Tumor Compensation Associated with Gene Therapy

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Antisense oligonucleotides (oligos) have been employed against in vivo and in vitro cancer models. While most oligos target growth factors or their receptors, others are directed against inhibitors of apoptosis and mediators of androgen activity. Some (produced by Onco negex Pharmaceuticals) have reached clinical trials for the treatment of prostate cancer (OGX-011), while others remain in preclinical development (OGX-225). Often administered in combination with traditional chemotherapy, these oligos target bcl-2, clusterin (OGX-011 in Phase II testing), heat shock protein 27 (OGX-427) or insulin growth factor binding proteins (OGX-225) [1]. Many represent efforts to restore tumor apoptosis by eliminating apoptosis inhibitors bcl-2 [2-4], or clusterin (OGX-11) associated with treatment resistance. Genta has also conducted a phase 3 test using oligos (Genasense; oblimersen) directed against bcl-2 for treating melanoma, chronic lymphocytic leukemia and various solid tumors [5].

Gene therapy has similar limitations, and while effective protocols require either translational suppression (with oligos) or replacement (of inactivated, mutated or deleted suppressor genes like PTEN) technology [6], both tumor and normal cells still express mostly the same genes. Targets for gene therapy are found in many pathways and it is likely that hundreds (or thousands) of genes are involved in malignant transformation. Although tumors can express an overall altered pattern of gene expression, the levels of many growth regulatory genes are similar to normal cells. Resistance develops because the biochemical pathways involved are complex and highly regulated by stimulatory and inhibitory factors, many altered by therapy. Tumors are essentially heterogeneous masses of rapidly growing and selectively adapted cells whose sole purpose is to survive and replicate. While doing so, those bearing mutations may adapt to evade therapeutic interventions are clonally selected. The best example is the emergence of hormone insensitive prostate cancer cells following androgen deprivation therapy, resulting in the increased expression of the autocrine loop consisting of transforming growth factor-alpha (TGF-α) and its binding site the epidermal growth factor receptor (EGFR). In 1994, these were the first targets suggested applicable for treatment of prostate cancer employing antisense oligos [7]. Just as bacteria and viruses mutate to evade antibiotic and antiviral agents, tumor cells are under similar selective pressure to evade therapy. Although newly developed forms of gene therapy provide specific ways to inhibit uncontrolled growth or promote (re-establish) apoptosis, the unintended consequences of intervention are poorly understood, and some may compensate for the intended effect. Antisense oligos are specifically directed through complementary base pairing to inhibit mRNA translation of genes; however, we find there are also non-specific effects on genes not targeted, including many from diverse regulatory pathways.

Our research evaluates the mechanisms and pathways by which tumors alter their dependence upon single gene influences by relying upon others through compensation [8]. If such therapy is to be successful, it is important to examine mechanisms by which tumors can evade this therapy through compensation. For gene therapy to ultimately be successful it must be made more specific or mechanisms of compensation identified and suppressed.

Acknowledgments

The Cellular Biology laboratory at the Hektoen Institute is supported, in part, by the Blum Kovier Foundation, the Cancer Federation, Safeway/Dominicks Campaign for Breast Cancer Awareness, Lawn Manor Beth Jacob Hebrew Congregation, the Max Goldenberg Foundation, the Sternfield Family Foundation, and the Herbert C. Wenske Foundation.

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Received October 29, 2012; Accepted November 02, 2012; Published November 04, 2012


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