Cholesterol accumulation in prostate cancer: a classic observation from a modern perspective.

Krycer JR, Brown AJ.
School of Biotechnology and Biomolecular Sciences, The University of New South Wales, Sydney, Australia.

Abstract
Prostate cancer (PCa) is the most common cancer in men in developed countries. Epidemiological studies have associated high blood-cholesterol levels with an increased risk of PCa, whilst cholesterol-lowering drugs (statins) reduce the risk of advanced PCa. Furthermore, normal prostate epithelial cells have an abnormally high cholesterol content, with cholesterol levels increasing further during progression to PCa. In this review, we explore why and how this occurs. Concurrent to this observation, intense efforts have been expended in cardiovascular research to better understand the regulators of cholesterol homeostasis. Here, we apply this knowledge to elucidate the molecular mechanisms driving the accumulation of cholesterol in PCa. For instance, recent evidence from our group and others shows that major signalling players in prostate growth and differentiation, such as androgens and Akt, modulate the key transcriptional regulators of cholesterol homeostasis to enhance cholesterol levels. This includes adjusting central carbon metabolism to sustain greater lipid synthesis. Perturbations in cholesterol homeostasis appear to be maintained even when PCa approaches the advanced, 'castration-resistant' state. Overall, this provides a link between cholesterol accumulation and PCa cell growth. Given there is currently no cure for castration-resistant PCa, could cholesterol metabolism be a novel target for PCa therapy? Overall, this review presents a picture that cholesterol metabolism is important for PCa development: growth-promoting factors stimulate cholesterol accumulation, which in turn presents a possible target for chemotherapy. Consequently, we recommend future investigations, both to better elucidate the mechanisms driving this accumulation and applying it in novel chemotherapeutic strategies.