Chromatin Readers and Nuclear Architecture

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BET (bromodomain and extraterminal motif) proteins are pharmacologic targets for the treatment of diverse diseases, yet the roles of individual BET family members remain unclear. We find that BRD2 but not BRD4 colocalizes with the architectural/insulator protein CCCTC-binding factor (CTCF) genome-wide. CTCF recruits BRD2 to co-bound sites, whereas BRD2 is dispensable for CTCF occupancy. Disruption of a CTCF/BRD2-occupied element positioned between two unrelated genes enables regulatory influence to spread from one gene to another, suggesting that CTCF and BRD2 form a transcriptional boundary. Accordingly, single molecule mRNA FISH reveals that upon site-specific CTCF disruption or BRD2 depletion, expression of the two genes becomes increasingly correlated. HiC shows that BRD2 depletion weakens boundaries co-occupied by CTCF and BRD2, but not those that lack BRD2. These findings indicate that BRD2 supports boundary activity and raise the possibility that pharmacologic BET inhibitors can influence gene expression in part by perturbing domain boundary function.