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PIWI-Interacting RNAs in brain health and disease: biogenesis, mechanisms, and therapeutic horizons

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Abstract

PIWI-interacting RNAs (piRNAs), a class of small non-coding RNAs originally identified for their role in transposon silencing in germ cells, have recently been recognized as pivotal regulators of gene expression in the central nervous system. Beyond their canonical functions in genome defense, emerging evidence highlights piRNAs as key modulators of neuronal development, synaptic plasticity, axonal regeneration, and neuroimmune interactions-processes central to brain function and dysfunction. This review provides a comprehensive overview of piRNA biogenesis, molecular mechanisms, and regulatory pathways relevant to neurobiology. We focus on the growing body of evidence implicating piRNA dysregulation in major neurological and neuropsychiatric disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, glioma, autism spectrum disorder, and schizophrenia. Importantly, we discuss the neuropharmacological implications of piRNA pathways as novel targets for therapeutic intervention and their potential utility as biomarkers for early diagnosis and treatment stratification. By integrating mechanistic insights with emerging translational evidence, this review highlights piRNAs as promising molecular targets in the development of next-generation neurotherapeutics aimed at modifying disease progression and improving brain health.