IMEG Seminar Series

The road to global science

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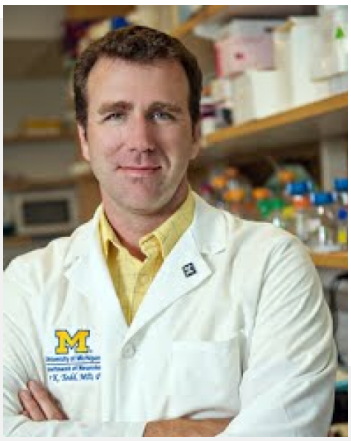

December 17 th, 2021, 9:00~10:00

CGG repeated-elicited neurodegeneration in Fragile X Tremor-Ataxia Syndrome

The seminar series is for all students and researchers in Kumamoto University.
Check your email and find the Zoom ID and passcode.

Fragile X-associated tremor ataxia syndrome (FXTAS) is caused by a transcribed trinucleotide CGG repeat expansion in the 5' UTR of *FMR1*. CGG repeats drive neurodegeneration through formation of aberrant repeat RNA - RNA binding protein complexes and by triggering repeat-associated non-AUG initiated ("RAN") translation of toxic proteins. Despite recent advances providing insights into these pathogenic mechanisms, no effective therapies exist for this progressive and fatal condition. To expand our knowledge about this condition and move towards therapeutic development, we used reporter assay systems in cell lines and primary neurons to identify novel *in-cell* CGG repeat RNA-protein interactors and both *cis* and *trans* modulators of CGG RAN translation. We then validated hits from these modifier and interactor screens in *Drosophila,* rodent and patient iPSC derived neuronal models of FXTAS. We found that RAN translation initiates both within CGG repeats and at conserved near-cognate codons upstream of the repeat. RAN translation can be modulated by altering expression of initiation factors that impact start codon fidelity, ribosomal quality control, and RNA secondary structure. CGG repeats also elicit translational frameshifts to generate chimeric proteins with enhanced toxicity and altered biophysical properties. Further, we identified novel CGG repeat RNA interacting proteins, including SRSF proteins and the kinases (e.g. SRPK1) that regulate their function, as modulators of RAN translation and suppressors of CGG repeat toxicity in *Drosophila* and rodent neuronal model systems. Lastly, we identified antisense oligonucleotides that selectively target RAN initiation sites to suppress repeat associated toxicity in rodent and human neurons. In sum, modifying the function and expression of CGG repeat binding proteins and CGG RAN translational modifiers represent viable therapeutic strategies worthy of further development in FXTAS and related repeat expansion disorders.

References

1. SRSF protein kinase 1 modulates RAN translation and suppresses CGG repeat toxicity. Malik I et al., EMBO Mol Med. 2021 Nov 8;13(11):e14163.
2. Human oncoprotein 5MP suppresses general and repeat-associated non-AUG translation via eIF3 by a common mechanism. Singh CR et al., Cell Rep. 2021 Jul 13;36(2):109376.
3. The RNA helicase DHX36-G4R1 modulates C9orf72 GGGGCC hexanucleotide repeat-associated translation. Tseng YJ et al., J Biol Chem. 2021 Aug;297(2):100914.
4. A native function for RAN translation and CGG repeats in regulating fragile X protein synthesis. Rodriguez CM et al., Nat Neurosci. 2020 Mar;23(3):386-397.
5. DDX3X and specific initiation factors modulate FMR1 repeat-associated non-AUG-initiated translation. Linsalata AE et al., EMBO Rep. 2019 Sep;20(9):e47498.
6. CGG Repeat-Associated Non-AUG Translation Utilizes a Cap-Dependent Scanning Mechanism of Initiation to Produce Toxic Proteins. Kearse MG et al., Mol Cell. 2016 Apr 21;62(2):314-322.
7. CGG repeat-associated translation mediates neurodegeneration in fragile X tremor ataxia syndrome. Todd PK et al., Neuron. 2013 May 8;78(3):440-55.

You will be fascinated by...

The "Repeatome"

Over half of the human genome is made of repetitive elements. The Todd lab has focused on the roles of repetitive elements and how they function in the nervous system.

CGG repeats in Neurological Disease

Fragile X syndrome result from nucleotide repeat expansion in non-coding regions of messenger RNAs.

From Biology to Critical

Studying the role of repetitive nucleotide would lead to the discovery of new therapeutic targets.

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