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Commentary

Neutrophil-mediated acute inflammatory response exerts a protective effect on chronic pain

Running title: Neutrophils, inflammation, and pain

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Abstract

Chronic pain constitutes a major problem for patients and physicians alike. Deciphering the mechanisms driving the evolution of acute pain into chronic may provide ways for preventing this entity. A recent study showed that neutrophil-driven inflammation in patients with acute pain was associated with pain resolution, while administration of non-steroid anti-inflammatory drugs (NSAIDs) in a mouse model led to prolonged pain in the longrun, as corroborated by a database analysis that showed an increased risk of chronic pain in patients having taken NSAIDs. The realization that neutrophil-driven inflammation may provide benefits has been shown in other medical settings as well; as such, abundantly administering anti-inflammatory compounds warrants more careful consideration and more studies like this are more than encouraged.

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Keywords- chronic pain; neutrophils; inflammation; non-steroid anti-inflammatory drugs.

INTRODUCTION

Chronic pain (CP) is a particularly disturbing symptom that leads patients to repeatedly seek medical attention and from several different specialties, often to no avail. Deciphering the pathways that mediate a transition from acute pain to CP remains more relevant than ever, since it could potentially provide methods of preventing it. The treatment of acute pain consists of several strategies with various degrees of supportive scientific literature, with the medicinal mainstay remaining non-steroidal anti-inflammatory drugs (NSAIDs) (1).

Transcriptomics consists a relatively new field of research, which goes beyond the basic genetic markup of a cell and focuses on its function, by assessing the entirety of RNA transcribed by a cell or tissue (2). In a very interesting newly published study in *Science Translational Medicine* (3), Parisien et al. (2022) performed a transcriptome-wide analysis on samples from patients with acute pain, and followed them for 3 months. Considerable changes in transcription profiles were reported for patients whose pain resolved, but not for those who developed CP. In the relieved patients, a decrease in neutrophils and an upregulation of CD8+ T-cells was shown over time, while the most significant change in gene expression was again found in neutrophil-specific genes, reflecting an increase of inflammatory pathways and neutrophil degranulation in the acute phase. In a mouse model, NSAID administration during the acute phase led to prolonged

pain, as opposed to administration of other analgesics with no anti-inflammatory properties, while depletion of neutrophils led to prolonged pain as well. On the contrary, injection of neutrophils or neutrophil-expressed proteins prevented CP. Taking these findings one step further, the researchers analyzed data from a large database and found that patients taking NSAIDs had a 1.76-fold risk of developing CPs than those not taking NSAIDs.

CONCLUSION

This study comes to add itself to a growing body of evidence that claims that inflammation is not an ubiquitous villain; this multifaceted cascade of reactions seems to serve several good purposes, especially during the acute phase (4), and inhibiting it might indeed prove detrimental in the long run. As shown here, granulocytes seem to be of particular importance in this sense; for instance, though anti-inflammatory drugs used in multiple sclerosis seem to carry some promise in targeting neuroinflammation in ischemic stroke, inhibiting polymorphonuclear cells led to worse outcomes (5). Studies like this are more than important, since proper pain treatment is very relevant in everyday practice and avoiding drugs that may be associated with CP can eventually prevent it, and its effects on overall health and quality of life.

AUTHORS CONTRIBUTION

AMA conceptualized and wrote the manuscript.
DA performed the relevant literature search and reviewed the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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