PRAXIS
PEPTIDE INSTITUTE

SHLP PEPTIDES

ADVANCED MECHANISM AND EVIDENCE GUIDE

MITOCHONDRIAL-DERIVED SMALL HUMANIN-LIKE PEPTIDE FAMILY SHLP1 THROUGH SHLP6
mitochondrial DNA • SHLP1-6 • SHLP2 • SHLP3 • metabolism • ROS • apoptosis • insulin sensitivity • cellular resilience

MEMORY KEY: SHLPS ARE SIX MITOCHONDRIAL MESSAGES, NOT ONE DRUG: FAMILY MEMBERSHIP DOES NOT MAKE THEIR FUNCTIONS OR EVIDENCE INTERCHANGEABLE.

Educational monograph • Meaningful discovery and mechanistic biology • SHLP2 best characterized • Early and uneven human translation

HOW TO USE THIS GUIDE

This guide converts a long-form research narrative into a repeatable learning system. Every future PPI molecule guide can use the same architecture, visual language, evidence labels, and memory devices.

01	IDENTITY What it is - and what it is not
02	PHYSIOLOGY The normal system before the compound
03	MECHANISM Target, pathway, and downstream logic
04	EVIDENCE Cell, animal, and human evidence separated
05	RISK Known concerns, unknowns, and translation limits
06	MONITORING What a legitimate research framework would measure
07	PATIENT CONTEXT Which phenotype might fit the biology
08	RECALL Memory hooks, seven questions, and bottom line

EVIDENCE CODE		CORE DISCIPLINE
	CELL = mechanistic ANIMAL = organism-level preclinical HUMAN = clinical translation	Mechanism does not equal outcome. Unknown does not equal failed - and unknown does not equal proven.

RAPID RECALL

Read this page first. These anchors provide the complete high-level story of Shlp Peptides; the remaining pages add mechanism, evidence, context, and nuance.

01	IDENTITY SHLP1 through SHLP6 are 20-38-amino-acid mitochondrial-derived peptides encoded within mitochondrial rRNA regions.
02	FAMILY RULE The six peptides are not one mechanism or one therapy. Each sequence requires its own functional and evidence assessment.
03	LEAD SIGNAL SHLP2 has the clearest translational story, linking mitochondrial function, insulin sensitivity, cytoprotection, and aging biology.
04	PARTNER SHLP3 also shows metabolic and cell-survival activity, while SHLP1, SHLP4, SHLP5, and SHLP6 remain less characterized.
05	SYSTEM Mitochondria act as signaling organelles, communicating metabolic state, oxidative stress, apoptosis, and adaptive needs.
06	CONTEXT Reducing ROS or apoptosis may protect stressed healthy tissue but is not universally beneficial in every cell or disease state.
07	EVIDENCE Mechanistic, cellular, and animal evidence is much stronger than large randomized human therapeutic evidence.
08	PRAXIS QUESTION Which SHLP is being discussed, what mitochondrial bottleneck exists, and does that exact peptide have evidence for it?

ONE-SENTENCE MEMORY
SHLPS ARE SIX MITOCHONDRIAL MESSAGES, NOT ONE DRUG: FAMILY MEMBERSHIP DOES NOT MAKE THEIR FUNCTIONS OR EVIDENCE INTERCHANGEABLE.

UNDERSTAND THE PEPTIDES

SHLPs - Small Humanin-Like Peptides 1 through 6 - are a family of mitochondrial-derived peptides encoded within short open-reading frames associated with the mitochondrial 16S rRNA gene region.

They were identified after Humanin and helped expand an important concept:

MITOCHONDRIAL DNA ENCODES MORE BIOLOGICAL INFORMATION THAN WE ONCE THOUGHT.

The known mitochondrial-derived peptide family includes:

- Humanin
- MOTS-c

SHLP1

SHLP2

SHLP3

SHLP4

SHLP5

SHLP6

Humanin and SHLP1-6 are encoded within the mitochondrial 16S rRNA / MT-RNR2 region, whereas MOTS-c is encoded within the 12S rRNA / MT-RNR1 region.

That makes SHLP biology conceptually important.

Mitochondria are not simply:

ATP FACTORIES.

They also generate:

SIGNALS ABOUT CELLULAR CONDITION.

And SHLPs appear to participate in communication involving:

- mitochondrial metabolism
- oxidative stress
- cell survival
- inflammation
- apoptosis
- insulin sensitivity
- neuroprotection
- aging biology

The most useful way to understand SHLPs is not:

“SIX MORE HUMANINS.”

They are related by mitochondrial origin and naming.

But they are:

NOT BIOLOGICALLY IDENTICAL.

A better description is:

A FAMILY OF MITOCHONDRIAL-DERIVED MICROPEPTIDES WITH DISTINCT AND SOMETIMES OPPOSING EFFECTS ON CELLULAR SURVIVAL, METABOLISM, STRESS RESPONSES, AND AGING PHYSIOLOGY.

That distinction is essential.

WHAT ARE SHLPS?

SHLP stands for:

SMALL HUMANIN-LIKE PEPTIDE.

Six have been identified:

SHLP1-SHLP6.

They are generally described as peptides of roughly:

20-38 AMINO ACIDS,

depending on the specific member and source.

They were discovered through analysis of:

• SMALL OPEN-READING FRAMES - sORFs

within mitochondrial DNA.

Historically, regions such as mitochondrial rRNA genes were assumed to function primarily as:

RNA.

The discovery of mitochondrial-derived peptides showed that those same genomic regions can contain:

HIDDEN PROTEIN-CODING INFORMATION.

That changed our understanding of:

THE MITOCHONDRIAL GENOME.

THE FAMILY MODEL

MITOCHONDRIAL DNA	→	**MT-RNR2 / 16S rRNA REGION**	→	**Multiple short open-reading frames**	→	**HUMANIN**

SHLP1

SHLP2

SHLP3

SHLP4

SHLP5

SHLP6	→	Different effects involving:

METABOLISM

APOPTOSIS

MITOCHONDRIAL FUNCTION

CELL SURVIVAL

STRESS RESPONSE

Again:

same genomic neighborhood.

Different:

BIOLOGICAL OUTPUTS.

SHLP1-6 ARE NOT ONE DRUG

This may be the single most important point in the guide.

The term:

“SHLP PEPTIDES”

can make the family sound like one interchangeable group.

It is not.

Early functional characterization showed that different SHLPs can have:

DIFFERENT EFFECTS ON CELL VIABILITY.

Researchers focused particularly on:

SHLP2

and:

SHLP3

because they demonstrated protective effects more similar to Humanin.

In contrast, other SHLPs showed different or less clearly protective profiles.

So:

SHLP FAMILY ≠ ONE MECHANISM.

WHY SHLP2 AND SHLP3 MATTER MOST

Among the six SHLPs:

SHLP2

and:

SHLP3

have been the most extensively characterized for:

- mitochondrial protection
- reduced reactive oxygen species
- metabolic regulation
- reduced apoptosis
- improved mitochondrial metabolism

The original 2016 study reported that both SHLP2 and SHLP3:

REDUCED APOPTOSIS

REDUCED ROS → IMPROVED MITOCHONDRIAL METABOLISM.

That gives them a strong conceptual identity:

MITOCHONDRIAL RESILIENCE SIGNALS.

THE SHLP2 / SHLP3 MODEL

CELLULAR STRESS → Mitochondrial dysfunction → ROS ↑ → Apoptosis signaling ↑ → Cell function ↓

SHLP2 / SHLP3 → Potential:

MITOCHONDRIAL METABOLISM ↑

ROS ↓

APOPTOSIS ↓ → Potential:

CELLULAR SURVIVAL + FUNCTION ↑

Again:

this is not simply:

“ANTIOXIDANT ACTIVITY.”

The peptides appear to influence:

THE ENTIRE MITOCHONDRIAL STRESS RESPONSE.

SHLP2

SHLP2 has become the best-characterized member of the family.

It is a:

26-AMINO-ACID MITOCHONDRIAL-DERIVED PEPTIDE.

One commonly reported sequence is:

MGVKFFTLSTRFFPSVQRAVPLWTNS.

Research has associated SHLP2 with:

- mitochondrial protection
- glucose metabolism
- retinal protection
- apoptosis reduction
- insulin sensitivity
- neuroprotection
- age-related biology

Among SHLPs:

SHLP2 HAS THE CLEAREST TRANSLATIONAL STORY SO FAR.

SHLP2 AND MITOCHONDRIAL FUNCTION

SHLP2 has been shown experimentally to preserve or enhance aspects of:

MITOCHONDRIAL FUNCTION.

Studies involving retinal pigment epithelial cells have reported:

- preservation of oxidative-phosphorylation complex proteins
- increased mitochondrial DNA copy number
- increased PGC-1α

improved mitochondrial staining and function.

This suggests SHLP2 may influence:

MITOCHONDRIAL BIOGENESIS + MAINTENANCE.

- PGC-1α

PGC-1α is one of the most important regulators of:

MITOCHONDRIAL BIOGENESIS.

It helps coordinate:

- mitochondrial replication
- energy production
- oxidative metabolism
- stress adaptation

So a model involving SHLP2 becomes:

SHLP2

Potential:

PGC-1α ↑	→	**Potential:**
MITOCHONDRIAL BIOGENESIS / FUNCTION ↑	→	**Potential:**

CELLULAR ENERGY CAPACITY ↑

Again:

this is especially relevant when mitochondrial dysfunction is:

A PRIMARY BOTTLENECK.

SHLP2 AND INSULIN SENSITIVITY

One of the strongest functional findings for SHLP2 involves:

GLUCOSE METABOLISM.

In hyperinsulinemic-euglycemic clamp experiments, intracerebral SHLP2:

- increased glucose uptake
- suppressed hepatic glucose production

suggesting improved:

PERIPHERAL + CENTRAL INSULIN ACTION.

That is a remarkable finding.

Because it suggests:

A MITOCHONDRIAL PEPTIDE SIGNAL IN THE BRAIN CAN ALTER WHOLE-BODY GLUCOSE METABOLISM.

THE SHLP2 METABOLIC MODEL

SHLP2	→	**Central metabolic signaling**	→	**Potential:**
INSULIN SENSITIVITY ↑		→		**GLUCOSE UPTAKE ↑**

and:

HEPATIC GLUCOSE PRODUCTION ↓

Potential:

GLUCOSE HOMEOSTASIS IMPROVES

This creates an interesting comparison with:

HUMANIN

which also influences insulin sensitivity through central signaling.

Again:

mitochondrial-derived peptides appear to participate in:

WHOLE-BODY METABOLIC COMMUNICATION.

• SHLP2 VS MOTS-c

Both belong to the mitochondrial-derived peptide family.

But their central mechanistic emphases differ.

• MOTS-c

Most strongly associated with:

AMPK

AICAR

- folate / purine metabolism
- glucose utilization
- exercise adaptation
- metabolic flexibility

SHLP2

More strongly associated with:

- mitochondrial preservation
- apoptosis reduction
- mitochondrial biogenesis-related signaling
- insulin sensitivity
- ROS control

So:

• MOTS-c = METABOLIC ADAPTATION SIGNAL

while:

SHLP2 = MITOCHONDRIAL PROTECTION + INSULIN-SENSITIZING SIGNAL

There is overlap.

But they are not:

INTERCHANGEABLE.

SHLP2 VS HUMANIN

Again:

same mitochondrial-derived peptide family.

HUMANIN

Dominant identity:

CYTOPROTECTION + APOPTOSIS REGULATION

especially through:

BAX

and survival signaling.

SHLP2

Dominant identity:

MITOCHONDRIAL FUNCTION + INSULIN SENSITIVITY + CYTOPROTECTION

Again:

overlap.

But:

HUMANIN'S BAX STORY IS BETTER DEFINED.

SHLP2'S METABOLIC / MITOCHONDRIAL STORY IS MORE PROMINENT.

SHLP3

SHLP3 has also demonstrated:

- reduced apoptosis
- reduced ROS
- improved mitochondrial metabolism
- effects on adipocyte differentiation

in experimental work.

This suggests SHLP3 may also participate in:

METABOLIC + CELL-SURVIVAL BIOLOGY.

But compared with SHLP2:

the translational literature is:

LESS DEVELOPED.

So SHLP3 should be considered:

BIOLOGICALLY INTERESTING

but:

LESS CHARACTERIZED.

ADIPOCYTE BIOLOGY

Both SHLP2 and SHLP3 were reported to enhance:

3T3-L1 PREADIPOCYTE DIFFERENTIATION.

That finding may sound counterintuitive.

Why would a peptide associated with insulin sensitivity promote:

ADIPOCYTE DIFFERENTIATION?

Because healthy adipose expansion can sometimes be:

METABOLICALLY PROTECTIVE.

A dysfunctional adipocyte unable to safely store lipid may redirect fat toward:

- liver
- muscle
- pancreas

leading to:

ECTOPIC FAT + INSULIN RESISTANCE.

Again:

MORE ADIPOSE CELLS ≠ AUTOMATICALLY WORSE METABOLISM.

Function matters.

THE ADIPOSE STORAGE MODEL

Excess energy	→	**If adipose tissue can:**
EXPAND APPROPRIATELY	→	**Lipids stored safely**

versus:

impaired adipocyte function	→	**Lipids spill into:**
LIVER + MUSCLE	→	**Potential:**

INSULIN RESISTANCE

So SHLP-related adipocyte differentiation may reflect:

METABOLIC STORAGE CAPACITY

rather than simply:

FAT GAIN.

This is an important nuance.

SHLP1

SHLP1 is part of the same mitochondrial peptide family.

But compared with SHLP2 and SHLP3:

its biological role is much less clearly defined.

The original discovery work demonstrated expression and biological activity, but SHLP1 has not developed the same depth of translational evidence.

That is important because:

FAMILY MEMBERS SHOULD NOT INHERIT EACH OTHER'S CLAIMS.

We should not say:

SHLP2 IMPROVES INSULIN SENSITIVITY

therefore:

ALL SHLPS IMPROVE INSULIN SENSITIVITY.

That would be inaccurate.

SHLP4

SHLP4 remains comparatively undercharacterized.

Some genomic/evolutionary analyses suggest portions of SHLP4 may be conserved, but the functional significance remains unresolved.

Again:

SEQUENCE CONSERVATION CAN SUGGEST BIOLOGICAL IMPORTANCE.

But it does not tell us:

WHAT THE PEPTIDE DOES.

SHLP5

SHLP5 is also comparatively poorly characterized.

There is much less evidence supporting a defined therapeutic identity.

That means:

UNKNOWN FUNCTION

should remain:

UNKNOWN FUNCTION.

Not:

ASSUMED MITOCHONDRIAL BENEFIT.

This is especially important in emerging peptide fields.

SHLP6

SHLP6 is particularly interesting from an evolutionary standpoint.

A 2023 analysis found stronger evidence of sequence conservation / synonymous-codon bias for:

HUMANIN

and:

SHLP6

than for several other SHLPs.

That may suggest stronger evolutionary pressure to preserve:

THE SHLP6 AMINO-ACID SEQUENCE.

But again:

that does not automatically establish:

A THERAPEUTIC ROLE.

Evolution can tell us:

THIS MAY MATTER.

It does not yet tell us:

HOW TO USE IT.

THE EVOLUTIONARY QUESTION

Mitochondrial rRNA regions already perform an essential function:

RIBOSOMAL RNA.

So how do we know a hidden peptide sequence is biologically important?

One approach is to ask:

HAS EVOLUTION CONSERVED THE AMINO-ACID SEQUENCE MORE THAN WOULD BE EXPECTED IF ONLY THE RNA MATTERED?

For Humanin and SHLP6:

there is evidence supporting:

ADDITIONAL PEPTIDE-LEVEL SELECTION.

For SHLP1, SHLP2, SHLP3, and SHLP5:

the evolutionary picture is:

LESS CLEAR.

That does not mean those peptides lack biological activity.

It means:

THEIR PHYSIOLOGICAL IMPORTANCE REMAINS AN OPEN QUESTION.

MITOCHONDRIAL STRESS SIGNALING

The broader SHLP family fits inside:

MITOCHONDRIAL RETROGRADE SIGNALING.

The mitochondrion senses:

• energy status

ROS

• nutrient availability

• membrane potential

• damage

Then:

MITOCHONDRIAL-DERIVED PEPTIDES

may help communicate that information to:

• cytoplasm	• nucleus
• neighboring cells	• distant tissues

This turns mitochondria into:

SIGNALING ORGANELLES.

Not merely:

ENERGY ORGANELLES.

THE RETROGRADE MODEL

MITOCHONDRIAL STATE CHANGES	→	**MDP production / signaling**	→	**SHLPs**	→	**Potential changes in:**

METABOLISM

APOPTOSIS

INSULIN SIGNALING

OXIDATIVE-STRESS RESPONSE	→	**Potential:**

CELLULAR ADAPTATION

That is the larger biological identity of the family.

OXIDATIVE STRESS

SHLP2 and SHLP3 reduce:

REACTIVE OXYGEN SPECIES

in experimental systems.

But again:

that does not necessarily mean they act as:

DIRECT ANTIOXIDANTS.

The more likely model involves:

IMPROVED MITOCHONDRIAL FUNCTION

less dysfunctional electron leakage → **less pathologic ROS generation**

plus:

CELLULAR STRESS-SIGNALING CHANGES.

That is very different from:

SCAVENGING A FREE RADICAL.

MITOCHONDRIAL QUALITY VS ROS SCAVENGING

Think of two different strategies.

STRATEGY 1

Mitochondria malfunction → **ROS produced** → **Take antioxidant** → **Try to neutralize ROS**

versus:

STRATEGY 2

Improve:

MITOCHONDRIAL FUNCTION

• Pathologic ROS generation ↓

The SHLP2 / SHLP3 research appears conceptually closer to:

STRATEGY 2.

That may be much more biologically important.

APOPTOSIS

SHLP2 and SHLP3 have demonstrated reductions in:

APOPTOSIS.

That places them alongside Humanin in:

CELL-SURVIVAL BIOLOGY.

But as with Humanin:

the important question is:

WHY IS THE CELL DYING?

A recoverable cell under:

METABOLIC STRESS

may benefit from survival signaling.

A severely damaged or malignant cell is a:

DIFFERENT CONTEXT.

Again:

ANTI-APOPTOTIC ≠ UNIVERSALLY BENEFICIAL.

NEUROPROTECTION

SHLP2 has demonstrated:

NEUROPROTECTIVE EFFECTS

in experimental systems.

Research summarized in cardiovascular and mitochondrial reviews links SHLP2 neuroprotection with activation of:

ERK

and:

STAT3.

These pathways participate in:

- cell survival
- stress response
- plasticity

This creates another interesting connection to:

HUMANIN,

which also uses:

STAT3-RELATED SURVIVAL SIGNALING.

Again:

the MDP family may share:

OVERLAPPING SURVIVAL NETWORKS

while retaining distinct upstream biology.

ERK AND STAT3

A simplified SHLP2 model may look like:

SHLP2

Potential:

- ERK phosphorylation

STAT3 phosphorylation	→	**Potential:**
CELL-SURVIVAL PROGRAMS	→	**Potential:**

NEUROPROTECTION

Again:

this is a mechanistic model.

Not a clinical claim that:

SHLP2 TREATS NEURODEGENERATIVE DISEASE.

RETINAL / MACULAR BIOLOGY

SHLP2 has attracted particular interest in:

RETINAL MITOCHONDRIAL DISEASE BIOLOGY.

Age-related macular degeneration involves:

- mitochondrial dysfunction
- oxidative stress
- retinal pigment epithelium injury
- inflammation

Experimental SHLP2 studies in retinal pigment epithelial systems have reported improvements in:

- mitochondrial function
- mtDNA copy number
- oxidative phosphorylation

PGC-1α signaling.

This is one of the stronger disease-specific mechanistic applications.

THE RETINAL MODEL

RPE MITOCHONDRIAL DYSFUNCTION	→	**ATP / OXPHOS dysfunction**	→	**ROS ↑**	→	**Cellular damage**	→	**Retinal support declines**

SHLP2	→	**Potential:**
MITOCHONDRIAL FUNCTION ↑	→	**Potential:**

CELLULAR RESILIENCE ↑

Again:

interesting translational biology.

Not yet:

ESTABLISHED AMD THERAPY.

AGING

SHLP2 appears especially relevant to:

AGING BIOLOGY.

The original characterization reported:

CIRCULATING SHLP2 LEVELS DECLINE WITH AGE.

That creates a compelling hypothesis:

AGING

SHLP2 signaling ↓ → Mitochondrial resilience ↓ → Insulin sensitivity ↓ → Cellular stress ↑

But again:

DECLINE WITH AGE ≠ CAUSE OF AGING.

It could be:

- causal
- compensatory
- consequential

That remains unresolved.

SEX DIFFERENCES

The original work also reported:

SEX-RELATED DIFFERENCES IN CIRCULATING SHLP2 LEVELS

in mice, with males showing higher levels than females in the groups studied.

That is interesting because mitochondrial physiology often differs according to:

- sex hormones
- tissue
- age
- metabolic state

Again:

ONE “NORMAL SHLP2 LEVEL” MAY BE TOO SIMPLISTIC.

Biology is contextual.

METABOLIC DISEASE

Modern reviews continue to emphasize SHLP2 particularly in:

- insulin sensitivity
- glucose homeostasis
- mitochondrial function
- oxidative stress

and identify SHLPs as emerging candidates in diabetes and metabolic disease biology.

This gives the family a clear conceptual position within:

METABOLIC MITOCHONDRIAL MEDICINE.

LIVER BIOLOGY

A 2026 review of mitochondrial-derived peptides in liver disease specifically highlighted SHLPs - especially SHLP2 - for their potential to:

- improve mitochondrial function
- enhance insulin sensitivity
- support glucose homeostasis

reduce oxidative stress.

That makes hepatic metabolism a logical future translational area.

Again:

METABOLIC SIGNALING

does not stop at:

THE MUSCLE OR BRAIN.

The liver is central to:

WHOLE-BODY GLUCOSE HOMEOSTASIS.

SHLP FAMILY COMPARISON

A practical way to understand the family is:

SHLP1

LESS CHARACTERIZED

Biological role remains unclear.

SHLP2

BEST CHARACTERIZED

Major themes:

- insulin sensitivity
- apoptosis reduction
- neuroprotection
- aging
- mitochondrial metabolism
- ROS reduction
- retinal biology

SHLP3

PROMISING BUT LESS DEVELOPED

Major themes:

- apoptosis reduction
- mitochondrial metabolism
- ROS reduction
- adipocyte biology

SHLP4

POORLY CHARACTERIZED

Potential evolutionary conservation in part of sequence, but functional role remains uncertain.

SHLP5

POORLY CHARACTERIZED

No well-established therapeutic identity.

SHLP6

EVOLUTIONARILY INTERESTING

Strong sequence-conservation signal but less well-defined translational physiology.

This is far more accurate than:

SHLP1-6 = SIX MITOCHONDRIAL ANTI-AGING PEPTIDES.

THE CORE MECHANISM MAP

MITOCHONDRIAL 16S rRNA / MT-RNR2 → **Short open-reading frames** → **SHLP1-6** → **Most established:**

SHLP2 / SHLP3 → **Potential:**

MITOCHONDRIAL METABOLISM ↑

ROS ↓

APOPTOSIS ↓

and particularly SHLP2:

INSULIN SENSITIVITY ↑

• PGC-1α / MITOCHONDRIAL BIOLOGY ↑

ERK / STAT3 SURVIVAL SIGNALING → **Potential:**

METABOLIC + CELLULAR RESILIENCE

The core concept is:

SHLPs ARE A FAMILY OF MITOCHONDRIAL SIGNALS, BUT EACH MEMBER MUST BE TREATED AS ITS OWN BIOLOGICAL MOLECULE.

WHAT THIS MECHANISM MAY SUGGEST

Mechanistically, SHLP research deserves interest in:

- insulin resistance
- mitochondrial dysfunction
- oxidative cellular stress
- retinal degeneration
- liver metabolic disease
- age-related loss of mitochondrial resilience
- type 2 diabetes
- metabolic aging
- neurodegeneration
- cardiovascular stress
- cellular apoptosis

Among the family:

SHLP2 currently has the strongest therapeutic research rationale.

WHAT THIS MECHANISM DOES NOT PROVE

SHLP biology does not prove that:

- all six SHLPs do the same thing
- all SHLPs are anti-aging
- SHLP2 treats Alzheimer's disease
- higher circulating SHLP2 is always better
- all SHLPs improve insulin sensitivity
- SHLP2 reverses diabetes
- SHLP2 treats macular degeneration
- low SHLP2 proves mitochondrial dysfunction

- SHLP3 has identical effects to SHLP2
- every mitochondrial disorder should be treated with an MDP
- evolutionary conservation proves clinical usefulness

Again:

FAMILY MEMBERSHIP ≠ SHARED PHARMACOLOGY.

THE EVIDENCE, POTENTIAL APPLICATIONS, AND LIMITATIONS

ENDOGENOUS / GENOMIC BIOLOGY

MEANINGFUL

SHLP1-6 are encoded within short open-reading frames in the mitochondrial 16S rRNA region and are part of the broader mitochondrial-derived peptide family.

This is now a recognized area of:

MITOCHONDRIAL SIGNALING BIOLOGY.

SHLP2 MECHANISTIC EVIDENCE

MEANINGFUL

SHLP2 has demonstrated:

- reduced apoptosis
- improved mitochondrial metabolism
- increased glucose uptake
- reduced ROS
- improved insulin sensitivity

reduced hepatic glucose output.

That gives it the strongest mechanistic profile among the six.

SHLP3 MECHANISTIC EVIDENCE

PROMISING

SHLP3 has shown:

- reduced apoptosis
- reduced ROS
- improved mitochondrial metabolism

adipocyte differentiation effects.

But the evidence base is:

SMALLER THAN SHLP2.

SHLP1, 4, 5, AND 6

EARLY / INCOMPLETELY CHARACTERIZED

There is biological and genomic evidence for the peptides.

But strong disease-specific therapeutic identities have:

NOT YET BEEN ESTABLISHED.

This is where restraint matters.

HUMAN THERAPEUTIC EVIDENCE

EARLY

The major SHLP therapeutic literature remains:

- cellular
- animal
- mechanistic

rather than:

LARGE RANDOMIZED HUMAN THERAPEUTIC TRIALS.

Again:

that does not erase the biology.

It tells us:

WHERE THE FIELD CURRENTLY STANDS.

- Research

INSULIN RESISTANCE

This may be SHLP2's strongest translational metabolic area.

If SHLP2 can improve:

CENTRAL + PERIPHERAL INSULIN ACTION,

then it may ultimately become relevant in:

- metabolic syndrome
- type 2 diabetes
- age-related insulin resistance

But insulin resistance is itself:

HETEROGENEOUS.

Potential drivers include:

- ectopic fat
- inflammation
- medications
- mitochondrial dysfunction
- sleep deprivation
- inactivity
- glucocorticoids

Again:

INSULIN RESISTANCE ≠ SHLP2 DEFICIENCY.

TYPE 2 DIABETES

SHLP2's effects on glucose uptake and hepatic glucose production make:

TYPE 2 DIABETES

mechanistically interesting.

But diabetes is more than:

INSULIN SENSITIVITY.

It also involves:

- beta-cell function
- adipose biology
- incretin signaling
- hepatic metabolism
- muscle glucose uptake
- glucagon

So SHLP2 would likely occupy:

ONE NODE IN A MULTISYSTEM DISEASE.

MITOCHONDRIAL DYSFUNCTION

This is the broader SHLP family niche.

If mitochondria are:

DYSFUNCTIONAL BUT RECOVERABLE,

a peptide that improves mitochondrial metabolism may be useful.

But mitochondrial dysfunction can arise from:

- nutrient excess
- toxins
- aging
- hypoxia
- mtDNA disease
- inflammation

Again:

THE CAUSE STILL MATTERS.

RETINAL DEGENERATION / AMD

SHLP2 has especially interesting preclinical relevance to:

RETINAL MITOCHONDRIAL STRESS.

Experimental work suggests:

MITOCHONDRIAL QUALITY IMPROVEMENT

rather than merely:

SYMPTOM SUPPRESSION.

This makes it an excellent example of:

TARGET THE CELLULAR DRIVER.

But the field still needs:

DIRECT HUMAN CLINICAL VALIDATION.

NEURODEGENERATION

Recent reviews include SHLPs among MDPs with potential relevance to:

- Alzheimer's disease
- Parkinson's disease
- Huntington's disease

through mechanisms involving:

- mitochondrial function
- oxidative stress
- neuroprotection

inflammation.

Again:

the MDP family is biologically relevant.

But:

SHLP-SPECIFIC DISEASE EVIDENCE SHOULD NOT BE EXAGGERATED.

CARDIOVASCULAR DISEASE

SHLPs are also increasingly discussed in cardiovascular biology because:

MITOCHONDRIAL DYSFUNCTION + APOPTOSIS + OXIDATIVE STRESS

are central to:

- ischemia
- vascular aging
- myocardial injury

Reviews now place SHLPs alongside Humanin and MOTS-c as emerging cardiovascular MDPs.

Again:

this is an:

EMERGING FIELD.

AGING

SHLP2's age-related decline is perhaps the strongest clue linking the family to:

GEROSCIENCE.

But there is a major difference between:

AGE-ASSOCIATED CHANGE

and:

AGE-CAUSING MECHANISM.

If SHLP2 falls with age:

it could mean:

LESS PROTECTIVE SIGNAL → MORE DYSFUNCTION.

Or:

aging could reduce mitochondrial capacity and:

SHLP2 FALLS AS A CONSEQUENCE.

Or both may be driven by:

A THIRD PROCESS.

Again:

CORRELATION ≠ DIRECTION OF CAUSATION.

WHAT WE KNOW

SHLP1-6 are small mitochondrial-derived peptides encoded within the mitochondrial 16S rRNA / MT-RNR2 region.

They belong to the same broad mitochondrial-derived peptide family as Humanin and MOTS-c.

SHLP family members are not functionally identical.

SHLP2 and SHLP3 have the best-characterized cytoprotective effects.

Both SHLP2 and SHLP3 have reduced apoptosis and ROS and improved mitochondrial metabolism in experimental systems.

SHLP2 has shown insulin-sensitizing effects in hyperinsulinemic-euglycemic clamp studies.

Central SHLP2 increased peripheral glucose uptake and reduced hepatic glucose production in experimental animals.

SHLP2 has also been linked to ERK and STAT3 phosphorylation in neuroprotective models.

Experimental retinal studies suggest SHLP2 can improve mitochondrial oxidative phosphorylation, mtDNA copy number, and PGC-1α-related mitochondrial biology.

Circulating SHLP2 has been reported to decline with age.

SHLP1, SHLP4, SHLP5, and SHLP6 remain much less therapeutically characterized.

Evolutionary analyses suggest Humanin and SHLP6 show particularly strong peptide-level conservation signals, while the evidence for several other SHLP sequences is less clear.

Direct modern human therapeutic evidence for SHLP administration remains limited.

WHAT WE THINK MAY BE HAPPENING

The SHLP family may represent:

A MITOCHONDRIAL INTERNAL COMMUNICATION NETWORK.

Mitochondrial function becomes stressed. → **Different short mitochondrial peptides may be produced or altered.** → **Each peptide communicates:**

A DIFFERENT ASPECT OF THE PROBLEM.

SHLP2 / SHLP3 may signal:

PRESERVE METABOLIC FUNCTION

REDUCE EXCESS ROS → **REDUCE PREMATURE CELL DEATH** → **SHLP2 additionally influences:**

WHOLE-BODY INSULIN ACTION.

In that model:

SHLPs are not six copies of:

ONE SIGNAL.

They may be more like:

SIX DIFFERENT MESSAGES FROM THE MITOCHONDRION.

We simply understand some messages:

BETTER THAN OTHERS.

That is probably the most useful way to frame the family today.

WHAT REMAINS CONTEXT-DEPENDENT

Important questions include:

Which SHLPs are reliably translated in human tissues?

What determines SHLP expression?

How much of each peptide enters circulation?

Which tissues produce the most SHLP2?

What are the receptors for SHLP2 and SHLP3?

Which effects are intracellular versus endocrine?

Why do different SHLPs produce different effects on cell survival?

How much of SHLP2 action depends on ERK?

How much depends on STAT3?

What drives its insulin-sensitizing effect?

Does SHLP2 directly alter hepatic signaling or primarily act through the brain?

Why do circulating levels fall with age?

Are low SHLP2 levels causal or compensatory?

How do sex hormones alter SHLP expression?

Can SHLP2 improve human insulin resistance?

Can SHLP2 preserve retinal function in humans?

Which neurodegenerative phenotype is most likely to respond?

Are SHLP2 and SHLP3 pharmacologically interchangeable?

Do SHLP4 or SHLP6 have major functions that remain undiscovered?

What is the human half-life of each peptide?

Can stable analogs preserve biological effects?

What long-term safety signals emerge from chronic metabolic signaling?

Can SHLP levels become useful biomarkers of mitochondrial resilience?

Again:

this is:

A VERY YOUNG FIELD.

Which means the unanswered questions are not a weakness.

They are:

THE NEXT RESEARCH MAP.

THE PRAXIS LENS

DO NOT BEGIN WITH “SHLPS”

Begin with:

WHICH SHLP - AND WHAT MITOCHONDRIAL PROBLEM ARE WE ACTUALLY TRYING TO CHANGE?

That distinction is essential.

Then:

PHYSIOLOGY

PATTERN → MECHANISM → EVIDENCE → RISK → MONITORING → DECISION

PHYSIOLOGY

Healthy mitochondrial function requires:

- substrate availability
- membrane potential
- redox control
- appropriate apoptosis
- electron transport
- ATP generation
- mitochondrial biogenesis
- nuclear-mitochondrial communication

SHLP2 and SHLP3 appear particularly relevant to:

METABOLISM + STRESS RESILIENCE + CELL SURVIVAL.

PATTERN

What is actually present?

insulin resistance?

mitochondrial dysfunction?

retinal degeneration?

neurodegenerative stress?

oxidative injury?

metabolic aging?

liver metabolic disease?

Again:

“LOW ENERGY” IS NOT A MITOCHONDRIAL DIAGNOSIS.

MECHANISM

Does a specific SHLP mechanism match:

THE ACTUAL BOTTLENECK?

If insulin resistance is being driven by:

SEVERE SLEEP DEPRIVATION,

sleep remains:

A PRIMARY INTERVENTION.

If mitochondrial dysfunction results from:

HYPOXIA,

restore:

OXYGEN DELIVERY.

If the problem appears to involve:

MITOCHONDRIAL METABOLIC DYSFUNCTION + INSULIN RESISTANCE,

SHLP2 becomes:

MUCH MORE MECHANISTICALLY INTERESTING.

Again:

PEPTIDE AFTER PHYSIOLOGY.

EVIDENCE

Ask:

WHICH SHLP?

SHLP2?

There is:

MEANINGFUL MECHANISTIC + ANIMAL METABOLIC EVIDENCE.

SHLP3?

There is:

EARLIER CYTOPROTECTIVE / METABOLIC EVIDENCE.

SHLP5?

The evidence is:

MUCH LESS DEVELOPED.

This prevents:

FAMILY-LEVEL OVERCLAIMING.

RISK

Potential considerations include:

- unknown human pharmacokinetics
- limited long-term exposure data
- inappropriate extrapolation between SHLP family members
- altered apoptosis in the wrong cellular context
- analog/product identity uncertainty
- assuming mitochondrial support corrects the upstream driver

using animal insulin-sensitivity findings as if they establish human diabetes treatment

Again:

the greatest risk may be:

CLAIMING PRECISION WHERE THE BIOLOGY IS STILL EARLY.

MONITORING

Monitoring should follow:

THE SPECIFIC HYPOTHESIS.

METABOLIC

- fasting glucose
- fasting insulin
- HbA1c
- glucose tolerance
- body composition
- hepatic metabolic markers

MITOCHONDRIAL / FUNCTIONAL

- exercise tolerance
- fatigue pattern
- tissue-specific functional outcomes

RETINAL

where clinically relevant:

- visual acuity
- retinal imaging
- disease-specific ophthalmic measures

NEUROLOGICAL

- cognition
- functional testing
- disease-specific measures

Again:

monitor:

THE OUTCOME THE SPECIFIC SHLP IS SUPPOSED TO CHANGE.

THE PRAXIS 5

MECHANISM

SHLP2 and SHLP3 primarily intersect with:

MITOCHONDRIAL METABOLISM + OXIDATIVE-STRESS RESPONSE + APOPTOSIS.

SHLP2 additionally has:

INSULIN-SENSITIZING + NEUROPROTECTIVE SIGNALS.

EVIDENCE

SHLP2 mechanistic evidence:

MEANINGFUL.

SHLP2 preclinical metabolic evidence:

MEANINGFUL.

SHLP3 evidence:

PROMISING BUT EARLIER.

SHLP1/4/5/6 functional evidence:

LESS DEVELOPED.

Direct human therapeutic evidence:

EARLY.

That is the appropriate evidence calibration.

RISK

The major conceptual mistake is:

TREATING SHLP1-6 AS ONE PEPTIDE.

They are:

A FAMILY.

Not:

ONE PHARMACOLOGY.

MONITORING

Monitor:

THE TARGET SYSTEM.

If SHLP2 is being considered for:

METABOLIC RESILIENCE,

then:

METABOLIC FUNCTION SHOULD IMPROVE.

If the hypothesis is:

MITOCHONDRIAL PROTECTION,

then:

THE TISSUE SHOULD BECOME MORE FUNCTIONAL OR RESILIENT.

PATIENT CONTEXT

A patient with:

INSULIN RESISTANCE

is not identical to:

someone with:

RETINAL MITOCHONDRIAL DYSFUNCTION.

A patient with:

PRIMARY MITOCHONDRIAL DISEASE

is not identical to:

someone with:

METABOLIC SYNDROME.

A patient considering:

SHLP2

is not automatically equivalent to someone considering:

SHLP6.

Same peptide family.

Different:

MOLECULE + SYSTEM + CONTEXT.

SEVEN QUESTIONS TO ASK BEFORE SHLP PEPTIDES

1. WHICH SHLP ARE WE ACTUALLY DISCUSSING?

This must come first.

2. WHAT MITOCHONDRIAL OR METABOLIC PROBLEM ARE WE TRYING TO CHANGE?

insulin resistance?

oxidative stress?

mitochondrial dysfunction?

apoptosis?

retinal stress?

3. DOES THAT SPECIFIC SHLP HAVE EVIDENCE FOR THAT MECHANISM?

Not:

DO SHLPS GENERALLY DO IT?

But:

DOES SHLP2, SHLP3, OR THE SPECIFIC MOLECULE DO IT?

4. WHAT TYPE OF EVIDENCE SUPPORTS THE CLAIM?

genomic?

cellular?

animal?

human biomarker?

human therapeutic?

5. IS THE MITOCHONDRIAL PROBLEM PRIMARY OR SECONDARY?

For example:

is dysfunction caused by:

hypoxia?

hyperglycemia?

medication?

inflammation?

nutrient deficiency?

6. WHAT WILL WE MONITOR?

glucose?

insulin?

mitochondrial function?

retinal function?

cognition?

disease-specific outcomes?

7. WHAT WOULD DEFINE SUCCESS?

Not:

“MITOCHONDRIA FELT BETTER.”

But:

THE SPECIFIC METABOLIC, CELLULAR, OR TISSUE-LEVEL FUNCTION IMPROVED IN A WAY CONSISTENT WITH THE MECHANISM OF THE SPECIFIC SHLP BEING USED.

KEY TAKEAWAYS

SHLP1-6 are mitochondrial-derived peptides encoded within the mitochondrial 16S rRNA / MT-RNR2 region.

They belong to the same broader mitochondrial-derived peptide family as Humanin and MOTS-c.

The SHLP family should not be treated as one interchangeable peptide therapy.

Different SHLP members have different biological effects.

SHLP2 is currently the best-characterized member.

SHLP2 and SHLP3 both reduced apoptosis and reactive oxygen species and improved mitochondrial metabolism in experimental systems.

SHLP2 also demonstrated insulin-sensitizing effects in hyperinsulinemic-euglycemic clamp studies.

Central SHLP2 increased glucose uptake and suppressed hepatic glucose production experimentally.

That provides an important link between mitochondrial signaling in the brain and whole-body glucose metabolism.

SHLP2 has also demonstrated mitochondrial-protective effects in retinal models.

Experimental findings include preservation of oxidative-phosphorylation components, increased mtDNA copy number, and increased PGC-1α-related signaling.

SHLP2 has neuroprotective effects associated with ERK and STAT3 phosphorylation.

SHLP3 shares several cytoprotective characteristics with SHLP2 but remains less extensively characterized.

SHLP1, SHLP4, SHLP5, and SHLP6 currently have much less developed therapeutic identities.

That lack of evidence should not be filled in by borrowing findings from SHLP2.

Evolutionary analyses suggest Humanin and SHLP6 may have particularly strong sequence-conservation signals.

That suggests potential biological importance but does not establish a clinical indication.

Circulating SHLP2 levels have been reported to decline with age.

That creates interest in metabolic aging and mitochondrial resilience.

But age association does not prove that low SHLP2 causes aging.

SHLP2 should not be reduced to a generic anti-aging peptide.

Its stronger conceptual identity is mitochondrial and metabolic resilience.

The SHLP family reinforces one of the most important lessons in modern mitochondrial biology: mitochondria do not merely produce energy; they produce information.

They generate small peptides that can influence cellular survival, metabolism, and communication across tissues.

• The best question is not “what do SHLP peptides do?”

The better question is “which SHLP are we discussing, what specific mitochondrial or metabolic problem is present, does that exact peptide have evidence for the failed node, and can the resulting change be demonstrated in the function of the tissue rather than inferred from membership in the mitochondrial peptide family?”

THE BOTTOM LINE

The SHLP family may ultimately become one of the most important discoveries in mitochondrial biology because it suggests something we did not appreciate for most of modern medicine:

THE MITOCHONDRIAL GENOME MAY CONTAIN A VOCABULARY.

Not merely:

GENES FOR ENERGY PRODUCTION.

But:

MESSAGES.

Humanin may say:

KEEP THIS STRESSED CELL ALIVE.

MOTS-c may say:

ADAPT METABOLISM TO THE ENERGY ENVIRONMENT.

And SHLP2 may be signaling something closer to:

PROTECT MITOCHONDRIAL FUNCTION AND IMPROVE THE WAY THE SYSTEM HANDLES ENERGY.

That gives us a much richer model:

MITOCHONDRIAL STRESS

Different MDPs released or regulated → **Different messages:**

SURVIVE

ADAPT

CHANGE METABOLISM

CONTROL ROS

MODIFY INSULIN ACTION → **Potential:**

WHOLE-CELL AND WHOLE-BODY ADAPTATION

And SHLP biology adds another crucial lesson:

A FAMILY NAME DOES NOT CREATE A SHARED MECHANISM.

SHLP2 is not:

SHLP5.

SHLP3 is not:

SHLP6.

The field has characterized some members far better than others.

So the correct scientific approach is not to fill the gaps with:

ASSUMPTION.

It is to leave the gaps open and:

STUDY THEM.

Because one of those poorly understood SHLPs may eventually turn out to regulate:

A COMPLETELY DIFFERENT MITOCHONDRIAL FUNCTION.

That is exactly why this field is so exciting.

So the Praxis question becomes:

“WHAT is the mitochondrial system trying to communicate, which SHLP carries the relevant signal, is the dominant failure insulin resistance, oxidative stress, apoptosis, mitochondrial biogenesis, or something entirely different, and can we connect that specific peptide mechanism to an objective improvement in cellular or whole-body function?”

That is the difference between:

CALLING SHLPS MITOCHONDRIAL ANTI-AGING PEPTIDES

and:

UNDERSTANDING MITOCHONDRIAL COMMUNICATION.

FINAL RECALL

IDENTIFY	LOCALIZE	VERIFY
Name the exact SHLP before assigning a mechanism	**Define the mitochondrial or metabolic bottleneck**	**Require peptide-specific functional outcomes**

STOP MEMORIZING PEPTIDES. START UNDERSTANDING THE SYSTEM.

Praxis Peptide Institute provides educational information and is not a substitute for individualized medical diagnosis or treatment. SHLP1-6 are emerging mitochondrial-derived peptides whose biological characterization varies substantially by individual peptide. SHLP2 and SHLP3 currently have the strongest mechanistic evidence involving mitochondrial metabolism, apoptosis, oxidative stress, and metabolic regulation, while several other family members remain much less characterized. Their relevance depends on the specific SHLP being considered, the mitochondrial or metabolic abnormality being targeted, tissue and disease context, age and sex, route and product identity, concurrent therapies, and the objective metabolic or functional outcome being monitored. Findings from one SHLP should not automatically be transferred to another family member.