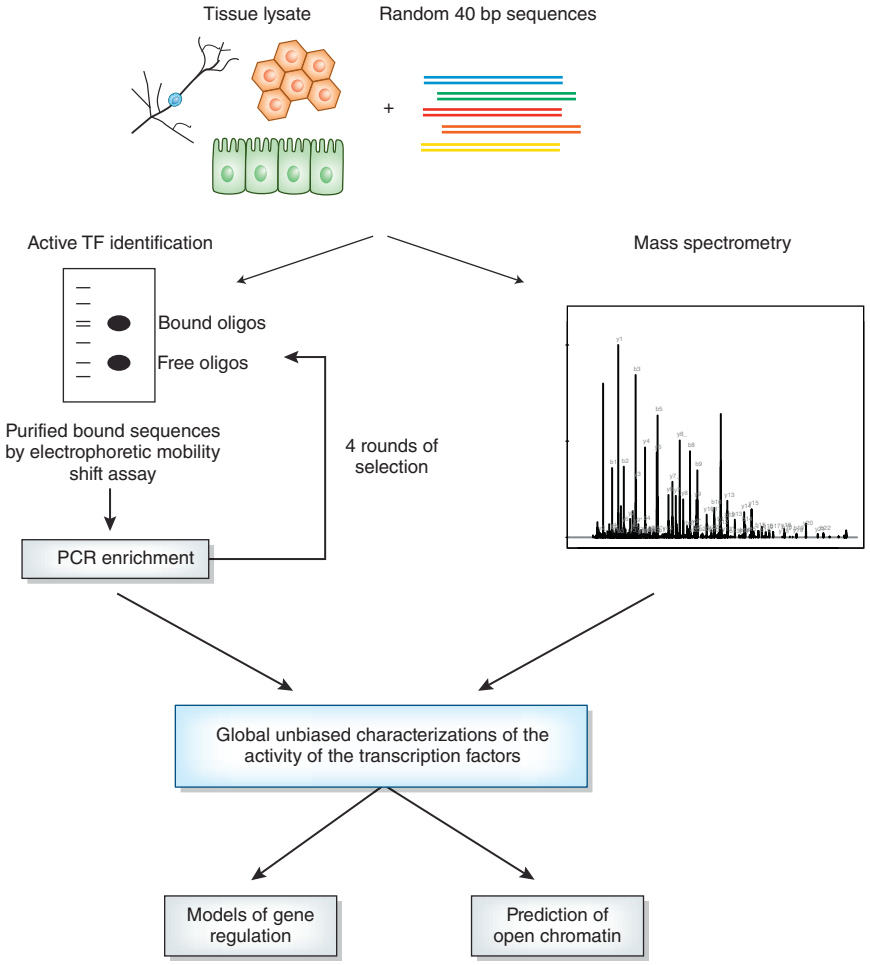

Figure 1 ATI combines affinity-based enrichment of oligonucleotides bound by nuclear proteins isolated from cells or tissues with mass spectrometric measurements of protein abundance to determine actively engaging transcription factors. This allows prediction of sites with open chromatin and refinement of models of gene regulation.

Protein-centric methods rely on antibodies to assess sequence-specific chromatin interactions with specific proteins[4]. Conventional chromatin immune precipitation (ChIP) is based on cross-linking DNA with associated proteins followed by immunoprecipitation and characterization of associated DNA after reverse cross-linking. Native ChIP avoids cross-linking by using gentler methods to fragment DNA, and the newer Cut&Run approach avoids cross-linking by antibody-mediated targeting of micrococcal nuclease (MNase) to bound genomic sites[5,6]. Although highly informative, all three methods rely on specific antibodies or the ability to tag endogenous proteins, which is difficult to standardize between all DNA-binding proteins. ATI, on the other hand, allows direct and equal competition of all available proteins for their target sequences.

Chromatin-centric assays are typically dependent on chromatin accessibility of specific enzymes, such as DNase, MNase, or transposase, as used in the assay for transposase-accessible chromatin (ATAC)-Seq[7]. These methods allow the identification of 'accessible' chromatin, which often correlates with sites of active transcription factor engagement, but they do not directly measure transcription factor binding.

ATI addresses several deficiencies of these methods by enabling comprehensive, unbiased detection of transcription factor activities in cell extracts. Further refinement of the technique will likely increase its power by improving the sensitivity to detect lower-affinity transcription factors and the ability to detect longer DNA motifs. In principle, the method could also be developed to explore RNA-binding proteins. Together with rapidly evolving sequencing tools, ATI will help elucidate the intricate transcriptional controls and gene regulatory networks that govern cell lineage identity and response to environmental stimuli.

COMPETING INTERESTS
The authors declare no competing interests.

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