**Supplemental Methods**

**RT-qPCR.** RNA was extracted from cultures of primary SMCs with TRIzol reagent (ThermoFisher 15596026) according to manufacturer’s instruction. Reverse transcription (RT) reactions contained 200-500 ng of total RNA. Ten to fifteen percent of the cDNA was subjected to qPCR with the following primer-probe sets from Applied Biosystems: MRTF-A: Mm00461840_m1, Myh11: Mm00443013_m1, and Acta2: Mm00725412_s1. The primer-probe set for 18S rRNA has been described (Klein et al. 2007). The levels of each tested transcript were normalized to 18S rRNA, and changes in RNA abundance were calculated using the ddCT method. The qPCR samples were analyzed as technical duplicates; sample means were calculated for each experiment.

**Immunoblotting.** For tissue immunoblotting, isolated aortas were thawed, chopped into small pieces and sonicated (using a Virtis Virsonic 475 cell disruptor) in ~150 μl lysis buffer (50 mM Tris-HCl pH 8, 250 mM NaCl, 2 mM EDTA, 1% NP-40) containing protease inhibitors (Cell Signaling Technologies 5872S). Lysates were collected by centrifugation (5 min at 4°C, 15,000 x g), and the supernatants were diluted into SDS sample buffer (50 mM Tris pH 6.8, 2% SDS, 10% glycerol, 0.01% Bromophenol blue, and 1% β-mercaptoethanol). For immunoblotting of cell lysates, isolated WT and HGPS SMCs were plated at confluence in 60-mm culture dishes and lysed directly in SDS sample buffer after a 72-h incubation with siRNA or adenovirus as indicated in the figures.

Samples were fractionated on 7.5% SDS polyacrylamide gels and electrophoretically transferred to nitrocellulose. Incubations with primary antibodies were performed overnight at 4°C with rocking in TBST (Tris-buffered saline with 0.1% Tween 20) with 5% milk or 2% BSA. Purchased primary antibodies were directed against: MRTF-A (Protein Tech #21166-1-AP used at a 1:200 dilution); smooth muscle actin (Sigma F3777 used at a 1:1000 dilution), smooth muscle myosin heavy chain (Protein Tech 21404-1-AP used at a 1:300 dilution), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH; Invitrogen MA5-15738 used at a 1:500 dilution). A rabbit antinesprin-2 antibody specific to the calponin homology domain (1:200 dilution) was generously provided by Gregg Gundersen (Columbia University). Some experiments used anti-FAK (BD
Transduction labs 610088 at a 1:300 dilution) or anti-α tubulin (Santa Cruz SC-8035 at a 1:300
dilution) as loading controls.

Incubations with secondary antibodies (ECL anti-mouse IgG HRP: GE healthcare 3143,
1:500 or ECL anti-rabbit IgG HRP: GE healthcare 3144) were performed for 2 hr at room
temperature in the same TBST buffer as the primary antibody. Bound antibodies were visualized
by enhanced chemiluminescence and quantified on a GE ImageQuant LAS4000.