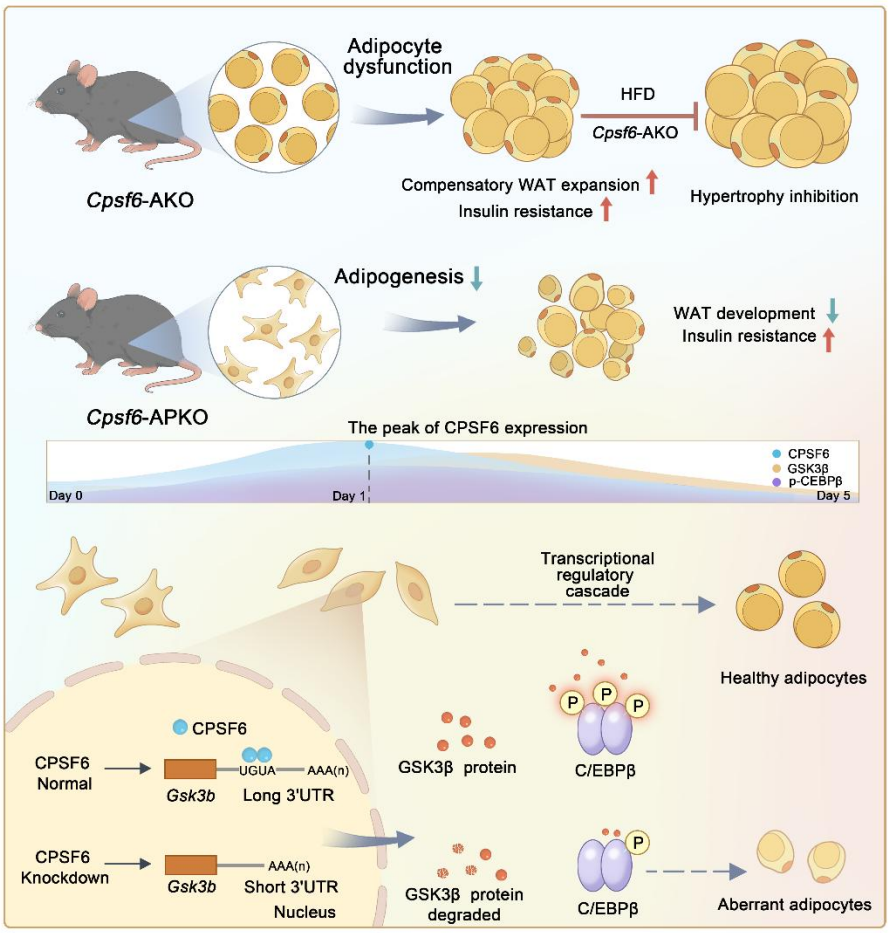
Graphical abstract



CPSF6 regulates adipose tissue development and metabolic homeostasis through alternative polyadenylation (APA)-mediated regulation of of *Gsk3b* transcripts. During early adipocyte differentiation, elevated CPSF6 promotes distal poly(A) site selection in *Gsk3b* mRNA, favoring the long 3'UTR isoform that sustains GSK3β expression. GSK3β then phosphorylates C/EBPβ, facilitating the adipogenic transcriptional program. Loss of *Cpsf6* shifts *Gsk3b* APA toward proximal poly(A) site usage, increasing the short 3'UTR isoform and reducing GSK3β expression, thereby impairing C/EBPβ phosphorylation and adipogenesis. *In vivo*, adipose progenitor-specific *Cpsf6* deficiency (*Pdgfra*-Cre; APKO) impairs adipogenesis and causes white adipose tissue (WAT) lipoatrophy. In mature adipocytes (*Adipoq*-Cre; AKO), *Cpsf6* deficiency causes adipocyte dysfunction, characterized by adipocyte enlargement and insulin resistance under chow-fed conditions, while limiting high-fat diet-induced adipose expansion and protecting against obesity. Thus, CPSF6-dependent *Gsk3b* APA establishes a mechanistic link between post-transcriptional RNA processing, adipogenesis and metabolic adaptation of adipose tissue.