

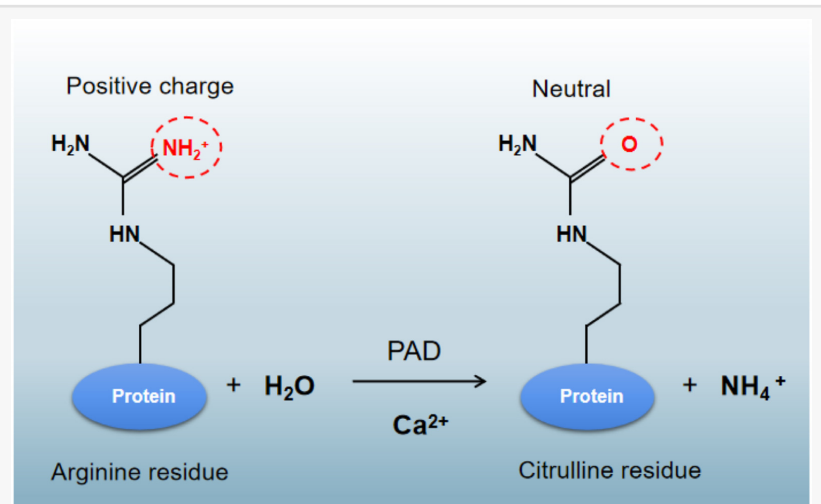
The Emerging Role of Citrullination in Gene Control and Therapeutic Innovation

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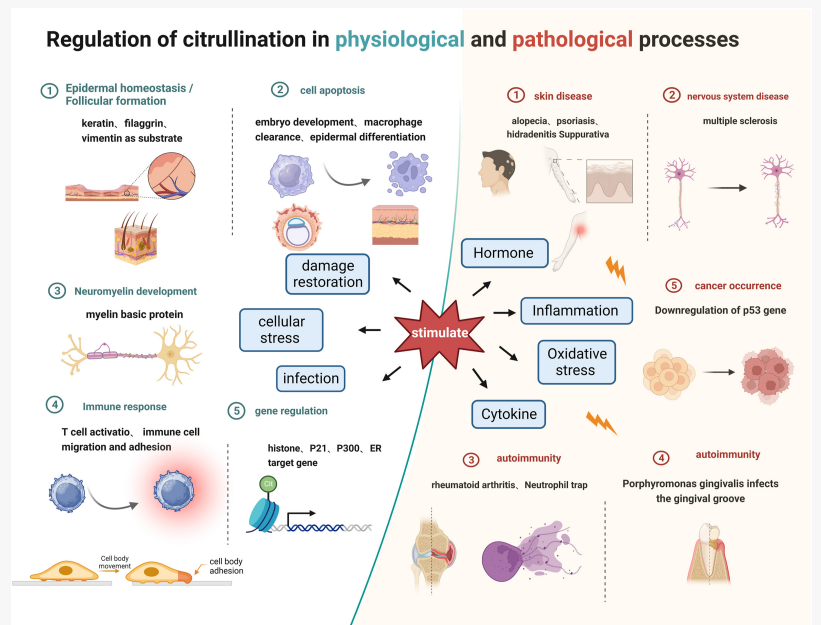
Citrullination, a transformative protein post-translational modification, is gaining recognition for its wide-ranging impact on cellular function and human disease. This process, driven by the enzyme family known as peptidyl arginine deiminases (PADs), converts the amino acid arginine into citrulline, neutralizing its charge and fundamentally altering protein structure and behavior.

Among its most significant effects is the modification of both histone and non-histone proteins, influencing critical pathways such as gene transcription, chromatin remodeling, cell signaling, and immune modulation. In particular, PAD2 and PAD4 have emerged as pivotal players in epigenetic regulation, affecting transcriptional activity by directly modifying histone tails or interacting with transcription factors and co-activators.

Through the citrullination of histones, these enzymes facilitate chromatin relaxation, enabling access for RNA polymerase II and transcriptional machinery to initiate gene expression. On the other hand, PADs also exhibit repressive functions by interfering with arginine methylation, demonstrating complex crosstalk with other



The reaction mechanism of protein arginine citrullination is catalyzed by PAD.

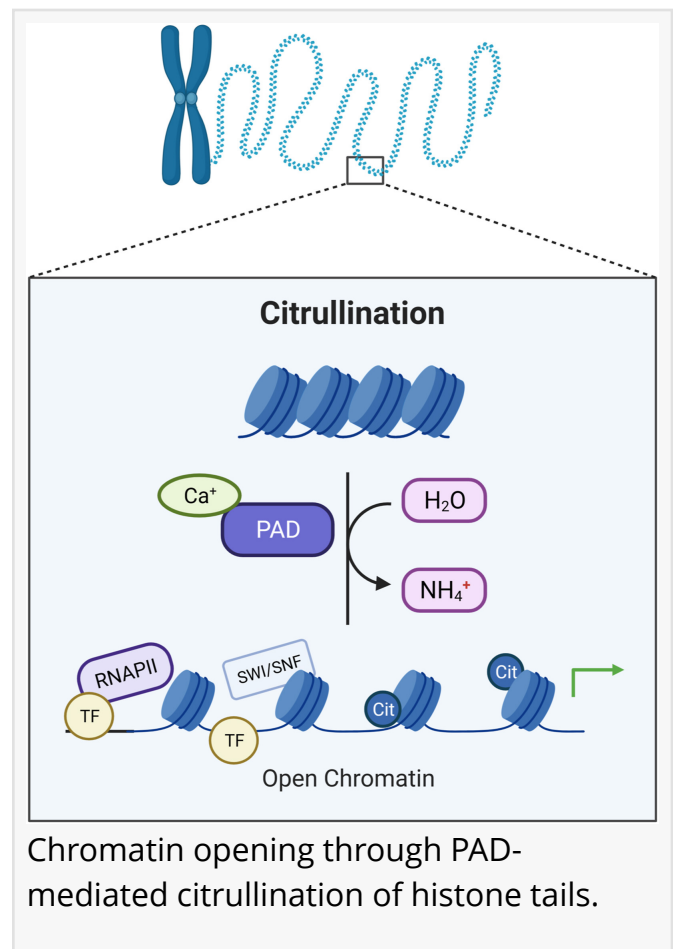


Protein citrullination in physiological and pathological processes.

modifications such as acetylation and phosphorylation. This multifaceted interaction allows for fine-tuned regulation of gene networks in both healthy and pathological states.

Citrullination has far-reaching implications across various physiological systems. It is crucial in maintaining skin integrity, regulating neuronal development, and guiding immune responses. Disruptions in PAD activity or expression are closely linked to conditions such as rheumatoid arthritis, multiple sclerosis, psoriasis, and a spectrum of cancers. The unique role of PADs in modifying key signaling proteins and regulatory complexes positions them as strategic targets in disease treatment and drug development.

Therapeutic interest in PADs has led to the discovery of both reversible and irreversible inhibitors, such as Cl-amidine, BB-Cl-amidine, and chloroacetamidine, which have demonstrated promising effects in preclinical models. These agents work by suppressing PAD activity and, consequently, modulating gene expression and inflammatory pathways.



Chromatin opening through PAD-mediated citrullination of histone tails.

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