Genética Molecular e Populacional

Course: Regulation of Gene Expression

Date: 5-9 June 2017
Location: i3S, Room B
Coordinator: Alexandra Moreira
Faculty and invited speakers: Isabel Pereira-Castro, Jaime Freitas, Miguel Branco, José Bessa, Nicholas Proudfoot.

Objectives:
Regulation of gene expression depends on a panoply of processes and factors, including chromatin remodelling, transcription, pre-mRNA processing, *cis*-regulatory elements, RNA binding proteins, miRNAs, mRNA localization and local translation. In this course international state-of-the-art research on the molecular basis of gene expression regulation and mRNA processing during the physiological events that occur in different types of cells and in different systems will be presented and discussed. Scientific challenges in the field and how they are experimentally addressed will be discussed with the students.

Outline of the course: Lectures, tutorials, paper discussions, research seminars, projects developed and presentations by the students.

Monday 5th – Alexandra Moreira & Jaime Freitas

Morning - Alexandra Moreira

1. Introduction.
2. *Lecture 1*: Overview of transcription and RNA processing. The mRNA factory model. Integration of co-transcriptional events. Mechanisms of mRNA 3' end formation in Eukaryotes.
3. *Research seminar and paper dissection*:

Pinto, PAB, Henriques, H, Freitas, MO, Martins, T, Domingues, RG, Wyrzykowska, PS, Coelho, PA, Carmo, AM, Sunkel, CE, Proudfoot, NJ and Moreira, A (2011) RNA polymerase II kinetics in *polo* polyadenylation signal selection, The EMBO Journal, 30: 2431–2444

Suggested reading:

a) Domingues, RG, Lago-Baldaia, I, Pereira-Castro, I, Fachini, JM, Oliveira, L, Drpic, D, Lopes, N, Henriques, T, Neilson, J, Carmo, AM and Moreira A (2016) CD5 expression is regulated during human T-cell activation by alternative polyadenylation, PTBP1 and miR-204, European Journal of Immunology, 46: 1490–1503.
b) Mayr C. (2016) Evolution and Biological Roles of Alternative 3'UTRs. Trends Cell Biol. 26(3):227-37.
c) Lutz CS, Moreira A (2011) Alternative mRNA polyadenylation in eukaryotes: and effective regulator of gene expression. Wiley Interdisciplinary Reviews – RNA, 2 : 23-31

Afternoon – Jaime Freitas

1. *Research seminar (discussion of ongoing projects)*:
    a) RNA Polymerase II elongation rate and polyadenylation signal selection.

       Analysis of alternative polyadenylation by 3' Region Extraction and Deep Sequencing (3'READS).

    b) Heph/PTB and Elav/HuR are recruited to *polo* upstream sequence element that modulates alternative polyadenylation

       Characterization of an RNA sequence element and protein factors involved in *polo* alternative polyadenylation.

Suggested reading:

1) Fong, N., Kim, H., Zhou, Y., Ji, X., Qiu, J., Saldi, T., et al. (2014). Pre-mRNA splicing is facilitated by an optimal RNA polymerase II elongation rate. *Genes & Development*, *28*(23), 2663–2676.

2) Danckwardt, S., Kaufmann, I., Gentzel, M., Foerstner, K. U., Gantzert, A.-S., Gehring, N. H., et al. (2007). Splicing factors stimulate polyadenylation via USEs at non-canonical 3 ' end formation signals. EMBO J, 26(11), 2658–2669.

Tuesday 6th – Miguel Branco

Morning

1. *Lecture: Introduction to Epigenetics*
2. *Students are presented with a research question to solve*

Afternoon

1. *Time to look into research question and prepare short presentation*
2. *Lecture: Transposons, Epigenetics and Gene Regulation*
3. *Short presentations by students*

Suggested reading:

1) Allis, C. D., & Jenuwein, T. (2016). The molecular hallmarks of epigenetic control. Nature Reviews Genetics, 17(8), 487–500.
2) Feinberg, A. P., Koldobskiy, M. A., & Göndör, A. (2016). Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. Nature Reviews Genetics, 17(5), 284–299.
3) Garcia-Perez, J. L., Widmann, T. J., & Adams, I. R. (2016). The impact of transposable elements on mammalian development. Development, 143(22), 4101–4114.
4) Chuong, E. B., Elde, N. C., & Feschotte, C. (2017). Regulatory activities of transposable elements: from conflicts to benefits. Nature Reviews Genetics, 18(2), 71–86.

Wednesday 7th – José Bessa & Alexandra Moreira

Morning – José Bessa

1. *Lecture:* Introduction to transcriptional cis-regulation.
3. *Research seminar:* The transcriptional cis-regulome of the zebrafish exocrine pancreas.

Suggested reading:

Shlyueva D, Stampfel G, Stark A. (2014) Transcriptional enhancers: from properties to genome-wide predictions. Nat Rev Genet. Apr;15(4):272-86.

Afternoon –Alexandra Moreira

1. *Lecture 2:* Alternative splicing, biological relevance and regulation. Alternative splicing & disease; RNA therapeutics.
2. *Paper dissection*:

   Glória, V, Martins de Araújo, M, Leal, R, de Almeida, SF, Carmo, AM and Moreira, A (2014) T cell activation regulates CD6 alternative splicing by transcription dynamics and SRSF1, J Immunol, 193(1): 391-399

Thursday 8th – Isabel Pereira-Castro & Alexandra Moreira

Morning - Isabel Pereira-Castro

1. *Research seminar* - Dissecting the molecular mechanisms controlling alternative polyadenylation in human T cells.
2. *Paper dissection*:

   Domingues RG, Lago-Baldaia I, Pereira-Castro I, Fachini JM, Oliveira L, Drpic D, Lopes N, Henriques T, Neilson JR, Carmo AM, Moreira A (2016) CD5 expression is regulated during human T-cell activation by alternative polyadenylation, PTBP1 and miR-204. Eur J Immunol.

Suggested reading:

5) Lutz CS, Moreira A (2011) Alternative mRNA polyadenylation in eukaryotes: and effective regulator of gene expression. Wiley Interdisciplinary Reviews – RNA, 2: 23-31
6) Sandberg R, Neilson JR, Sarma A, Sharp PA, Burge CB (2008) Proliferating cells express mRNAs with shortened 3' untranslated regions and fewer microRNA target sites. Science, 320(5883):1643-7.

Afternoon - Alexandra Moreira

1. *Lecture* – The 3'UTR: a platform for gene expression regulation. The role of RNA binding proteins and alternative polyadenylation in mRNA localization and local translation.
2. *Paper dissection:*

   Braz SO, Cruz A, Lobo A, Bravo J, Moreira-Ribeiro J, Pereira-Castro I, Freitas J, Relvas JB, Summavielle T and Moreira A. (2017) Expression of Rac1 alternative 3' UTRs is a cell specific mechanism with a function in dendrite outgrowth in cortical neurons, Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms doi: 10.1016/j.bbagrm.2017.03.002.

Suggested reading:

1) Kelsey C. Martin and Anne Ephrussi (2009) mRNA Localization: Gene Expression in the Spatial Dimension. Cell. 136(4): 719.
2) Hosung Jung, Christos G. Gkogkas, Nahum Sonenberg, Christine E. Holt (2014) Remote Control of Gene Function by Local Translation. Cell 157: 26–40

Friday 9th – Nick Proudfoot & Students presentations

Morning – Nick Proudfoot

Paper dissection:

M.Schlackow, T.Nojima T.Gomes T, Dhir A, Carmo-Fonseca M, Proudfoot NJ. (2017) Distinctive Patterns of Transcription and RNA Processing for Human lincRNAs. Mol. Cell 65: 25-38

Suggested reading:

1. T.Nojima, T.Gomes, A.R.F.Grosso, H.Kimura, M.J.Dye, S.Dhir, M.Carmo-Fonseca and N.J.Proudfoot (2015) Mammalian NET-seq analysis reveals genome-wide nascent transcription coupled to RNA processing Cell 161: 526-540
2. N.J.Proudfoot (2016) Transcriptional termination in mammals: Stopping theRNA polymerase II juggernaut. Science 352(6291): 1-9 - Review

Afternoon - students will present their projects and the course will be evaluated.

Faculty contact list:

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