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HEPCIDIN, ANAEMIA, AND PROSTATE CANCER

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Sir,

Anaemia is a common haematological abnormality in patients with cancer. The anaemia of chronic disease or inflammation is thought to be a result of induction of the iron-regulatory hormone, hepcidin, by inflammatory cytokines, especially interleukin 6 (IL-6) [1]. Elevation of hepcidin by IL-6 leads to hypoferraemia associated with anaemia and iron-restricted erythropoiesis [2]. A recent study showed that patients with certain early-stage malignancies are less prone to developing anaemia of chronic disease [3]. Among more than 1400 men with prostate cancer, the odds of developing anaemia before diagnosis were not increased. We hypothesized that the paucity of significant anaemia during the early stages of prostate cancer may be due to potentially balanced effects of hepcidin-regulating cytokines produced by prostate cancer cells. Like IL-6, growth differentiation factor 15 (GDF15), also a cytokine, is overexpressed in prostate cancer tissues [4,5]. However, unlike IL-6, GDF15 suppresses hepcidin expression [6]. Hepcidin, IL-6 and GDF15, as well as iron and haematological variables were therefore examined to determine the potential role of iron-restricted anaemia in men with prostate cancer.

In all, 29 men with prostate cancer were recruited for this preliminary study and grouped according to the presence or absence of metastatic bone disease. All studies were conducted at the National Institutes of Health (NIH) and were approved by both the Office of Human Subjects Research and the Institutional Review Board. Mild anaemia (defined here as a haemoglobin [Hb] level of 10.0–13.7 g/dL) was detected in >80% of men in both groups (Fig. 1). As expected, Hb levels were lower in men with metastatic bone disease, with a mean (SD) Hb of 11.6 (1.4) g/dL ($P = 0.009$) and haematocrit (Hct) of 36.5 (4.1)% ($P = 0.025$), than in men without metastasis, with a mean (SD) Hb of 12.8 (0.8) g/dL and Hct of 39.4 (2.1)%. None of the 29 men had received erythropoietin or transfused blood, and only one had received iron supplements within the 6 weeks prior to the study. The iron parameters were within the normal range in >80% of the men.

ELISA-based assay systems were used to examine the serum levels of hepcidin, GDF15 and IL-6 [6, 7]. As shown in the attached Figure 1A, 23 of 29 men studied had measurable hepcidin within the assay's normal range (10–298 ng/mL) [7]. Five men had hepcidin levels at or near the lower limit of the assay (5.0 ng/mL). Serum hepcidin level increased beyond the normal range only in one man. In the absence of bone metastasis, hepcidin levels clustered in the low normal range, with a mean value of 42 ng/mL. Even with bone metastasis, over half of the men maintained hepcidin levels of <100 ng/mL, but values were more broadly distributed within the normal range. Statistical analyses showed that the mean (SD) hepcidin level was significantly increased, at 121 (111) ng/mL ($P = 0.028$) in men with

bone metastasis compared with men with no metastasis, at 42.0 (64.2) ng/mL. Further comparison showed that IL-6 levels increased in men with bone metastasis (Fig. 1B), while GDF15 levels increased in both groups. However, increases in GDF15 were more robust and consistent in the men with metastatic disease (Fig. 1C).

These data support the notion that hepcidin regulation, and its contribution to subsequent development of anaemia, is complex in men with prostate cancer. In addition to IL-6, serum GDF15 may play a role in hepcidin regulation. Increased serum GDF15 is associated with disease progression in men with prostate cancer, and expression of GDF15 is significantly higher in cancerous prostatic tissue than in normal tissue [4, 5]. Larger studies are needed to determine if the high level of GDF15 combined with mild elevation of serum IL-6 have balanced effects upon serum hepcidin levels in men with prostate cancer.

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FIG. 1.

Hepcidin, IL-6, and GDF15 levels in men with prostate cancer with or with no bone metastasis. Serum concentrations of (A) hepcidin, (B) IL-6, and (C) GDF15 from men with prostate cancer, without (–, 14 men) or with (+, 15 men) bone metastasis. Bars denote mean values; grey areas denote normal range determined from healthy male donors; asterisks denote statistical significance (Student's *t*-test $P < 0.05$).