A Dynein Motor Attachment Complex Regulates TGFß/Smad3 Signaling

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Abstract:

Our previous results have demonstrated that km23-2 has functions in TGFß signaling that are distinct from those for km23-1. In the current report, we demonstrate that blockade of km23-2 decreased TGFß activation of the human Smad7 promoter Smad7-Luc, an endogenous Smad3-target promoter. Luminescence-based mammalian interaction mapping (LUMIER) analyses showed that TGFß stimulated the interaction of km23-2 preferentially with Smad3, relative to that with Smad2. Size exclusion chromatography experiments revealed that km23-2 and Smad3 were recruited into the same complex after TGFß treatment. Moreover, in the presence of TGFß, but not in the absence, km23-2 was present in early endosomes with the TGFß receptors (TßRs) and Smad3. Collectively, our data indicate that km23-2 is a critical signaling intermediate in a Smad3-dependent TGFß signaling pathway. We also provide evidence of the novel finding that TGFß stimulates the rapid recruitment of the km23-2 dimer to the dynein intermediate chain (DIC) of the dynein complex, whereas a kinase-deficient form of TßRII prevented this interaction. Finally, we demonstrate for the first time that TGFß stimulated not only assembly of the dynein motor attachment complex, but also triggered the tethering of the km23-2-Smad3 cargo to the other dynein components. Thus, our data demonstrate a novel function for km23-2 as a motor receptor to recruit Smad3 to the dynein complex for intracellular transport, thereby mediating Smad3-dependent TGFß signaling.

Key Word:
TGFß, km23, Smad, signaling, receptor, dynein.