Differently Regulated Gene-Specific Activity of Enhancers Located at the Boundary of Sub topologically Associated Domains: TCRα Enhancer.

Abstract

Enhancers activate transcription through long-distance interactions with their cognate promoters within a particular sub topologically associated domain (sub-TAD). The TCRα enhancer (Eα) is located at the sub-TAD boundary between the TCRα and DAD1 genes and regulates transcription toward both sides in an ∼1-Mb region. Analysis of Eα activity in transcribing the unrearranged TCRα gene at the 5′-sub-TAD has defined Eα as inactive in CD4−CD8− thymocytes, active in CD4+CD8+ thymocytes, and strongly downregulated in CD4+ and CD8+ thymocytes and αβ T lymphocytes. Despite its strongly reduced activity, Eα is still required for high TCRα transcription and expression of TCRαβ in mouse and human T lymphocytes, requiring collaboration with distant sequences for such functions. Because VαJα rearrangements in T lymphocytes do not induce novel long-range interactions between Eα and other genomic regions that remain in cis after recombination, strong Eα connectivity with the 3′-sub-TAD might prevent reduced transcription of the rearranged TCRα gene. Our analyses of transcriptional enhancer dependence during T cell development and non-T lineage tissues at the 3′-sub-TAD revealed that Eα can activate the transcription of specific genes, even when it is inactive to transcribe the TCRα gene at the 5′-sub-TAD. Hence distinct requirements for Eα function are necessary at specific genes at both sub-TADs, implying that enhancers do not merely function as chromatin loop anchors that nucleate the formation of factor condensates to increase gene transcription initiated at their cognate promoters. The observed different regulated Eα activity for activating specific genes at its flanking sub-TADs may be a general feature for enhancers located at sub-TAD boundaries.

Antisense oligonucleotides (ASOs) are short synthetic single-stranded DNA/RNA-like oligonucleotides, which are designed to selectively bind RNA (Watson–Crick pairing) to regulate protein expression. Here, protein expression is regulated by affecting processing or translation of target RNA or by activation of RNase H and subsequent degradation of target RNA, due to their potential to modify protein expression, ASOs are currently used to treat diseases such as hereditary transthyretin amyloidosis.In order to use ASOs as therapeutic agents, they are modified to achieve better bioavailability and higher target RNA specificity .For this purpose, DNA nucleotides of ASOs are replaced with locked nucleic acid (LNA) nucleotides .Here, GapmeRs, made of LNA bases flanking a central DNA sequence, provide a potent target mRNA inhibition. Mechanistically, GapmeRs form DNA-RNA hybrids after binding their target RNA. These DNA-RNA hybrids are

recognized by RNase H catalyzing RNA cleavage.

BIOGRAPHY

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