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Investigating how splicing factor homeostasis shapes transcriptomes in pluripotency and differentiation



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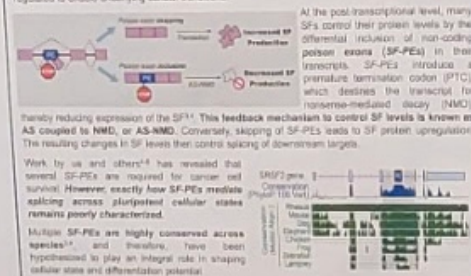
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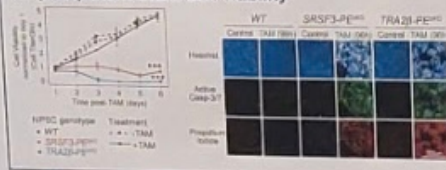
Background

Alternative splicing (AS) is a key contributor to cellular and tissue identity, influencing developmental, oncogenic, and aging processes¹. AS enables a single gene to give rise to a multitude of mRNA transcripts that can diversify the proteome when translated.

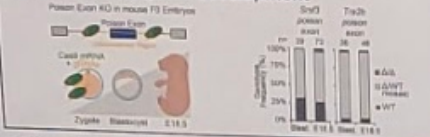
AS is regulated by splicing factors (SFs), which are RNA-binding proteins that activate or repress splicing in a dose-dependent manner. SFs are critical for organism development and must be tightly regulated to ensure underlying cellular transitions.



SRSF3 and TRA2β poison exons are required for pluripotent stem cell viability



SRSF3 and TRA2β poison exons are required for mouse embryonic development



Conclusions & perspectives

- SFs maintain homeostasis via AS-NMD.
- Specific SF-PEs are required for human pluripotent stem cell and mouse embryonic viability.
- Overarching hypothesis: AS mediates pluripotent stem cell identity and ability to differentiate.
- Our findings will reveal how SF-PEs modulate transcription, safeguard pluripotency, and drive differentiation, with potential to advance cancer therapeutics and regenerative medicine.

References

1. Smith et al., Nat Rev Genet 2011
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5. Leclair et al., Nature 2017
6. Leclair et al., Nature 2017
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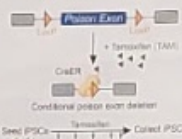
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Modeling poison exon conditional KO in human iPSCs

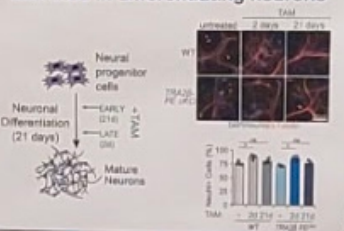
1. Tamoxifen-inducible CreER enables recombination of LoxP sites flanking PE and homozygous PE deletion



2. SRSF3- and TRA2β-PE cKO leads to INCREASED levels of corresponding SF protein

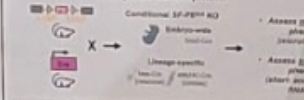


TRA2β poison exon conditional KO is tolerated in differentiating neurons

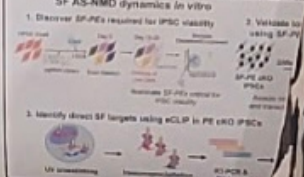


Proposed future directions

AIM 1: Characterize how Srsf3- and Tra2β-PEs shape mouse embryonic development



AIM 2: Define pluripotency- and differentiation-associated SF AS-NMD dynamics in vitro



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