Marked Decrease in Compliance in Myometrium of SmAV-hypomorph Mouse

No organ in the human body is as compliant as the pregnant uterus. Similar to other types of smooth muscles, stretching the uterine smooth muscle (USM) triggers a myogenic contraction.1-3 Few studies have been performed to understand how USM can accommodate the stretch from fetal growth without causing premature contraction (i.e. mechanoadaptation). Smooth muscle archvillin (SmAV) is a newly identified regulator of the ERK pathway,4 that was implicated as an adaptor protein in uterine focal adhesion (FA) signaling.2 We hypothesize that SmAV regulates mechanoadaptation and USM compliance via FA signaling.

SmAV-hypomorph mice were obtained from EJ Luna, UMass Medical School. They have impaired reproduction with smaller litter sizes and far fewer second and third offspring litters (Personal communication, Elizabeth Luna). By using non-pregnant USM from SmAV-hypomorph mice and Bl/6 wild-type mice from which they were derived, we demonstrate that USM of SmAV-hypomorph mice is significantly more stiff (less compliant) than control USM when stretched to 2x slack length in the organ bath. Treatment with 10µM of the Src inhibitor PP2 significantly increases the compliance of USM of wild type mice, but not of SmAV-hypomorph mice. To investigate the relationship between SmAV and USM compliance, screening by anti-phosphotyrosine immunoblotting reveals a significant increase in the densitometry of tyrosine phosphorylated bands at 130kD and 125kD in response to stretch in USM from Bl/6 mice, but not from SmAV-hypomorph mice. PP2 prevents stretch-induced tyrosine phosphorylation. The 130kD and 125kD bands were identified as Cas (a scaffolding protein) and focal adhesion kinase (FAK) by Western blotting with protein-specific antibodies. However, by using a phospho-Y165 Cas antibody, we demonstrate that stretch is able to induce a significant increase in Cas pY-165 phosphorylation both in USM from Bl/6 and SmAV-hypomorph mice. Pretreatment with PP2 markedly suppresses the stretch-induced increase in Cas tyrosine phosphorylation. Significant stretch-induced and Src-dependent phosphorylation of FAK pY-925, a site involved in downstream ERK signaling, but not FAK 397 is observed in USM of wild-type Bl/6 mice. The USM of SmAV-hypomorph mice, in contrast, fails to show stretch-induced FAK tyrosine phosphorylation at either site, consistent with a role for SmAV in the regulation of FA signaling.

Here, we demonstrate that SmAV and Src regulate USM compliance and FA signal transduction in response to stretch. An incomplete understanding of the mechanism of USM mechanoadaptation during pregnancy has hindered the development of effective treatments for preterm labor. Targeting Src kinase and USM compliance may render a novel approach for the development of drugs to prevent preterm labor.