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Structure and Dynamics of Human Translation Initiation Pathway: From 43s Pic Assembly to Late 48s Ic Remodeling

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Translation initiation in human cells is a precisely regulated process shaping the proteome. Initiation factors (eIFs) dynamically assemble on the 40S ribosomal subunit to facilitate start site selection and 80S ribosome formation. By mapping the ordered recruitment and remodeling of initiation factors, we define key structural transitions leading to the 43S pre-initiation complex (43S PIC).

Our findings establish eIF3 as a pivotal coordinator of early factor recruitment, priming the 40S subunit for eIF1, eIF1A, and the ternary complex (eIF2–GTP–Met-tRNAiMet) binding. The 48S initiation complex (48S IC) undergoes multi-step conformational remodeling as it transits from mRNA scanning to a start site commitment. Structural analysis reveals how mRNA context modulates ribosomal and eIF interactions, driving the shift from an open scanning state to a committed closed conformation. GTPase-driven fluctuations of 48S-bound eIF2 finalize start site selection, promoting eIF5B recruitment and initiator Met-tRNAiMet handover preparing for subunit joining.

Finally, we show that eIF3 remains a key regulator at the 48S-to-80S transition, coordinating factor exchange and displacement of its eIF3c N-terminal domain. These findings highlight critical commitment steps in translation initiation and provide a structural basis for understanding eIF3 function during & beyond translation initiation.