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Antagonistic Activities of *Sox2* and *Brachyury* Control the Fate Choice of Neuro-Mesodermal Progenitors

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SUMMARY

The spinal cord and mesodermal tissues of the trunk such as the vertebral column and skeletal musculature derive from neuro-mesodermal progenitors (NMPs). *Sox2*, *Brachyury* (*T*), and *Tbx6* have been correlated with NMP potency and lineage choice; however, their exact role and interaction in these processes have not yet been revealed. Here we present a global analysis of NMPs and their descending lineages performed on purified cells from embryonic day 8.5 wild-type and mutant embryos. We show that *T*, cooperatively with WNT signaling, controls the progenitor state and the switch toward the mesodermal fate. *Sox2* acts antagonistically and promotes neural development. *T* is also involved in remodeling the chromatin for mesodermal development. *Tbx6* reinforces the mesodermal fate choice, represses the progenitor state, and confers paraxial fate commitment. Our findings refine previous models and establish molecular principles underlying mammalian trunk development, comprising NMP maintenance, lineage choice, and mesoderm formation.

INTRODUCTION

The trunk of murine embryos forms by continuous recruitment of cells generated in the primitive streak (PS), node-streak border (NSB), and caudal lateral ectoderm (CLE), located at the caudal end of the embryo, into the neural or mesodermal lineage thereby elongating the body anlage (Wilson et al., 2009). The source of cells giving rise to the spinal cord and mesodermal tissues, comprising the vertebral column, skeletal musculature, ventral body wall, kidneys, gonads, limbs, and others, is a resident progenitor cell type with self-renewing capability, the neuro-mesodermal progenitor (NMP) (Garriock et al., 2015; Gouti et al., 2014; Henrique et al., 2015; Rodrigo Albors and Storey, 2016; Tzouanacou et al., 2009; Wymeersch et al., 2016). NMPs are characterized by co-expression of the stem cell factor and key neural progenitor cell (NPC) regulator Sox2, and of the pan-mesodermal control factor Brachyury (T) (Bergsland et al., 2011; Boyer et al., 2005; Herrmann et al., 1990; Kispert et al., 1995; Wilkinson et al., 1990; Wymeersch et al., 2016). Recent grafting experiments carried out in embryonic day 8.5 (E8.5) embryos showed that the fate of NMP descendants correlates with the relative levels of Sox2 or T protein expression and with their position in the PS/CLE (Wymeersch et al., 2016). This study also confirmed previous reports demonstrating the dependence of mesoderm formation in the trunk on WNT signaling (Jurberg et al., 2014; Martin and Kimelman, 2012; Takada et al., 1994; Tsakiridis et al., 2014). *T* was the first regulator shown to play an essential role in trunk development: *T* knockout embryos show a bulky PS, lack posterior mesoderm, arrest axis elongation, and therefore lack the trunk and tail (Chesley and Dunn, 1936; Herrmann, 1991; Yanagisawa et al., 1981). *T* acts together with *Wnt3a*, *Fgfr1*, and *Fgf4*/*Fgf8* in trunk mesoderm development and is a target of WNT and fibroblast growth factor (FGF) signaling (Chapman and Papaioannou, 1998; Ciruna and Rossant, 2001; Naiche et al., 2011; Yamaguchi et al., 1999). Studies in zebrafish have shown that *T*, by controlling *Wnt3a* and the retinoic acid inhibitor *Cyp26a1*, establishes the mesodermal progenitor niche (Martin and Kimelman, 2010). Work in *Xenopus* demonstrated the importance of the *T* ortholog *Xbra* in neuro-mesodermal stem cell maintenance and in mesoderm formation (Gentsch et al., 2013). Thus, the combined genetic and fate mapping data would suggest that *T* is involved in the maintenance and mesodermal fate choice of NMPs. Recent reports, however, claimed that *Tbx6* in mouse and its functional homolog in zebrafish *Tbx16* suppress *Sox2* and the neural fate, and recruit progenitors into the mesodermal lineage (Bouldin et al., 2015; Takemoto et al., 2011). To resolve these partly conflictive conclusions, we have carried out a broad investigation of the role and interaction of *T*, *Sox2*, and *Tbx6* in NMPs and in fate decisions of NMP descendants during trunk development, based