Transgelin functions as a suppressor via inhibition of ARA54-enhanced androgen receptor transactivation and prostate cancer cell growth.

張育嘉

Yang Z;Chang YJ;Miyamoto H;Ni J;Niu Y;Chen Z;Chen YL;Yao JL;di Sant'Agnese PA;Chang C

摘要

Abstract

The androgen receptor (AR) requires coregulators for its optimal function. However, whether AR coregulators further need interacting protein(s) for their proper function remains unclear. Here we describe transgelin as the first ARA54-associated negative modulator for AR. Transgelin suppressed ARA54-enhanced AR function in ARA54-positive, but not in ARA54-negative, cells. Transgelin suppressed AR transactivation via interruption of ARA54 homodimerization and AR-ARA54 heterodimerization, resulting in the cytoplasmic retention of AR and ARA54. Stable transfection of transgelin in LNCaP cells suppressed AR-mediated cell growth and prostate-specific antigen expression, whereas this suppressive effect was abolished by the addition of ARA54-small interfering RNA. Results from tissue surveys showing decreased expression of transgelin in prostate cancer specimens further strengthened the suppressor role of transgelin. Our findings reveal the novel mechanisms of how transgelin functions as a suppressor to inhibit prostate cancer cell growth. They also demonstrate that AR coregulators, like ARA54, might have dual in vivo roles functioning as both a direct coactivator and as an indirect mediator in AR function. The finding that a protein can modulate AR function without direct interaction with AR might provide a new therapeutic approach, with fewer side effects, to battle prostate cancer by targeting AR indirectly.