The underlying molecular mechanisms of musculoskeletal pain

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Biological pathways of musculoskeletal pain

Chronic musculoskeletal pain, defined as a pain perceived in musculoskeletal tissues that lasts or recurs for more than 3 months, often leads to significant functional impairment and emotional distress. It can be categorized as primary (not directly linked to known diseases or injuries) or secondary (resulting from conditions affecting bones, joints, muscles, or soft tissues). In physiological conditions, nerve fibers (Aδ and C-sensory) remain silent until activated by noxious stimuli like mechanical strain, acidification, or elevated pressure. These stimuli trigger Aδ mechanoreceptors, causing sharp pain that transitions to a lingering, less intense ache carried by C-fibers. Nociception in bone and joint tissue is regulated by the nerve fibers due to the presence of several receptors, such as acid-sensing ion channel (ASIC) 1, ASIC3, and transient receptor potential channel-vanilloid subfamily member 1 (TRPV1), activated when extracellular pH falls to around 4. In skeletal muscle, prolonged activation of purinergic receptors (e.g., P2X3-R) and TRPV1 receptors serve as pain transducers and leads to upregulation and long-lasting hyperalgesia. Nociceptors are also target of other molecular components such as protein involved in the inflammatory cascade, which plays a pivotal role in the peripheral sensitization of pain.

Inflammatory mediators lead pain sensitization

Inflammation can induce two distinct pain-related phenomena: allodynia, characterized by the perception of pain in response to normally non-painful stimuli, and hyperalgesia, characterized by an exaggerated pain response to typically painful stimuli. These effects are brought about by the sensitization of sensory nerve fibers. In cases of inflammation or tissue injury, damaged cells and immune cells release a range of substances referred to as inflammatory mediators. These include bradykinin, nerve growth factor (NGF), prostaglandin E2 (PGE2), pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and chemokines. These inflammatory mediators have a dual effect on peripheral nociceptors: they can directly sensitize them, increasing sensitivity, and indirectly promote inflammation, leading to the release of prostaglandins, which further exacerbate pain. In the clinic, presurgical assessment of inflammatory markers have recently been shown to hold a predictive value for the experience of pain after surgery, suggesting a potential use in the clinic. Furthermore, recent data indicate that preoperative inflammation markers operate within networks, and these preoperative inflammatory networks may be associated with chronic postoperative pain following joint replacement surgery. While inflammatory mediators play a pivotal role in driving musculoskeletal pain by sensitizing nociceptors and exacerbating pain, recent research has revealed a significant connection between epigenetic changes and the regulation of inflammatory mediators, further highlighting epigenetic changes involvement in musculoskeletal pain.
The epigenetics involvement in musculoskeletal pain

Epigenetics refers to the study of those molecular modifications which modulate gene expression without altering the DNA sequence\(^7\). These changes, includes DNA methylation, histone protein modifications and the action of non-coding RNAs (ncRNAs) which can regulate gene expression profiles in pain-sensing neurons and immune cells, culminating in sustained pain perception\(^7\). DNA methylation involves the addition of methyl groups to targeted genomic regions, effectively silencing the expression of pain-related genes\(^7\). For instance, the evaluation of hyper- and hypo-methylation of a subset of genes in T-cells from patients experiencing painful low back pain has revealed an association between methylation levels and the severity of the patients’ pain. This observation underscores sex-specific expression patterns and hints at potential novel therapeutic avenues involving epigenetic reprogramming, as well as the identification of predictive biomarkers for chronic pain risk\(^6\). NcRNAs is a class of RNA that include molecules of different length, such as microRNAs (miRNAs), and long ncRNAs (lncRNAs), which primary role of resides in the modulation of gene expression, transcriptional and translational levels\(^7\). Despite numerous investigations underscoring the implication of miRNAs and lncRNAs in musculoskeletal pain-related conditions, this area remains an emerging frontier within pain research warranting further investigations. Research has revealed associations between preoperative circulating long and miRNAs and the manifestation of chronic post-surgical pain one year following total joint replacement surgery\(^3,5\). Additionally, these findings suggests that subsets of lncRNAs and miRNAs may contain potential prognostic value and are clearly involved in the regulation of pro-inflammatory cytokines, like interleukin 1\(\beta\) (IL-1 beta), IL-6, and TNF-alpha, implicated in the sensitization of nociceptors.

Conclusions

In conclusion, deciphering the molecular intricacies behind this pain is essential for the development of precise and effective therapeutic interventions. Inflammatory mediators, epigenetic modifications, and the involvement of specific microRNAs all play pivotal roles in initiating, perpetuating, and predicting musculoskeletal pain. Targeting these molecular mechanisms through tailored therapies offers hope for improved pain management and a better quality of life for those grappling with this debilitating condition but the evidence to support this is lacking. Continued research in this topic remains paramount to advancing our understanding and treatment of musculoskeletal pain.

References
