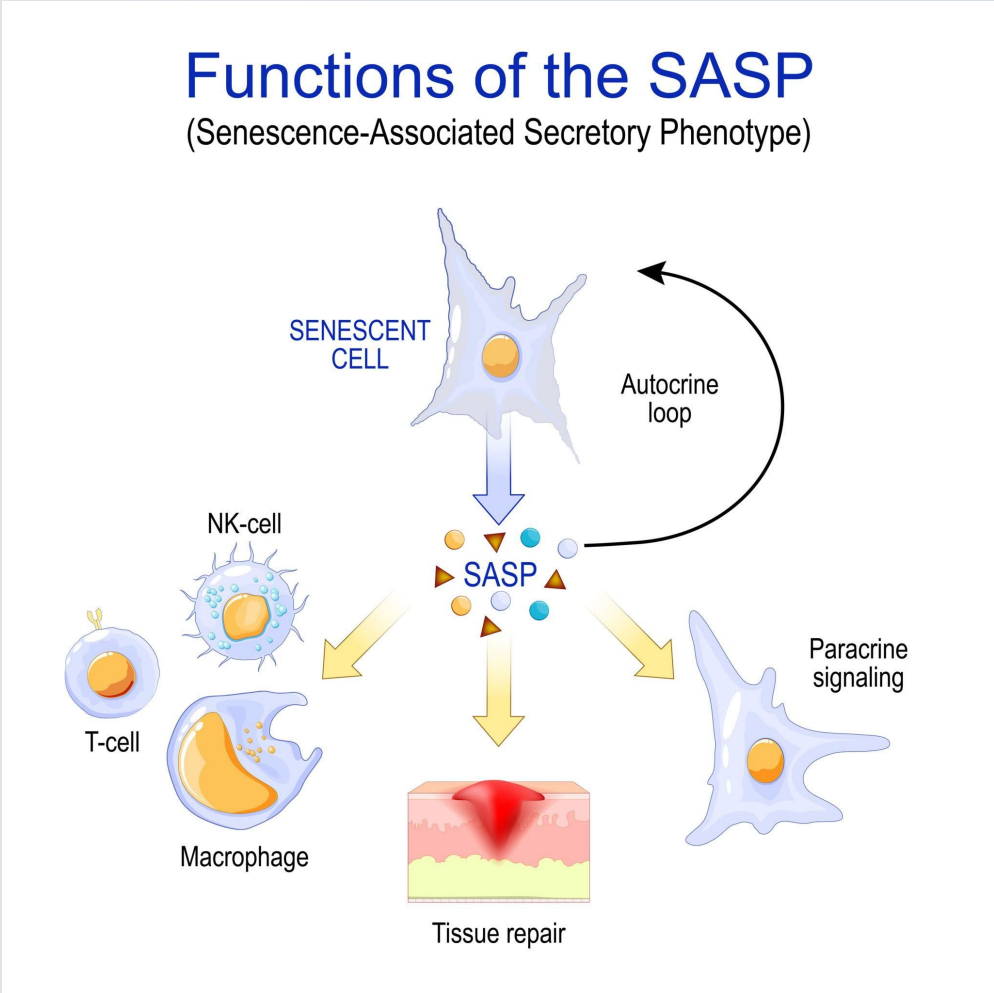
Senescence Cells

- Degrade cell signaling
- Mitochondria dysfunction
- Disrupt nearby tissue function
- Secrete factors – recruit inflammatory cells
- Remodel ECM
- Trigger unwanted cell death
- Induce fibrosis
- Inhibit stem cell function
- Affect NAD, leak electrons – ROS
- Increase inflammation



Cell Senescence





Top 3 Peptides in Podiatry and Coenzyme NAD+

- BPC – 157
- TB-500
- GHK-Cu
- NAD+

Why these 3 peptides ?

Orthopedic is a cellular problem before it becomes a tissue issue
(Example: arthritis, delayed wound healing)

Peptides are amplifiers

Understand the molecular pathway to understand which amplifier (peptide) to use for wound healing

Share convergence of multiple pathways

Angiogenesis – Increase collagen via fibroblast - Mitochondria efficiency– Redox balancing – ECM changes – Determine repair speed and quality

Not FDA approved

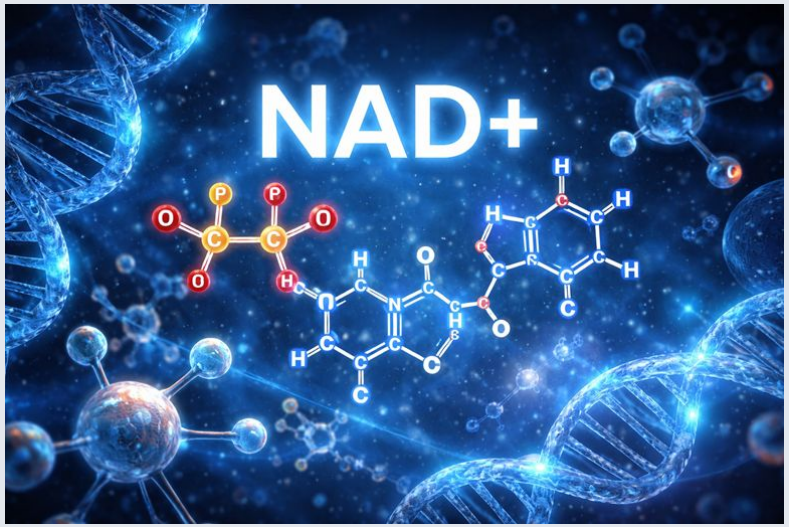
Journal AAOS | Global Research & Reviews

Therapeutic Peptides in Orthopaedics:
Applications, Challenges, and Future Directions

Therapeutic peptides are emerging as **promising adjuncts** in the management of orthopaedic injuries, grounded in their ability to modulate molecular signaling networks central to cellular medicine. By acting on key pathways such as PI3K/Akt, mTOR, MAPK, TGF-β, and AMPK, peptides exert influence over tissue regeneration, ation, inflammation resolution, and neuromuscular recovery. Wound-healing peptides such as BPC-157, TB-500, and GHK-Cu promote angiogenesis, integrin-mediated extracellular matrix remodeling, and fibroblast activation, whereas growth hormone secretagogues like ipamorelin, CJC-1295, tesamorelin, sermorelin, and AOD-9604 activate IGF-1 signaling and satellite cell repair. Recovery-enhancing agents such as epitalon, delta sleep-inducing peptide, and pinealon target circadian and mitochondrial regulators, and neuroactive peptides like selank, semax, and dihexa enhance brain-derived neurotrophic factor and HGF/ Met pathways critical to neuroplasticity. This review integrates current mechanistic insights with orthopedic relevance, emphasizing safety, and future datal care.

Authored by William A Seeds, Omar F Rahman, Steven J Lee

Nicotinamide Adenine Dinucleotide (NAD+)

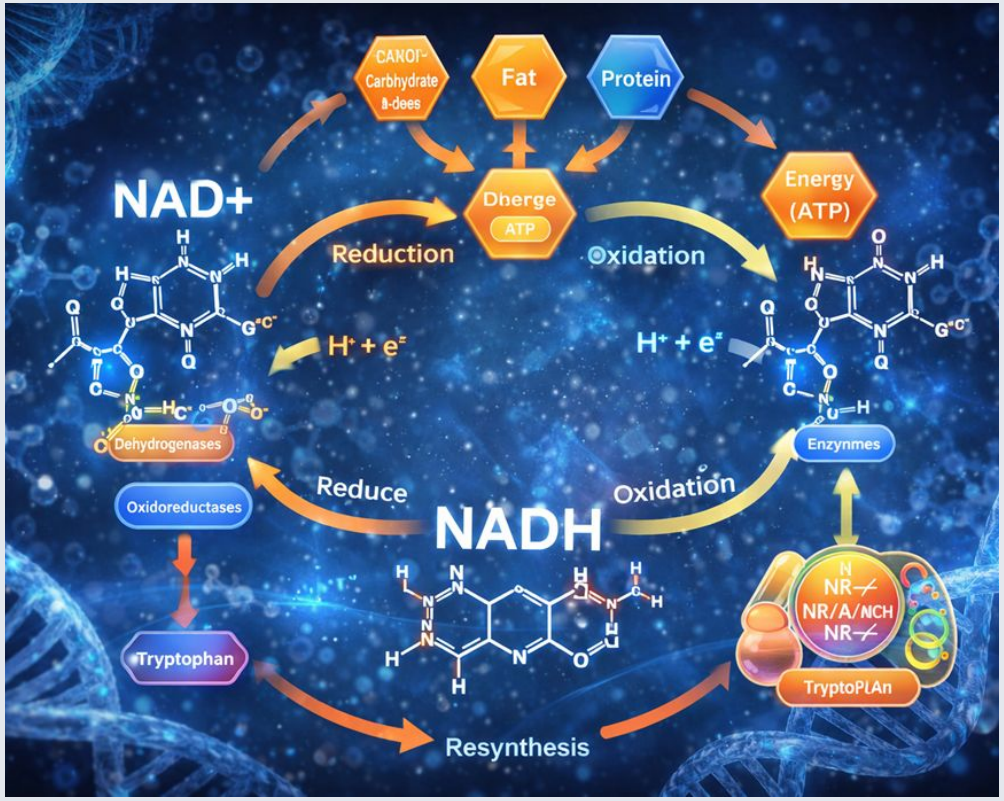


- Coenzyme – assist enzymes in energy production
- Dinucleotide connected by a phosphate group
- Peptides built from aa
- NAD made from nucleotides
- Electron acceptor in the E transport chain

<u>Electron transport chain</u>
NAD+ - oxidized form
NADH – reduced form

ROLE

- Glycolysis
- Krebs Cycle
- Oxidative Phosphorylation
- Supply H+ ion in the E transport chain for ATP production



Cellular Efficiency

- Maximize use of substrate – glucose/ fatty acid/protein for cellular respiration

Mitochondria Coupling

- Amount of oxygen consumed vs the amount of ATP produced using the least amount of glucose

For nicotinamide mononucleotide (NMN), clinical studies have tested doses ranging from **300 mg to 1,000 mg once or twice daily**.

MIB-626, an Oral Formulation of a Microcrystalline Unique Polymorph of B-Nicotinamide Mononucleotide, Increases Circulating Nicotinamide Adenine Dinucleotide and Its Metabolome in Middle-Aged and Older Adults.

The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2023. Pencina KM, Lavu S, Dos Santos M, et al.

Towards Personalized Nicotinamide Mononucleotide (NMN) Supplementation: Nicotinamide Adenine Dinucleotide (NAD) Concentration.

Mechanisms of Ageing and Development. 2024. Kuerec AH, Wang W, Yi L, et al.

Evaluation of Safety and Effectiveness of NAD in Different Clinical Conditions: A Systematic Review.

American Journal of Physiology. Endocrinology and Metabolism. 2024. Gindri IM, Ferrari G, Pinto LPS, et al.

TB-500

- **TB-500** is a **synthetic peptide** that mimics a naturally occurring protein fragment called **Thymosin beta-4 (Tβ4)**.
- **TB-500** is the lab-manufactured version of the **active region** of **Tβ4**.

TB-500 is a **fragment of Thymosin beta-4**

- a 43-amino-acid peptide found in platelets and WBCs
- Produced in the thymus gland
- Immune modulator
- Stimulate T-cell and antibody production
- **Tβ4** gene is upregulated after injuries
- Actin sequestering peptide
- Stimulate TGF-B and VEGF pathway

- Thymosin beta-4 plays a role in:
  - Cell migration
  - Wound healing
  - Angiogenesis
  - Actin regulation (cytoskeleton organization)
  - Decrease fibrosis in ligaments, tendons, muscles
  - Aids pressure and venous ulcers

- Enhance collagen deposition
- Anti-inflammatory
- Promotes hair growth
- Antiviral/antimicrobial
- Improves neuroplasticity, cardiac vessels

Tβ4 in action (TB-500)

Inflammatory cytokines	Cell migration	Wound healing
↓ **NF-kB**	↑ **TGF-B**	**VEGF, PAI-1**
IL-1, TNF-alpha	↓ **MMPs**	Kinase protein

Dosing

- Between 300 mcg and 1 g daily subQ
- Do not dose > 3 months
- Cycle 1 month off
- Works well with BPC-157 and GHK-Cu
- **(GLOW)**

Venous Stasis Ulcers Study

A **phase 2, double-blind, placebo-controlled, dose-escalation study** enrolled 73 patients across eight European sites (Italy and Poland).

Key findings:

Safety: Acceptable profile comparable to placebo across all doses

Efficacy: The 0.03% dose showed potential to accelerate wound healing

Complete healing: Achieved within 3 months in approximately 25% of patients, particularly those with small to moderate wounds or mild to moderate severity

The Effect of Thymosin Treatment of Venous Ulcers.

Annals of the New York Academy of Sciences. 2010. Guarnera G, DeRosa A, Camerini R

Pressure Ulcers and Stasis Ulcers Study

Phase 2 trials demonstrated that **Tβ4 accelerated healing by almost a month** in patients who healed, compared to standard care. [4-5] The peptide was safe and well-tolerated across these studies

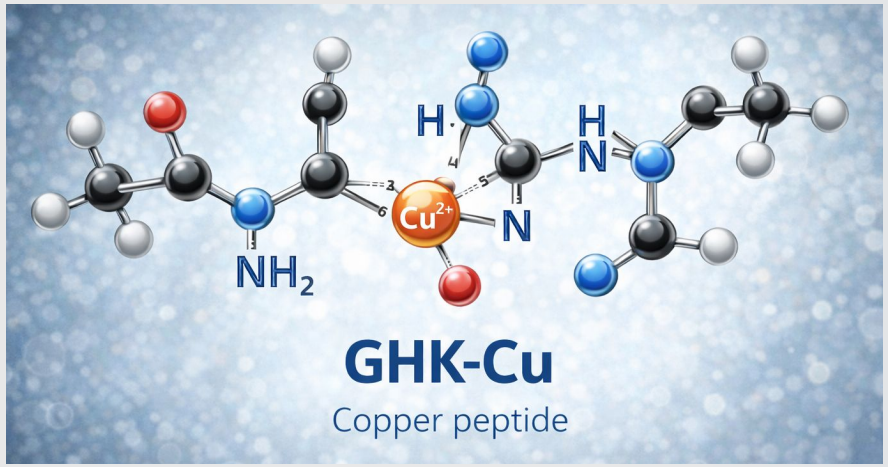
Thymosin B4 Promotes Dermal Healing.

Vitamins and Hormones. 2016. Kleinman HK, Sosne G.

GHK-Cu

- Naturally occurring **copper** complex
- **Tripeptide - G**lycyl –L-**H**istidyl – L-**K**lysine
- Strong affinity for **Cu**

- GHK-Cu - found in plasma, saliva , urine
- Decline in GHK-Cu as we age
- At 20, GHK-Cu plasma levels = 200ng/ml
- By 60, declines to 80 ng/ml
- Side effects: Copper toxicity; blue nail color changes



Role

- Activates wound healing
- Attract immune cells
- Stimulate collagen and glycosaminoglycans
- Improve stem cells
- Defend against tumors
- Antioxidant / Anti-inflammatory
- Modulate MMPs and inhibitors

GHK-CU

Immunity

- Modulate cytokines
- Reduce oxidative stress

Metabolic

- Enhance Mitochondria respiration
- Reduce ROS

Angiogenesis

- VEGF pathway
- Activate TGF-B
- ECM remodelling

Dosing (topical / Sub Q)

- GHK-Cu topical concentration– 0.05% - 0.5%
  - 0.05-0.1% chronic wounds (maintenance)
  - 0.1-0.5% active stimulation (collagen, granulation)
- 1-2mg/day subQ for 6-week intervals
- Can be used 3-4 times a year/ Cycle 1-2 months off
- Works well with BPC-157 and TB-500
- **(GLOW)**

Studies

- **GHK-Cu stimulates collagen synthesis at concentrations as low as 10^{-9} M, with effects beginning at 10^{-12} to 10^{-11} M in fibroblast cultures.**

Stimulation of Collagen Synthesis in Fibroblast Cultures by the Tripeptide-Copper Complex Glycyl-L-Histidyl-L-Lysine-Cu2+.

FEBS Letters. 1988. Maquart FX, Pickart L, Laurent M, et al.

Stimulation of Sulfated Glycosaminoglycan Synthesis by the Tripeptide-Copper Complex Glycyl-L-Histidyl-L-Lysine-Cu2+.

Life Sciences. 1991. Wegrowski Y, Maquart FX, Borel JP.

- **GHK-Cu has a long history of safe use in wound healing and cosmetic applications**

The Human Tripeptide GHK-Cu in Prevention of Oxidative Stress and Degenerative Conditions of Aging: Implications for Cognitive Health.
Oxidative Medicine and Cellular Longevity. 2012. Pickart L, Vasquez-Soltero JM, Margolina A.

Diabetic Ulcer Trial

The most significant clinical trial of GHK-Cu in humans was a multicenter, randomized, evaluator-blinded, placebo-controlled study in diabetic neuropathic ulcers, which demonstrated that topical GHK-Cu significantly enhanced wound closure compared to vehicle control.

The trial enrolled patients with diabetic neuropathic ulcers in a standardized wound care protocol including sharp debridement, daily application of GHK-Cu gel (marketed as Iamin Gel), standardized pressure-relieving footwear, and patient education.

Key findings included**:**

Median area closure: 98.5% with GHK-Cu vs. 60.8% with vehicle ($p < 0.05$)

Healing rate: Three times faster with GHK-Cu compared to standard care and vehicle

Infection rate: 7% with GHK-Cu vs. 34% with vehicle ($p < 0.05$)

Timing: Treatment commence immediately after initial debridement for optimal enhancement

The study demonstrated that larger plantar ulcers, which typically fail to respond adequately to standardized wound care alone, showed particularly pronounced improvement with GHK-Cu treatment.

Enhanced Healing of Ulcers in Patients With Diabetes by Topical Treatment With Glycyl-L-Histidyl-L-Lysine Copper.
Wound Repair and Regeneration : Official Publication of the Wound Healing Society the European Tissue Repair Society. 1994. Mulder GD, Patt LM, Sanders L, et al.

GLOW

Shared pathways – **used in aesthetics**

- Angiogenesis
- ECM changes
- Redox balancing and mitochondria efficiency
- Collagen production via fibroblast

BPC – vascular repair , affect tendon , ligament , muscle , nerve; enhance fibroblast migration. Improve tendon structure and biomechanical strength

TB-500- actin and cell migration, repair of cytoskeleton and complement vascular peptide, promote progenitor cell recruitment. Aid with collagen reformation/ organization and prevent XS collagen. Early phase healing and acts upstream of structural remodeling

GHK-Cu – collagen turnover for dermal wound healing, connective tissue repair – stimulate fibroblast proliferation; MMP degradation and synthesis collagen, active antioxidant pathway ; redox balance and matrix quality in healing. Buffer redox cycling. Support ECM. Anabolic signaling for repair

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Questions ??

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Joanne N. Balkaran

a certification in

Peptide Therapy

and merits recognition as a perennial scholar of clinically-validated Cellular Medicine-based therapies.

WILLIAM A. SEEDS MD
FOUNDER AND ACADEMIC CHAIRMAN

SEEDS SCIENTIFIC RESEARCH & PERFORMANCE

Thank you

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