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The Role of Mediator Subunit MED12 in Adipogenesis

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Mediator, a large protein complex exclusive to eukaryotes, is a master regulator of cell-type specific gene expression. Mediator functions as an adapter that connects activators bound at enhancers to the transcription pre-initiation complex (PIC) located at the promoter. Our research focuses on how Mediator influences the differentiation of adipose-derived mesenchymal stem cells (ASCs). ASCs are harvested from adult donors and have the ability to self-renew and can differentiate down chondrogenic, osteogenic, and adipogenic lineages. We recently published findings indicating that knockdown of the Mediator subunit MED31 reduces adipogenesis in bone marrow-derived MSCs. We are now focused on MED12, a subunit of the Mediator complex kinase domain that appears to have a significant role in maintaining cell state. Our goal is to understand MED12's dual role as both a Mediator subunit in the regulatory kinase module and as a coactivator of transcription. We hypothesize that the loss of MED12 disrupts adipogenic differentiation in ASCs. Previously published research indicates MED12 coactivates β-catenin, a driver of adipogenesis, but little research currently links MED12 to the regulation of adipogenesis. We have performed siRNA-mediated knockdowns of MED12 in ASCs prior to inducing adipogenesis. ASCs display reduced adipogenesis as demonstrated by images of cell morphology and lipid vesicle staining. We have also optimized our sonication protocol for chromatin immunoprecipitation (ChIP) experiments and we are currently investigating MED12 genomic occupancy in order to determine the direct gene targets of MED12 during adipogenesis. Overall, this research is important for elucidating the requirements for proper regulation of differentiation of clinically-relevant ASCs, and the broader understanding of Mediator's function in ASCs will help foster their use in clinical applications such as regenerative medicine.