

Expert's comments:

Obesity, especially when estimated on the basis of body mass index, is associated with a moderately increased risk of PCa, and especially of advanced disease [1]. This association may be explained by various mechanisms, such as endocrine effects of obesity causing changes in androgen and estrogen metabolism and effects on adipokines, insulin, and insulin-like growth factors. Adipose tissue also produces several cytokines, and IL-6 particularly has been found to be involved in PCa growth and progression [2,3]. Most of these studies have been performed on PCa cell lines derived from metastatic disease, and it is not clear whether IL-6 also contributes to the development of cancer [2].

The finding of high local production of IL-6 in periprostatic tissue and the increase in patients with high-grade cancer is intriguing. It may indicate that chronic exposure of the prostate to high concentrations of IL-6 contributes to tumor aggressiveness, but Finley et al do not exclude the possibility that the tumor induces IL-6 production in surrounding tissues.

This study may provide new insights into the role of IL-6 in the development of aggressive PCa [2], but a number of questions still need to be answered. It would be interesting to know what induces the high expression of IL-6 in adipose tissue from patients with aggressive PCa. Although the concentrations of IL-6 in periprostatic tissue are much higher than in plasma, it is not clear whether IL-6 can exert an effect locally by diffusing into the prostate. It seems more likely that IL-6 reaches the prostate through circulation. The contribution of periprostatic adipose tissue to the circulating concentrations of IL-6 is probably small in comparison to other sources.

Other studies have shown elevated serum IL-6 levels in advanced disease, but in the study of Finley et al, the serum concentrations were not related to tumor grade. Thus, the clinical relevance of IL-6 production in periprostatic adipose tissue requires further study. Interestingly, as Finley et al acknowledge, obesity is known to cause increased serum concentrations of IL-6. Increased IL-6 concentrations in the prostate may also result from local

production, which can be induced by infections and inflammation in the prostate [3].

IL-6 may induce PCa progression in several ways: It can contribute to neuroendocrine differentiation, induce intra-prostatic androgen production, and activate the androgen receptor. These mechanisms are thought to contribute to development of hormone-refractory PCa [2]. Furthermore, IL-6 may induce expression of serine peptidase inhibitor, Kazal type 1 (SPINK1) [4], increased tissue expression of which is a prognostic factor for adverse outcome in PCa [5]. Thus, there is increasing evidence for the role of IL-6 in PCa development and progression to therapy-resistant disease.

High IL-6 production is intriguing. Even if the mechanisms that link this finding to aggressive PCa need to be determined, the results of Finley et al provide further impetus for studies of the role of IL-6 in PCa. Elucidation of these results may contribute to development of novel therapies for PCa.

Conflicts of interest: The author has nothing to disclose.

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Re: Effects of Simvastatin, Acetylsalicylic Acid, and Rosiglitazone on Proliferation of Normal and Cancerous Prostate Epithelial Cells at Therapeutic Concentrations

Murtola TJ, Pennanen P, Syväälä H, Bläuer M, Ylikomi T, Tammela TLJ

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Experts' summary:

Murtola et al investigated the treatment of multiple prostate cell lines using acetylsalicylic acid, a commonly used nonsteroidal anti-inflammatory drug (NSAIDs); simvastatin, a common cholesterol-lowering drug; and rosiglitazone, an antidiabetic drug with anti-inflammatory properties. All compounds were used at concentrations representative of typical plasma concentrations as well as at

concentrations slightly higher than physiologic. Using three established primary epithelial cell lines, two immortalized normal prostate lines, and two cell lines representative of advanced stage prostate cancer (PCa), the authors found that acetylsalicylic acid and simvastatin had the greatest effect on inhibiting cell growth, whereas rosiglitazone had little to no effect. More specifically, acetylsalicylic acid and simvastatin were most effective in the primary and immortalized cells and not in the cancerous lines. Therefore, the authors concluded that in vitro, statins and acetylsalicylic acid are most effective for treatment of early stage PCa but have no effect on advanced stage disease.

Experts' comments:

The use of statins as prevention or treatment of PCa raises as many questions as it does hopes [1]. As HMG-CoA reductase

inhibitors, statins quickly and effectively lower serum cholesterol levels, with low doses and minimal side effects. Initially thought to be useful as chemoprevention, recent epidemiologic data showed that statins actually do not prevent the occurrence of PCa but instead appear to slow the advancement of the disease [2]. Thus, such studies reveal the opportunity to use statins more as a novel therapeutic for PCa rather than as chemoprevention.

How statins prevent the advancement of PCa remains unclear. Some studies suggest that lowering cholesterol is the primary target [3], whereas others believe the answer lies within the anti-inflammatory properties of the drug [4]. The truth probably lies in the middle: Other preclinical studies looking at statin–NSAID therapy show a greater response with the drugs in combination than with either drug alone [5]. In a similar manner, the authors show that anti-inflammatory–statin therapy was an effective treatment in primary epithelial cells, as proven by rosiglitazone–simvastatin combination treatment. No study prior to this one, however, has shown growth inhibition of cancer cells using statins and NSAIDs at physiologic concentrations. Therefore, although older men are faced with a multitude of increased health risks, urologists in the near future may have a new reason to say, “Take your statin.”

Conflicts of interest: The authors have nothing to disclose.

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