

# Muscle Control: Genome-Wide Binding Of Musculin Mirrors Myod Binding

December 16, 2013

G Brennan

Proper organ and tissue development requires a precise pattern of gene expression and repression as cells progress from proliferative states to terminal differentiation. In the normal development of skeletal muscle the transcription factor MyoD promotes muscle differentiation (myogenesis), binding at tens of thousands of sites across the genome and promoting histone acetylation (Cao, 2010). The myogenic activity of MyoD is opposed by several transcription factors including Musculin (MSC), which inhibits MyoD by occluding MyoD binding sites and by competing with MyoD for E-protein binding partners. In a recent study published in *Skeletal Muscle*, graduate student Kyle L. MacQuarrie, along with Drs. Zizhen Yao, Abraham P. Fong, and Stephen J. Tapscott of the Human Biology Division, determined that MSC binds broadly across the genome in a similar but non-identical pattern to MyoD, suggesting that MSC may play a broad role in regulating MyoD activity during muscle development.

Transcription factor binding patterns vary widely; some, like MyoD, bind broadly across the genome while others are restricted to binding only near the genes they regulate. However, it was unknown whether MSC, one of several MyoD transcriptional inhibitors, would bind at a subset of MyoD binding sites or more broadly. To address this question, MacQuarrie, et al. employed a ChIP-seq approach and found that endogenous MSC binds genome-wide in a pattern very similar to MyoD. The team identified three types of binding sites: those shared between MyoD and MSC, sites that bound only one of the two proteins, and sites that overlapped but were not identical (see figure). While the binding patterns were broadly similar, MSC was slightly more enriched near transcription start sites. Motif analysis of the preferred binding site showed that MSC preferentially binds more GC-rich sequences than MyoD. Therefore, shared but non-identical binding sites may be explained by two E-boxes in close proximity that have different MyoD and MSC binding preferences. Similarly, the bias in MSC binding sites for increased GC content may explain the increased propensity for MSC to bind near transcription start sites, which tend to be GC-rich.

MyoD binding induces histone acetylation to promote myogenesis; therefore the team asked whether MSC acts to inhibit MyoD by limiting histone acetylation. Paradoxically, MacQuarrie, *et al.*

found that histone acetylation was enriched at MSC binding sites. However, these MSC binding sites did not correlate with differential gene regulation. Furthermore, MSC binding tended to occur in DNase hypersensitive regions, suggesting that the increased association of MSC is due to binding open, accessible chromatin rather than modifying histones. In addition, MSC binding site sequence recognition was less stringent than the requirements for MyoD binding, which may insure that MSC binding sites are less likely to be disrupted by mutation.

Several muscle diseases, such as the pediatric cancer rhabdomyosarcoma, are the result of improper muscle differentiation. Therefore, it is essential to understand the complex interplay between transcription factors that promote and inhibit differentiation. "This study identifies MSC as having the capacity to widely affect the crucial action that MyoD plays in controlling muscle both in normal development and in disease. The more we understand the way that skeletal muscle cells behave on a fundamental level...the greater the chance we have to make advancements in treating the diseases that affect and involve skeletal muscle," said Kyle L. MacQuarrie.

[MacQuarrie KL, Yao Z, Fong AP, Tapscott SJ](#). 2013. Genome-wide binding of the basic helix-loop-helix myogenic inhibitor myosin has substantial overlap with MyoD: implications for buffering activity. *Skelet Muscle*. Epub ahead of print. Doi:10.1186/2044-5040-3-26.

See also: [Cao Y, Yao Z, Sarkar D, Lawrence M, Sanchez GJ, Parker MH, MacQuarrie KL, Davison J, Morgan MT, Ruzzo WL, Gentleman RC, Tapscott SJ](#). 2010. Genome-wide MyoD binding in skeletal muscle cells: a potential for broad cellular reprogramming. *Dev Cell*. 18:662-74.

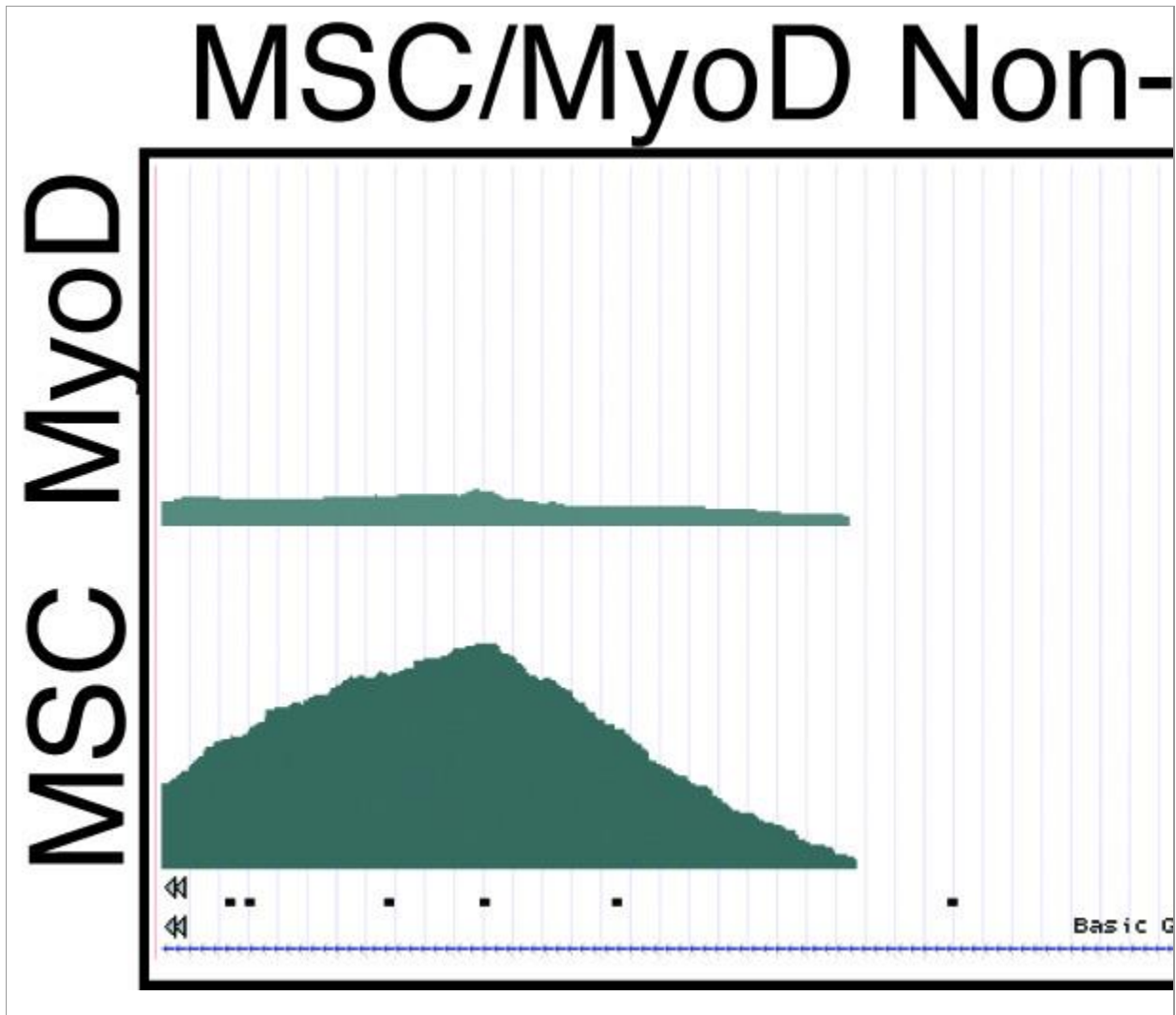


Image courtesy Kyle L. MacQuarrie

Binding pattern of MyoD (top) or musclin (bottom) upstream of a troponin gene (TNNT2), demonstrating a similar but non-identical binding pattern for the two proteins.