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The role of transcriptional factor brachyury in the development and repair of nucleus pulposus

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Abstract: Transcription factor Brachyury, a protein containing 435 amino acids, has been widely investigated and reported in notochord differentiation and nucleus pulposus development. The crucial functions and underlying mechanisms by Brachyury are discussed in this paper, which suggests Brachyury can be developed into a potential novel target for the therapy of intervertebral disc degeneration.

Abbreviations

IVD:	Intervertebral disc
NP:	Nucleus pulposus
NC:	Notochordal
iPSC:	Induced pluripotent stem cells
PSM:	Primitive streak mesoderm

Introduction

Current therapeutic modalities for low back pain arising from intervertebral disc (IVD) degeneration mainly target the symptoms alleviation while failing to treat the underlying disease pathology (Tang *et al.*, 2021).

Various studies have attempted to develop early-stage intervention to retard and reverse the IVD degeneration process. Recapitulation of the embryonic patterning process of the IVD may help develop novel biological repair approaches for disc degeneration (Cornejo *et al.*, 2015). The central nucleus pulposus (NP) tissue plays a pivotal role in maintaining the function of IVD. It is the mainly affected structure in IVD degeneration (Rodrigues-Pinto *et al.*, 2014), which demonstrates decreased cellularity, water content and proteoglycans.

Various studies have evidenced that the entire cell subpopulations of the NP are descended from the embryonic notochord (Shapiro and Risbud, 2010). The transcriptional factors playing vital roles in the notochord development have been attempted to rescue the function of degenerated nucleus pulposus cells.

Main Text

Transcription factor Brachyury, a protein of 435 amino acids, binds with the canonical T-domain DNA sequence: TCACACCT. Brachyury regulates posterior mesoderm formation and notochord differentiation by directly activating downstream mesoderm-specific genes (Chen *et al.*, 2020a; Chen *et al.*, 2020b; Xu *et al.*, 2020). The embryonic notochord is considered to be the developmental origin of mature adult NP tissue (Richardson *et al.*, 2017). Brachyury has widely been recognized as the specific marker for the notochordal (NC) cells (Tang *et al.*, 2016). The human notochord and juvenile NP are populated by larger and vacuolated NC cells, which gradually disappear and are replaced by a population of small and round "chondrocyte-like" NP cells after puberty (Risbud *et al.*, 2015). There is a long-held controversy on the ontogeny and heterogeneity of morphologically distinct NC and NP cells. Minogue *et al.* (2010) found NP cells isolated from adult bovine and human discs also expressed Brachyury, the mRNA level expression remained unchanged in the degenerated human nucleus pulposus, which is suggestive of a common ontogeny of the NP and NC cells. Further study by Richardson *et al.* (2017) showed Brachyury protein was expressed in the cells of adult human nucleus pulposus tissue, but significantly lower positivity was demonstrated in mature adult compared to young and significantly lower positivity in severely degenerated tissues compared to non-degenerated. Various convincing evidence suggest that most cells in adult nucleus pulposus tissue differentiate along the

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notochordal lineage, morphological differences of NC and NP cells represent different physiological or pathological stages of aging and degeneration (Risbud *et al.*, 2015). Brachyury, a traditional marker of NC cells, has been considered as a critical phenotypic marker of healthy NP (Risbud *et al.*, 2015) and helps to evidence the homology of NC and NP cells.

Several studies have reported that Brachyury was transfected into degenerated NP cells or human induced pluripotent stem cells (iPSC), aiming to promote these cells to transmit or differentiate into healthy NP cells, which can produce more extracellular matrix and restore the homeostasis of disc microenvironment. Brachyury lent virus transfection promoted and enhanced the differentiation of human iPSC toward NP-like cells *in vitro* (Tang *et al.*, 2018). Tang *et al.* (2019) demonstrated nonviral Brachyury transfection into mildly degenerated human NP cells promoted the phenotype transition into a pro-anabolic and anti-catabolic/inflammatory one, and significantly increased glycosaminoglycan accumulation *in vitro*, which suggests Brachyury has the potential to be developed into an useful target for the treatment of IVD degeneration. Sheyn *et al.* (2019) reported stepwise differentiation strategy of human iPSCs into NC cells. Brachyury-encoding plasmids were nucleofected into primitive streak mesoderm (PSM) cells, which were induced and differentiated from iPSCs, to acquire NC cells. Further testing *in vivo* in the porcine model showed that the acquired NC cells had a protective role on discs from degeneration.

We have found that Brachyury can promote proteoglycan synthesis by nucleus pulposus cells. Whether Brachyury transfection into remaining degenerated nucleus pulposus cells or exogenously sourced cells can facilitate the transition toward a healthy nucleus pulposus phenotype in the harsh degenerated disc microenvironment requires more in-depth investigations.

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