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## Increased akt signaling resulting from the loss of androgen responsiveness in prostate cancer

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The mechanisms responsible for converting androgen-sensitive (AS) prostate cancer into its androgen-insensitive (AI) variant have not been well understood. Malignant transformation is characterized by the E- to N-cadherin phenotypal conversion, resulting in greater tumor invasiveness and disease progression as major hallmarks of the epithelial-mesenchymal transition (EMT) via increased expression of vimentin, nuclear localization of beta-catenin, as well as, increased production of transcription factors such as Snail, Twist that inhibit E-cadherin. Our results demonstrate that androgens induce the EMT pattern in prostate cell with Snail activation and lead to significant changes in prostate cancer cell migration and altered invasion potential. Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the regulatory enzyme of intracellular cholesterol synthesis and thereby the androgens. Cholesterol was shown to regulate the phosphatidylinositol 3-kinase/Akt pathway activation, as well as the EMT. Silencing of the HMGCR expression by siRNA or by the statins, significantly reduced nuclear translocation of beta-catenin. However, longer silencing of HMGCR in AS cells resulted in elevated p-Akt level or enhanced expression of nuclear beta-catenin. Knockdown of the HMGCR and/or Akt radically inhibited N-cadherin expression in the AI cells, and increased the E-cadherin re-expression. Additionally we have shown extensively abolished EMT markers such as Snail, vimentin as well as inhibition of the prostate cells migration due to decreased metalloproteinases MMP-2, MMP-9 and MMP-13 activities.

These results indicate that silencing of the HMGCAR and/or Akt are critical for the signaling pathway and this process seems to participate in an inhibition of development of the aggressive prostate cancer forms.

### Biography

Joanna Dulińska-Litewka, received her PhD degree in molecular biochemistry from the Jagiellonian University, Medical College, Krakow, Poland in 1998. She has participated in numerous courses and research scholarships in Australia, Germany, Hungary, France, Russia, to name but the few. Her research interests focus on cell and molecular biology based investigations of the expression, characterization and function of nuclear receptors, hormonal regulation, adhesion molecules and signaling pathways molecules in respect to their role and participation in tumorigenesis and cancer progression particularly with regard to prostate and breast cancers. She has published more than 40 papers in reputable journals and has been also serving as a reviewer in several distinguished journals.

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