The Composite Matrix-Afferent Reset (CMAR) Hypothesis

A Testable Framework Linking Extracellular-Matrix Mechanics, Proprioceptive Force Transduction, Neuromuscular Regulation, and Tissue Mechanical Memory

From Mechanical Disturbance → Altered Receptor Deformation → Altered Afferent → ECM Remodeling → Persistent Dysfunction ... and How to Test and Potentially Reset It.

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KEY CONCEPTS

Extracellular Matrix (ECM)
- Stiffness / viscoelasticity
- Collagen architecture
- Hydration and cross-linking
- Force transmission
- Changes with injury, aging, disease

Golgi Tendon Organ (GTO)
- Group Ib afferent endings
- Interwoven with collagen
- Forse transmissal via ECM deformation

PIEZO2 Mechanosensor
- Mechanosensitive ion channel
- Rapid ionic/electrical response
- Present in proprioceppors and other mechanosensitive cells

YAP/TAZ Mechanotransduction
- Mechanically regulated transcriptional co-activators
- Involved in tissue adaptation and ECM remodeling

Intervention (Hypothesis)
- Verified mechanical perturbation
- Standardized loading challenge (e.g., eccentric)
- Optional IFC/IFT (conditioning variable)
- Controlled experimental testing required
- Not an established clinical sequence

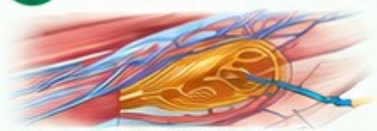
I. CORE CMAR HYPOTHESIS (PRIMARY MECHANISTIC PATHWAY)

Altered tissue mechanics → altered receptor deformation → altered afferent output → altered neuromuscular function

1 Altered ECM Mechanics Force Transmission

- Pathological or adaptive changes in ECM stiffness, viscoelasticity, or architecture
- Altered collagen organization
- Modified local force transmission to the GTO
- Influenced by injury, aging, loading velocity, etc.

2 Altered Receptor-Region Deformation (GTO-Focused)



- Changed mechanical input and deformation of GTO endings
- Group Ib afferents interwoven with collagen bundles
- Altered relationship between external force and receptor strain properties

3 Altered Afferent Output and Sensorimotor Processing

- Modified Group Ib firing patterns
- Changes in spinal interneurons
- Altered sensorimotor processing
- May affect tone, reflex excitability, and motor control

4 Neuromuscular Consequences (Downstream Extension)

- Changes in reflex excitability
- Altered muscle activation and control
- Impaired motor function
- Context dependent (e.g., spasticity, pain)
- **Must not be used as evidence for the core mechanism**

MODEL CONTEXT

The CMAR hypothesis builds on established anatomy and physics, but proposes that altered ECM mechanics and GTO deformation can influence afferent signalling, downstream neuromuscular outcomes, and a self-reinforcing tissue-memory loop.

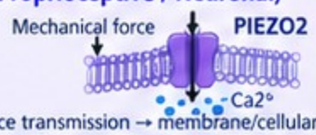
All components are hypotheses requiring experimental validation.

Not an established clinical mechanism.

II. PARALLEL AND DOWNSTREAM MECHANISMS (EXPERIMENTAL EXTENSIONS)

Biologically distinct but potentially interacting processes within a common ECM environment

A PIEZO2-Associated Mechanosensation (Proprioceptive / Neuronal)



- ECM force transmission → membrane/cellular deformation
- PIEZO2-associated mechanosensitive signalling
- Rapid ionic/electrical cellular response
- Primary role in acute mechanosensation
- Functions independently of YAP/TAZ

Potential interaction ◄- - -►

B YAP/TAZ-Associated Mechanotransduction (Cellular / Non-neuronal)

- ECM force transmission → cytoskeletal/mechanical force
- YAP/TAZ regulation → nuclear signalling / transcription
- Longer-term cellular adaptation and ECM remodeling
- Mechanically regulated in fibroblasts, tenocytes, myocytes
- Functions independently of PIEZO2

◄-►

C ECM Remodeling & Tissue Adaptation (Longer-Term Extension)

- Changes in ECM composition and structure
- Altered collagen organization and cross-linking
- Viscoelastic changes and altered mechanics
- Contributions from PIEZO2- and/or YAP/TAZ pathways
- Represents a potential tissue "memory" mechanism
- Requires separate experimental validation

III. THE SELF-REINFORCING MECHANO-EPIGENETIC TISSUE-MEMORY LOOP

How initial mechanical disturbance can lead to persistent dysfunction

INITIATING FACTORS
- Injury (acute or repetitive)
- Overuse / abnormal loading
- Poor biomechanics / posture
- Aging and degenerative changes
- Inflammation / disuse
- Systemic or metabolic factors

Once established, this loop can maintain an abnormal tissue state, sustained afferent input, and ongoing neuromuscular dysfunction even after the initial insult has resolved.

POTENTIAL CONSEQUENCES
- Persistent increases in ECM stiffness
- Sustained altered GTO input
- Maladaptive reflex and motor patterns
- Tissue hypo/hyperexcitability
- Chronic pain and dysfunction
- Diffjcult to reverse without

PROPOSED CMAR INTERVENTION: TESTING WHETHER THE LOOP CAN BE DISRUPTED
- Normalize tissue mechanics (manual therapy)
- Modulate afferent input (mechanical perturbation)
- Promote adaptive cellular remodeling
- Optional IFC/IFT (conditioning variable)
- Aim to restore more normal neuromuscular function
- Requires controlled experimental validation

IV. PROPOSED EXPERIMENTAL INTERVENTION SEQUENCE (TO TEST THE CMAR HYPOTHESIS)

Hypothesized sequence. Timing and role of IFC/IFT have not been established and should be tested as an independent variable.

CMAR Test Phase (Experimental, not established)
- Modify local ECM mechanics
- Alter viscoelastic behaviour
- Prepare tissue environment

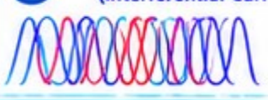
1 Verified Mechanical Perturbation (Manual therapy)

- Targeted intervention to modify local tissue mechanics / ECM state
- e.g., joint/tissue mobilization

2 Standardized Loading Challenge (Eccentric or Controlled Loading)

- Defined mechanical stimulus
- Increases GTO mechanical loading
- Enhances Group Ib afferent activity
- Provides directional stimulus for testing

3 Optional Conditioning Variable (Interferential Current Therapy – IFC/IFT)



- Tested as an adjunct (pre, during, or post loading – timing not established)
- May augment mechanosensory signalling
- Requires independent evaluation

OVERALL GOAL
Disrupt a mechanically maintained state and restore more adaptiviss, and neuromuscular function.

PREDICTED OUTCOMES (TESTABLE ACROSS MULTIPLE LEVELS)

Tissue Mechanics
- ↓ Stiffness (where applicable)
- ↑ Viscoelasticity
- More normal collagen organization

Neurophysiology
- Normalized reflex excitability
- Improved sensorimotor integration

Muscle Function
- Improved muscle length
- Reduced hypertonicity
- Enhanced strength and motor control

Clinical Outcomes
- Reduced pain
- Improved function
- Better movement quality
- Enhanced quality of life

LEGEND
- Hypothesized pathway
- Potential interaction
- Optional / not established
- Core CMAR pathway (testable)
- Secondary/extension pathway
- Cellular process

All mechanistic and therapeutic claims remain hypotheses.

Figure 1. Integrated conceptual model of the Composite Matrix-Afferent Reset (CMAR) Hypothesis.

This figure summarizes the hypothesized mechanisms, parallel pathways, self-reinforcing tissue-memory loop, and proposed experimental intervention sequence. The core CMAR proposition requires experimental demonstration that altered mechanotransduction alters afferent output. Downstream, cellular, and IFC/IFT components are experimentally separable extensions and are not required to validate the core mechanism.

"Start with the mechanics. Reset the pathway. Restore the function."