G-quadruplexes in Muscle Stem Cells and Muscle Regeneration

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Skeletal muscle has a remarkable ability to regenerate owing to its resident stem cells (also called satellite cells, SCs). SCs are normally quiescent; when stimulated by damage, they activate and expand to form new fibers. The mechanisms underlying SC proliferative progression remain poorly understood. Here we show that DHX36, a helicase that unwinds RNA G-quadruplex (rG4) structures, is essential for muscle regeneration by regulating SC expansion. DHX36 (initially named RHAU) is barely expressed at quiescence but is highly induced during SC activation and proliferation. Inducible deletion of Dhx36 in adult SCs causes defective proliferation and muscle regeneration after damage. System-wide mapping in proliferating SCs revealed DHX36 binding predominantly to rG4 structures at various regions of mRNAs, while integrated polysome profiling showed that DHX36 promotes mRNA translation via 5'-untranslated region (UTR) rG4 binding. Furthermore, we demonstrate that DHX36 specifically regulates the translation of Gnai2 mRNA by unwinding its 5'-UTR rG4 structures and identify GNAI2 as a downstream effector of DHX36 for SC expansion. Our findings uncover DHX36 as an indispensable post-transcriptional regulator of SC function and muscle regeneration acting through binding and unwinding rG4 structures at 5'-UTR of target mRNAs. Moreover, we recently develop G4 CUT&RUN to map the endogenous DNA G-quadruplex (dG4) formation in SC during activation and find the dynamic dG4 landscape in SCs. Specially, the global dG4 formation is dramatically increased upon SC activation and these dG4 sites are closely correlated with open chromatin and active transcription, suggesting a regulatory function of dG4 in muscle stem cells and muscle regeneration.