

POSTER PRESENTATION

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# The 4-D landscape of the inflammatory response

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## Background

It is widely accepted that chromatin 'responds' to physiological cues via protein:DNA interactions and nucleosome rearrangement [1,2], and that transcription plays a key role in its higher-order organization [3]. What remains elusive is how the nuclear landscape reshapes, in 3-D space and time, to facilitate such responses to unfold.

## Materials and methods

We add tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) to primary human endothelial cells and induce the inflammatory cascade; this is orchestrated by the transcription factor NF- $\kappa$ B [4]. We monitor the response for 0-85 min post-induction using ChIP nucleosome-positioning studies, and chromosome conformation capture, all coupled to next-generation sequencing. We also apply a new approach, where the isolation of 'transcription factories' [5] is followed by RNA-seq to uncover nascent transcriptomes.

## Results

First, we redefine early, intermediate, late, and oscillating TNF $\alpha$ -responsive genes, based on changing levels of nascent RNA. We then examine how these co-associate in specialized 'factories', some of which further specialize in transcribing responsive non-coding genes [6]. Contacts are driven by NF- $\kappa$ B, and evolve as genes are differentially turned on and off over time. We also monitor nucleosome rearrangements genome-wide; these correlate with poised promoters before induction, and with nucleosome depletion as a result of transcriptional activation, NF- $\kappa$ B binding, enhancer activity in TNF $\alpha$ -stimulated chromosomal domains.

## Conclusions

We provide evidence for a prompt, within <30 min, reshaping of the genome in response to inflammation.

This entails *de novo* associations of co-regulated coding and non-coding sequences in specialized 3-D networks that evolve over time, as well as extensive nucleosome depletion. We expect all extracellular cues to signal through analogous specialized networks and reassess our parsimonious model [7] for transcriptional regulation accordingly.

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