SM04755, a Potential Disease-Modifying Treatment for Tendinopathy, Modulates the Wnt Pathway via Inhibition of CLKs and DYRK1A

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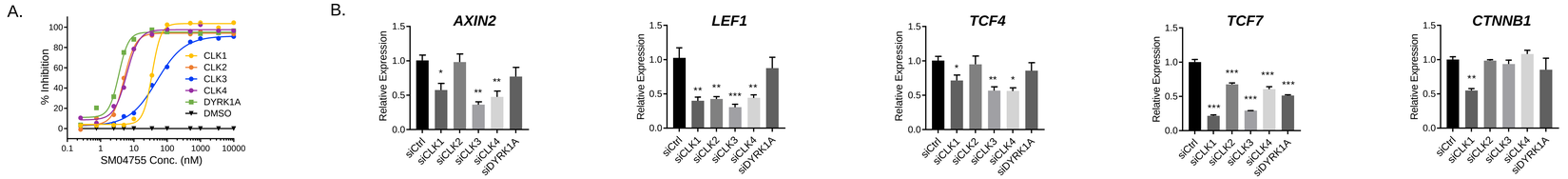
Background

- Tendinopathy is associated with pain, inflammation, tendon degeneration, and failed healing. Despite the high prevalence of tendinopathy, its underlying pathogenesis is not fully understood[1]
- Wnt signaling plays an important role in tendinopathy[2] by modulating inflammation, tenocyte lineage specification, protease production, and tendon homeostasis[3,4]
- SM04755, a novel, topical, small-molecule Wnt pathway inhibitor, has previously been shown to inhibit inflammation, protect tenocytes, and increase tenocyte differentiation in nonclinical models[5]
- The mechanism of action of SM04755 leading to Wnt pathway inhibition, tenocyte differentiation and protection, and anti-inflammatory activity is described

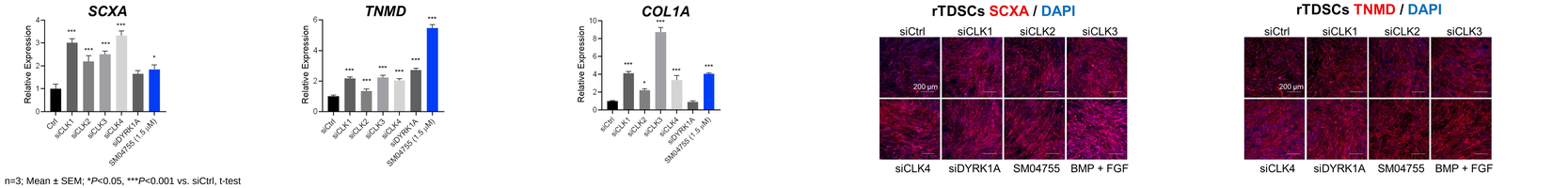
Results

Figure 1. SM04755 was a potent inhibitor of CDC-like kinases (CLKs) and dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A). Inhibition of CLKs and DYRK1A inhibited the Wnt pathway in rTDSCs



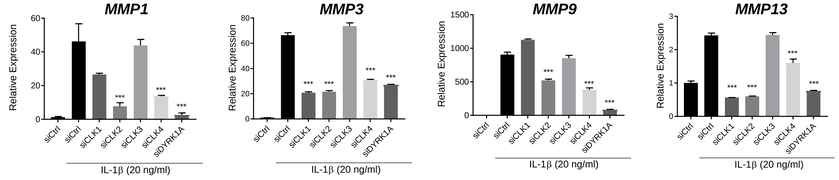
A. Kinase inhibition assay **B.** n=3; Mean ± SEM; **P*<0.05, ***P*<0.01, ****P*<0.01 vs. siCtrl, t-test

Figure 2. Inhibition of CLKs and DYRK1A induced tenocyte differentiation *in vitro*



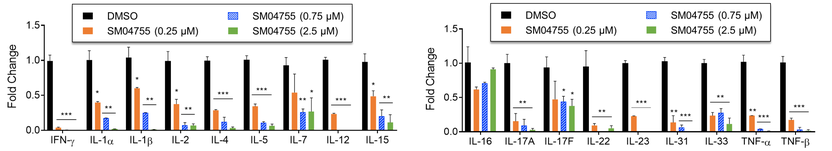
n=3; Mean ± SEM; **P*<0.05, ****P*<0.001 vs. siCtrl, t-test

Figure 3. Inhibition of CLK1, 2, 4, and DYRK1A reduced catabolic protease expression *in vitro*



Rat tenocytes; n=3; Mean ± SEM; ****P*<0.001 vs. siCtrl, one-way ANOVA

Figure 4. SM04755 demonstrated anti-inflammatory effects *in vitro*



PBMCs stimulated with LPS; n=3; Mean ± SEM; **P*<0.05, ***P*<0.01, ****P*<0.001 vs. DMSO

Conclusions

- **SM04755 inhibited intranuclear CLKs and DYRK1A, leading to Wnt pathway inhibition**
- **CLK and DYRK1A inhibition induced tenocyte differentiation and reduced tendon-destroying proteases in tenocytes**
- **SM04755 inhibited inflammatory signaling mediators and cytokine production**
- **SM04755, as a single agent, may potentially benefit symptoms and provide disease modification in tendinopathy**
- **Human tendinopathy trials are planned**

Methods

- A kinome screen (318 kinases) was performed. Kinase inhibition was assessed by Thermo Fisher Z'-LYTE™ and LanthaScreen kinase assays (**Fig. 1A**)
- SM04755 and siRNA knockdown effects on gene expression in rat tendon-derived stem cells (rTDSCs) (**Fig. 1B**) and rat tenocytes (**Fig. 3**) were measured by qRT-PCR using TaqMan® primers. Gene expression was normalized to GAPDH
- SM04755 and siRNA knockdown effects on tenocyte marker expression in rTDSCs were assessed by immunostaining (**Fig. 2**)
- SM04755 effects on cytokine production in PBMCs stimulated with LPS were measured by MSD-based ELISA (**Fig. 4**)

References

1. Scott A, et al. *J Orthop Sports Phys Ther*. 2015.
2. Jelinsky SA, et al. *BMC Musculoskelet Disord*. 2011.
3. Lui PP, et al. *Rheumatol (United Kingdom)*. 2013.
4. Deshmukh V, et al. *Osteoarthr Cartil*. 2018.
5. Deshmukh V, et al. *Arthritis and Rheum*. 2016.

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