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Aire-Dependent Transcripts have Shortened 3'UTRs and Show Greater Stability by Evading Microrna-Mediated Repression

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Abstract : Aire induces ectopic expression of a large repertoire of tissue-specific antigen (TSA) genes in thymic medullary epithelial cells (MECs), driving immunological self-tolerance in maturing T cells. Although important mechanisms of Aire-induced transcription have recently been disclosed through the identification and the study of Aire's partners, the fine transcriptional functions underlied by a number of them and conferred to Aire are still unknown. Alternative cleavage and polyadenylation (APA) is an essential mRNA processing step regulated by the termination complex consisting of 85 proteins, 10 of them have been related to Aire. We evaluated APA in MECs in vivo by microarray analysis with mRNA-spanning probes and RNA deep sequencing. We uncovered the preference of Aire-dependent transcripts for short-3'UTR isoforms and for proximal poly(A) site selection marked by the increased binding of the cleavage factor Cstf-64. RNA interference of the 10 Aire-related proteins revealed that Clp1, a member of the core termination complex, exerts a profound effect on short 3'UTR isoform preference. Clp1 is also significantly upregulated in the MECs compared to 25 mouse tissues in which we found that TSA expression is associated with longer 3'UTR isoforms. Aire-dependent transcripts escape a global 3'UTR lengthening associated with MEC differentiation, thereby potentiating the repressive effect of microRNAs that are globally upregulated in mature MECs. Consistent with these findings, RNA deep sequencing of actinomycinD-treated MECs revealed the increased stability of short 3'UTR Aire-induced transcripts, resulting in TSA transcripts accumulation and contributing for their enrichment in the MECs.

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