Regulation of SREBP-1 by Polyunsaturated Fatty Acids

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Sterol regulatory element binding protein 1 (SREBP-1) is a master transcriptional regulator that controls the transcription of genes required for lipid and fatty acid production. Previous studies have shown that polyunsaturated fatty acids (PUFAs), such as omega-3 fatty acid eicosapentaenoic acid (EPA), inhibit SREBP-1 activity. However, the molecular mechanism of this inhibition remains poorly understood. One possibility is that PUFA blocks the transcription and/or translation of SREBP1. SREBP-1 is produced as a membrane-bound inactive precursor that requires two sequential proteolytic cleavages to release its active N-Terminal Domain (NTD) to enter the nucleus and regulate transcription. Therefore, another possibility is that PUFA can regulate the proteolytic processing of SREBP-1 and/or the stability of SREBP-1(NTD). To distinguish these possibilities, CRISPR-Cas9 gene-editing technology was used to generate a novel cell line that only expresses the SREBP-1(NTD), but not the membrane-bound SREBP-1 precursor. This cell line enables the study of the effect of PUFA on SREBP-1(NTD) independent of its effect on the proteolytic processing of SREBP-1 precursor protein. Both control and SREBP-1(NTD) cells were treated with EPA simultaneously, real time polymerase reaction chain (PCR) and protein immunoblotting were performed to analyze SREBP-1 mRNA and protein levels. SREBP-1 expression, in the mRNA and protein form, was downregulated significantly in both the wild type and SREBP-1(NTD) cell line. The disproportionately greater reduction of SREBP-1(NTD) at the protein level suggests that the degradation of SREBP-1(NTD) is accelerated by EPA. These results suggest that EPA inhibits the transcription of SREBP-1 and accelerates the degradation of SREBP-1(NTD) protein.