Postdoc opportunity

Treisman lab, Crick Institute

The Signalling and Transcription group focusses on the SRF transcription factor network, a major nuclear target of Rho and Ras, two important signalling pathways involved in oncogenic transformation, invasion and metastasis. Our main interest is in the biology of SRF and its two cofactor families, the TCFs and the MRTFs, and the molecular mechanisms underlying their control by Ras-ERK and Rho-actin signalling (Olson and Nordheim, 2010; Posern and Treisman, 2006). We use a multidisciplinary approach, involving biochemistry, structural biology, cell biology and genomics, applied to both tissue culture and mouse cancer and immune models.

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Applications: full CV and references by 16th April 2020 please
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Molecular mechanisms of signal-regulated MRTF activation

We have defined the direct genomic targets for SRF, and shown that Rho-actin signalling to the MRTFs is a major contributor to the fibroblast growth factor response (Esnault et al., 2014). We characterised the kinetics of ERK-induced TCF phosphorylation (Mylona et al., 2016). We evaluated the contribution of the TCFs to the transcriptional and chromatin response to ERK activation, showing that their activation is required for histone modifications at the TSS (Esnault et al., 2017). We also showed that the TCFs compete with the MRTFs for access to SRF, and that this determines the cell contractile response (Gualdrini et al., 2016). Finally we have examined the relationship between MRTF/SRF signalling and the YAP/TEAD pathway, showing that the two pathways are mutually dependent (Foster et al., 2017).

We are especially interested in the molecular mechanisms controlling MRTF activation, particularly the role played by G-actin, the relationship between MRTF phosphorylation and

transcriptional activation, and how MRTF/SRF regulation controls the cellular response to growth factor and mechanical stimuli. Control of MRTF subcellular localisation is a major mechanism by which MRTF activity is regulated by G-actin (Miralles et al., 2003).

Our previous studies have shown that nuclear G-actin suppresses MRTF target gene transcription (Vartiainen et al., 2007). Our recent data show that this involves control both of MRTF-SRF interaction and DNA binding, and RNA polymerase II recruitment and initiation: we are using biochemical and genomic approaches to elucidate the molecular mechanisms involved. A second area of interest concerns the relationship between signalling to the MRTFs and chromatin modifications at their target genes. Here we will establish the modifiers involved, the role played by the modifications in facilitating transcription, and their relation to chromatin modifications induced by the TCF proteins. Finally we are interested in elucidating how external environment determines the subcellular location of the MRTFs under resting conditions, and how MRTF/SRF signalling is linked to the effects of tissue mechanics on stem cell differentiation and the pro-tumorigenic activity of cancer associated fibroblasts.

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