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Commentary

The Role of Non-Coding RNAs in Modulating Wnt/β-Catenin Signaling in Stem Cells: A Regulatory Nexus in Development and Regeneration

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DESCRIPTION

The Wnt/β-catenin signaling pathway plays a pivotal role in regulating stem cell fate, pluripotency and differentiation. In both embryonic and adult stem cells, this pathway serves as a molecular switch that dictates self-renewal versus lineage commitment. In recent years, a growing body of evidence has highlighted the essential role of non-coding RNAs (ncRNAs) in modulating this pathway, offering a new layer of regulatory complexity with far-reaching implications in developmental biology, regenerative medicine and disease modeling. Non-coding RNAs, particularly long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs (circRNAs), have emerged as powerful regulators of gene expression. Despite lacking protein-coding potential, these RNA molecules are involved in chromatin remodeling, mRNA stability, transcriptional repression or activation and competitive binding to microRNAs. Their involvement in modulating Wnt/β-catenin signaling reflects a sophisticated network of post-transcriptional control that fine-tunes signaling intensity and duration within stem cell niches.

MicroRNAs are perhaps the most extensively studied class of ncRNAs in this context. Several miRNAs, such as miR-34, miR-135 and miR-29, have been shown to directly target β-catenin or its transcriptional co-activators, thereby suppressing Wnt signaling and inhibiting stem cell proliferation. Conversely, other miRNAs like miR-17-92 cluster promote Wnt/β-catenin signaling by targeting negative regulators such as GSK-3β and APC. This duality illustrates how miRNAs can serve either as enhancers or repressors, depending on cellular context and developmental stage. LncRNAs have also emerged as critical scaffolds and sponges that indirectly influence Wnt/β-catenin signaling. One example is the lncRNA LincRNA-ROR, which acts as a competing endogenous RNA (ceRNA) by sequestering miR-145, a known repressor of β-catenin. This relieves the repression on β-catenin and enhances Wnt activity, supporting the maintenance of pluripotency in embryonic stem cells. Other lncRNAs such as H19 and TUNA have been implicated in promoting neural differentiation via interactions with Wnt pathway components. These findings suggest that lncRNAs are not just passive transcriptional byproducts but active participants in stem cell regulation.

Another layer of complexity is introduced by circRNAs, a more recently characterized class of ncRNAs. Due to their covalently closed loop structure, circRNAs exhibit remarkable stability and often function as miRNA sponges. CircRNAs like circAxin1 have been shown to bind miR-1305, modulating β-catenin expression and influencing osteogenic differentiation in mesenchymal stem cells. Although this area is still in its early stages, the potential of circRNAs as modulators of Wnt signaling opens up promising avenues for research and therapeutic development. The dynamic and context-dependent interaction between ncRNAs and Wnt signaling suggests a feedback loop where signaling cues can regulate ncRNA expression and ncRNAs, in turn, fine-tune the pathway's output. For instance, Wnt signaling can induce or repress the transcription of specific miRNAs or lncRNAs that then modulate β-catenin stability or its nuclear activity. This feedback regulation ensures that stem cell behavior is precisely controlled in response to developmental or environmental cues.

From a therapeutic standpoint, targeting ncRNAs represents a novel strategy to modulate Wnt/β-catenin signaling in regenerative medicine. Enhancing Wnt activity through miRNA inhibition could improve stem cell expansion and tissue repair, while suppressing it via ncRNA overexpression could be beneficial in conditions where stem cell proliferation needs to be restrained, such as in cancer stem cells. Moreover, engineered ncRNAs or antisense oligonucleotides could serve as targeted therapeutics that manipulate Wnt signaling with high specificity and minimal toxicity. However, there are significant challenges. Many ncRNAs exhibit tissue-specific and developmentally restricted expression patterns and their functional redundancy complicates loss-of-function studies. Furthermore, efficient delivery of ncRNA-based therapeutics remains a major hurdle. Nonetheless, advances in single-cell sequencing, RNA structure prediction and delivery technologies are gradually addressing these limitations.

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CONCLUSION

The interplay between non-coding RNAs and the Wnt/β-catenin pathway represents a critical regulatory axis in stem cell biology. Through a finely balanced network of miRNAs, lncRNAs, and circRNAs, ncRNAs orchestrate the delicate equilibrium between stem cell maintenance and differentiation. This multilayered control ensures that stem cells respond appropriately to intrinsic signals and environmental stimuli during development, regeneration and tissue homeostasis. Unraveling the roles of specific ncRNAs in this context not only enhances our fundamental understanding of cell signaling but also provides new tools for manipulating stem cell fate. As research progresses, ncRNA-based strategies may offer powerful and selective interventions in regenerative therapies and disease treatment, making this an exciting frontier in stem cell and molecular biology.