Folate Deprivation/Antagonist Therapy for Early Stage Prostate Cancer

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Recent research by Bistulfi and colleagues at Roswell Park raises the intriguing possibility that institution of mild folate deficiency, and/or treatment with low-dose methotrexate (a folate antagonist), might have potential in the management of early-stage prostate cancer.[1]

This research was conducted with transgenic mice which spontaneously develop prostate cancer at maturity because they are bioengineered to express oncogenic viral proteins in their prostates when their testosterone rises (so-called TRAMP mice). These researchers observed that, if they fed these mice a diet mildly deficient in folate (.3 mg/kg diet), development of their cancers was substantially retarded, relative to mice fed a normal diet (2 mg/kg diet). Yet supplementation with folate in this model (10 X normal diet) did not make the cancers grow faster than in the normally fed mice - in fact, there was a non-significant trend for their cancers to be of a lower grade. The most straightforward interpretation of these findings is that folate deficiency impaired the efficiency of cell replication by impeding folate-catalyzed synthesis of thymidine, required for DNA synthesis – but that the folate content of the normal diet was sufficient to optimize thymidine availability.

The authors predicted this effect, because their previous work had established that the prostate – and early prostate cancers arising from it – have an anomalously high requirement for folate.[2] This appears to reflect the fact that the prostate makes large amount of polyamines, prominent constituents of seminal fluid. Polyamine synthesis employs S-adenosylmethionine as a substrate, and this in turn puts a stress on the folate pool in prostate cells; this pool is substantially tied up as 5-methylfolate to support the continuing methionine synthesis required to sustain polyamine production. Inhibition of polyamine synthesis in prostate cells lines, whether transformed or not, markedly decreased the concentration of folate required to support a maximal growth rate.[2]

These findings may seem hard to square with the fact that treatment with the folate antagonist methotrexate hasn't been found useful in several previous clinical trials with advanced prostate cancer patients[3-6] (excepting a study in which methotrexate was a component of an anti-angiogenic regimen with metronomic cyclophosphamide[7]). But Bistulfi and colleagues propose a logical explanation for this. The rapid polyamine synthesis in prostate tissue is driven by testosterone activity.[8-10] Yet chemotherapy trials in prostate cancer are typically done in patients with advanced cancer who are already receiving androgen antagonist therapy. Such therapy would be expected to suppress polyamine synthesis in the cancer, thereby lowering the cancer's requirement for folate. So patients with early-stage prostate cancer – before androgen deprivation has been implemented – would be expected to be more responsive to folate antagonism/deprivation than those with more advanced, pre-treated cancers.

Another seeming difficulty with this thesis is that low folate status has not been associated with a notably reduced prostate cancer risk in human epidemiology; indeed, some case-control studies observe an *inverse* association between habitual folate intake and risk for prostate cancer or advanced prostate cancer, and a recent meta-analysis of such studies finds a non-significant trend toward reduced risk at

higher intakes.[11-15] This phenomenon likely reflects an antimutagenic effect of adequate folate nutrition. The impairment of thymidine availability associated with folate deficiency should not only slow cellular replication, but also increase risk for mutation and genetic lability – as Bistulfi and colleagues have demonstrated with prostate cancer cell lines.[16] These findings are less germane to the TRAMP model because no further mutational events are required for cancer induction in these mice. Hence, in humans, low folate status would be expected to have countervailing effects on prostate cancer induction – increasing risk for mutations that induce transformation, while concurrently retarding proliferation of initiated cells.

However, recent meta-analysese of placebo-controlled clinical trials of folate supplementation suggests that initiation of such supplementation, at least in the short-run, may increase risk for emergence of new prostate cancer by about 20%[17, 18] - possibly because this supplementation optimizes the proliferation of small occult lesions. In other recent studies, the proliferation rate of Gleason 7 prostate cancer cells in prostates removed surgically was found to correlate positively with serum folate levels, and the rate of increase in PSA levels for men with localized prostate cancer practicing "watchful waiting" tended to be higher in those with higher serum folate.[19, 20] *In vitro*, the rate of growth of two of three prostate cancer cell lines was found to be higher at 100 nM folate (high physiological) than at 20 nM (average physiological); as might be expected, the growth rate of these cell lines was lowest at 4 nM, a level associated with deficiency.[21]

The discovery that early, yet-untreated prostate cancers have an anomalously high requirement for folate to sustain optimal proliferation raises the intriguing prospect that a low-folate diet, and/or low-dose methotrexate therapy, may have clinical potential in this setting. In particular, it might be fruitful to determine whether several months of folate deprivation/antagonism, commencing after local extirpation of the prostate cancer, might lessen risk for subsequent recurrence.

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