

Carnosol, a diterpene present in rosemary, increases ELP1 levels in familial Dysautonomia (FD) patient-derived cells and healthy adults: a possible therapy for FD

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Abstract

Recent research on Familial Dysautonomia (FD) has focused on the development of therapeutics that facilitate the production of the correctly spliced, exon 20-containing, transcript in cells and individuals bearing the splice-altering, FD-causing, mutation in the ELP1 gene. We report here the ability of carnosol, a diterpene present in plant species of the Lamiaceae family, including rosemary, to enhance the cellular presence of the correctly spliced ELP1 transcript in FD patient-derived fibroblasts by upregulating transcription of the ELP1 gene and correcting the aberrant splicing of the ELP1 transcript. Carnosol treatment also elevates the level of the RBM24 and RBM38 proteins, two multifunctional RNA binding proteins. Transfection-mediated expression of either of these RBMs facilitates the inclusion of exon 20 sequence into the transcript generated from a minigene bearing ELP1 genomic sequence containing the FD-causing mutation. Suppression of the carnosol-mediated induction of either of these RBMs, using targeting siRNAs, limited the carnosol-mediated inclusion of the ELP1 exon 20 sequence. Carnosol treatment of FD patient PBMCs facilitates the inclusion of exon 20 into the ELP1 transcript. Increased levels of the ELP1 and RBM38 transcripts and the alternative splicing of the SIRT2 transcript, a sentinel for exon 20 inclusion in the FD-derived ELP1 transcript, are observed in RNA isolated from whole blood of healthy adults following the ingestion of carnosol-containing rosemary extract. These findings and the excellent safety profile of rosemary together justify an expedited clinical study of the impact of carnosol on the FD patient population.