Androgen independent (AI) prostate cancer cells, which often overexpress the androgen receptor (AR), have developed mechanisms to bypass the negative effects of androgen deprivation therapy (ADT) and can maintain AR signaling in the absence of hormone. In normal prostate cancer (PCa) cells, ADT is detrimental to the cell and induces apoptosis. These cells depend on the presence of DHT (dihydrotestosterone) for activation of AR signaling. AI PCa cells commandeer the use of various cofactors and transcription factors to enhance AR signaling in the absence of androgen in order to evade ADT induced inhibition of AR. AI PCa cells can also use these supplementary proteins and transcription factors as coactivators of AR signaling to increase the sensitivity of AR to DHT. Some antioxidants have been shown to enhance AR signaling in prostate cancer cells. Here we investigate the role of the antioxidant transcription factor Nrf1 (NF-E2 related factor 1) in regulating the expression and activity of AR in AI PCa cells. In a panel of prostate cancer cell lines representing non-tumorigenic to androgen independent prostate cancer cells, we found Nrf1 to be more highly expressed in the androgen independent prostate cancer cell line, C42B. Using nuclear protein from control, charcoal stripped FBS (CSFBS), and 1nM and 10nM DHT treated LNCaP (androgen dependent and tumorigenic) and C42B cells, westerns showed that the inactive 120 kD isoform of Nrf1 was detected under all treatment conditions. The active p65 isoform of Nrf1 was only found in C42B cells and its levels changed in an androgen responsive manner. This suggests that Nrf1 may be bound to the nuclear envelope through its N-terminal domain in both LNCaP and C42B cells but is only activated and cleaved into its active p65 isoform in C42B cells. In comparison to CSFBS treatment, LNCaP cells showed dose dependent increases in AR expression in response to DHT treatment in westerns, but in C42B cells, AR protein expression was restored to basal (untreated) levels at a greatly reduced concentration of DHT (1nM). Nrf1 siRNA resulted in decreases in AR expression and also reduced expression of AR responsive genes. In PSA luciferase assays, the overexpression of Nrf1 increased PSA Luc activity whereas Nrf1 siRNA decreased PSA Luc activity in C42B cells. This effect was more clearly seen when DHT concentrations varied. The response of AR to Nrf1 siRNA or expression vector in control and DHT treated C42B cells in RT-PCR, westerns, and luciferase assays suggests that Nrf1 may be a coactivator of AR expression and activity in androgen independent PCa cells. The ability of AI PCa cells to enact this mechanism in an androgen responsive manner may have significant implications on the efficacy of ADT and antiandrogen treatment in AI PCa cells. The targeting of this mechanism in prostate cancer patients with AI PCa may increase the efficacy of ADT and antiandrogen therapy in these patients.