Journal of Genetic Syndromes & Gene Therapy

Rubenstein, J Genet Syndr Gene Ther 2012, 3:4
DOI: 10.4172/2157-7412.1000e117

Editorial Open Access

Tumor Compensation Associated with Gene Therapy

Marvin Rubenstein[1-4]*, Courtney M P Hollowell[2] and Patrick Guinan[1,2,4,5]

[1]Division of Cellular Biology, Hektoen Institute for Medical Research, USA
[2]Division of Urology, Stroger Hospital of Cook County, USA
[3]Department of Biochemistry, Rush University Medical Center, USA
[4]Department of Urology, Rush University Medical Center, USA
[5]Department of Urology, University of Illinois at Chicago, Chicago, USA

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 Oncogenex 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 able 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 Kovler Foundation, the Cancer Federation, Safeway/Dominicks Campaign for Breast Cancer Awareness, Lawn Manor Beth Jacob Hebrew Congregation, the Max Goldenberg Foundation, the Sternfeld Family Foundation, and the Herbert C. Wenske Foundation.

References

1. Eder IE, Culig Z, Ramoner R, Thurnher M, Putz T, et al. (2000) Inhibition of LncaP prostate cancer cells by means of androgen receptor antisense oligonucleotides. Cancer Gene Ther 7: 997-1007.
2. Mu Z, Hachem P, Pollack A (2005) Antisense Bcl-2 sensitizes prostate cancer cells to radiation. Prostate 65: 331-340.
3. Yip KW, Mocanu JD, Au PY, Sleep GT, Huang D, et al. (2005) Combination bcl-2 antisense and radiation therapy for nasopharyngeal cancer. Clin Cancer Res 11: 8131-8144.
4. Yamanaka K, Miyake H, Zangemeister-wittke U, Jansen B, Gleave M (2004) Novel bispecific antisense oligonucleotides inhibiting both Bcl-2 and Bcl-xL expression induce apoptosis and enhance chemosensitivity in human androgen-independent prostate cancer cells. Proc Amer Assoc Cancer Res 45.
5. Kling J (2010) Safety signal dampens reception for mipomersen antisense. Nat Biotechnol 28: 295-297.
6. Huang H, Cheville JC, Pan Y, Roche PC, Schmidt LJ, et al. (2001) PTEN induces chemosensitivity in PTEN-mutated prostate cancer cells by suppression of Bcl-2 expression. J Biol Chem 276: 38830-38836.
7. Rubenstein M, Dunea G, Guinan P (1994) Growth factor deprivation therapy utilizing antisense oligonucleotides. Drug News and Perspectives 7: 517-524.
8. Rubenstein M, Hollowell CMP, Guinan P (2011) Inhibition of bcl-2 by antisense oligonucleotides is followed by a compensatory suppression of caspase-3 in LNCaP cells. European Journal of Clinical and Medical Oncology 3: 1-6.

***Corresponding author:** Dr. Marvin Rubenstein, Division of Cellular Biology, Hektoen Institute for Medical Research, 2240 West Ogden Avenue, 2nd floor, Chicago, IL 60612, USA, Tel: 312-864-4621; Fax: 312-768-6010; E-mail: DrMarv@Prodigy.net

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

Citation: Rubenstein M, Hollowell CMP, Guinan P (2012) Tumor Compensation Associated with Gene Therapy. J Genet Syndr Gene Ther 3:e117. doi:10.4172/2157-7412.1000e117