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Redifferentiation Therapy in Thyroid Cancer

Jin-Woo Park, M.D.

Department of Surgery, Chungbuk National University College of Medicine

Differentiated thyroid cancer of follicular cell origin (DTC) is a fascinating tumor because of its varying aggressiveness. Luckily most patients with these cancers, despite regional metastasis, can be cured by surgical resection, radioiodine ablation and thyrotropin (TSH) suppression therapy. Unfortunately some patients with well differentiated thyroid cancer that fail to respond to conventional treatment and also patients with poorly differentiated thyroid cancers or anaplastic thyroid cancers are not successfully treated by this combined therapy. These tumors unfortunately may grow rapidly, invade adjacent structures and spread to other parts of the body. During the dedifferentiation process, these carcinomas lose thyroid specific gene expressions including the ability to take up and organify radioiodine and to make thyroglobulin (Tg). The methods used to treat patients with DTC are therefore usually not effective in these patients. These tumors also usually fail to respond to alternative treatment with external radiation or systemic cancer chemotherapy. We therefore need to develop new treatments for these unfortunate patients.

Recent advances in molecular and cellular biology make it possible to develop new therapeutic approaches to thyroid cancer. Genes related with thyroid specific functions are also promising targets for cancer therapy. Redifferentiation therapy targets thyroid specific genes in order to restore thyroid specific differentiated function and thus to make these tumors respond to conventional therapy. Redifferentiating agents and gene therapy using thyroid specific genes have been studied for this purpose. Most of therapeutic approaches described here have been established effects *in vitro* but have not yet been used clinically. Careful clinical trials and analyses should be performed. **(Korean J Endocrine Surg 2002;2:83-89)**

Corresponding Author: Jin-Woo Park, Department of Surgery, Chungbuk National University College of Medicine, 62 Gae sin-dong, Heungdeok-gu, Chungju 361-763, Korea. Tel: 043-269-6037, Fax: 043-266-6037, E-mail: jwpark@med.chungbuk.ac.kr

Re-differentiating Agents

Thyroid cancers of follicular cell origin (papillary and follicular cancers) are usually well differentiated and behave in a non-aggressive manner. However, some lose differentiated functions (dedifferentiation) and behave more aggressively. These cancers are or become refractor Re-differentiating agentsy to thyroid specific therapies that are based on differentiated thyroid function such as radioiodine therapy and TSH suppressive therapy. Restoring differentiated functions in these tumors may both slow tumor growth and also resensitize these thyroid cancers to thyroid specific therapy such as treatment with radioactive iodine. Redifferentiating therapies are tissue specific and generally less toxic than nonspecific chemotherapy. Several redifferentiating agents have been reported to be effective in human thyroid cancers including: (1) retinoids, (2) aromatic fatty acids, (3) peroxisome proliferator-activated receptor gamma (PPARγ) agonists, and (*4*) histone deacetylase inhibitors.

1) Retinoids

Retinoids has been shown to modulate cell growth and differentiation by binding to their receptors.(*1*) The mechanism of action of retinods is not completely understood. There are 2 classes of receptors: retinoic acid receptor (RAR) and retinoid X receptor (RXR). Each class has 3 subtypes, i.e. α, β and γ. Although RAR and RXR function as either homodimers or heterodimers, RAR-RXR heterodimers and RXR-RXR homodimers are predominant. To activate transcriptional activity, RAR-RXR heterodimers bind to RA response element (RARE) and RXR homodimers bind retinoid X response element (RXRE) (Fig. 1). (*1,2*) RXRs also heterodimerize with the vitamin D receptor (VDR), thyroid hormone receptor (T3R), and peroxisome proliferator-activated receptors (PPAR).(*3*)

There are several natural retinoids/ligands such as alltrans-retinoic acid (*all-trans-RA*), *13-cis*-RA, and *9-cis*-RA. *Alltrans*RA binds only with RAR but 9-cis-RA binds with both RAR and RXR. *13-cis*-RA converts to *all-trans*-RA *in vivo*. There are also

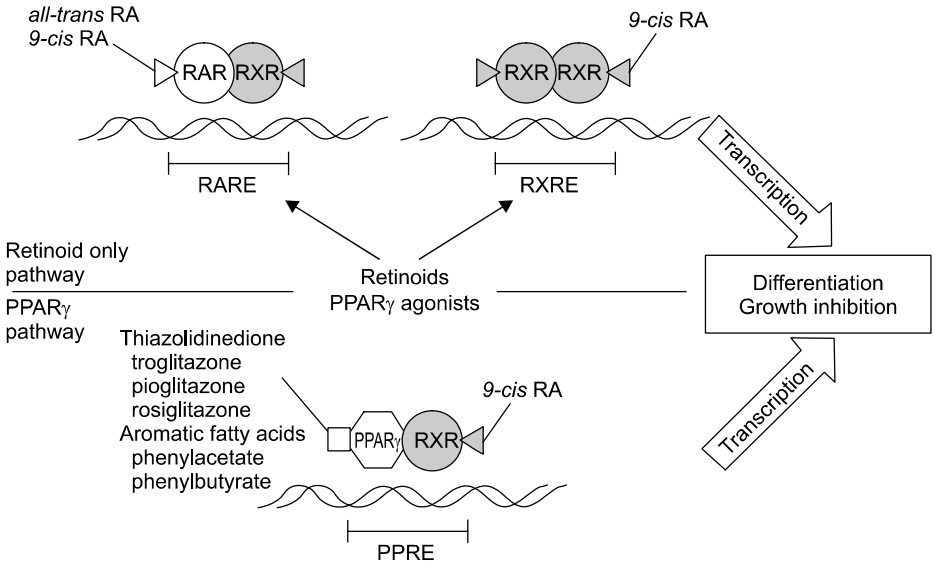

Fig. 1. Basic mechanisms of action of retinoids and peroxisome proliferator-activated receptor gamma (PPARγ). The retinoid receptors are activated by specific ligands: retinoic acid receptor (RAR) by *all-trans* retinoic acid (*all-trans* RA) or *9-cis* retinoic acid (9-cis RA); retinoid X receptor (RXR) by 9-cis RA. The PPARγ is activated by specific ligands such as thiozolidinedione (TZD) derivatives or aromatic fatty acids. Activated receptors bind with each other and form homo- or heterodimers. These in turn bind to specific response elements to promote the transcription of target genes: retinoic acid response element (RARE), retinoid X response element (RXRE), and PPAR response element (PPRE). The transcription of these genes then induces growth inhibition and redifferentiation.

synthetic ligands such as LGD1550 (RAR α/β/γ agonist), tazarotene (RARβ/γ agonist), AM80 (RAR α agonist), and LGD1069 (RXR agonist).

The antiproliferative and redifferentiating effects of retinoids have been demonstrated in many human cancers including thyroid cancer.(*4,5*) Retinoic acid (RA) induces cell cycle arrest in the G0/1 phase with a reduced level of cyclin D1 and CDK-2 mRNA and protein which leads to reduced phosphorylation of the retinoblastoma protein.(*6*) RA treatment increased mRNA for the sodium/iodide symporter (NIS) and radioactive iodine uptake in vitro in human thyroid cancer cells.(*7-9*) In clinical trials, about 40% of patients treated with RA have had increased radioiodine uptake.(*10*)

Although these effects are generally reversible and usually do not result in a dramatic clinical response, some patients are helped by this treatment and combined treatment with other drugs may improve the effect of this therapy.

2) Aromatic fatty acids: phenylacetate, phenylbutyrate

There is increasing evidence that aromatic fatty acids such as phenylacetate and phenylbutyrate inhibit tumor growth and induce redifferentiation *in vitro, in vivo,* and also in patients in some clinical trials.(*11-14*) Aromatic fatty acids act through multiple mechanisms. It can block the tumor cell access to free glutamine and also block the isoprenylation of *ras* family proteins.(*15*) Histone deacetylase inhibition and PPARγ activation are other suggested mechanisms of action.(*16-18*)

Phenylacetate is a metabolite of phenylalanine. It accumulates in phenylketoneuria and is associated with brain damage. It has been used to treat children who have urea cycle disorders. Phenylbutyrate metabolizes to phenylacetate in humans. Phenylacetate causes differentiation and apoptosis in human cancer cell lines at concentrations that have been safely used in humans. Phenylbutyrate seems to be more potent in inducing apoptosis than phenylacetate.(*19*) Treatment with aromatic fatty acids also increases the sensitivity to chemotherapy when it is combined with chemotherapeutic drugs.(*20-22*)

Kebebew et al reported that phenylacetate induced cytostasis in the G0/1 cell phase and increased radioiodine uptake in thyroid carcinoma cell lines.(*23*) Phenylacetate also decreased the growth response to TSH, inhibited thyroglobulin secretion, and the secretion of VEGF (vascular endothelial growth factor) in the thyroid cancer cell lines.(*23*)

Differentiating agents can be synergistic or additive in combination with other differentiating agents that act by different mechanisms. Thus the combination of retinoic acid and phe-

nylacetate had a synergistic antiproliferative effect in follicular thyroid cancer cell lines.(*24*) Phenylbutyrate also seems to induce more apoptosis than phenylacetate at the same concentration in the thyroid cancer cell lines.

3) PPARγ agonist

PPAR belongs to the nuclear hormone receptor superfamily implicated in inhibition of cell proliferation and induction of cell redifferentiation.(*25*) PPAR has three isoforms, -α, -δ, -γ. They are ligand dependent transcription factors that must form heterodimers with the RXRα receptor in order to bind to their response elements (PPRE) and activate transcription (Fig. 1).(*26*)

Among numerous PPARγ agonists, thiazolidinedione (TZD) derivative anti-diabetic drugs such as troglitazone, pioglitazone, and rosiglitazone are newly discovered potent PPARg agonists.(*27,28*) Recent investigations document that TZD derivatives are not only insulin sensitizers but also inhibit proliferation of human breast, prostate, bladder, colon, lung and gastric cancer cells *in vitro* and/or *in vivo*.(*29-34*)

In thyroid carcinogenesis, PPARγ appears to play an important role especially in follicular thyroid cancer. A chromosomal translocation creating a fusion protein of PAX8-PPARγ1 was found in five of eight follicular thyroid carcinomas, but not in follicular thyroid adenomas or papillary thyroid carcinomas and this abnormal fusion protein is a dominant negative suppressor of wild-type PPARγ activity.(*35*)

Ohta et al reported antiproliferative effects *in vitro* and growth inhibition *in vivo* of troglitazone in papillary thyroid cancer cell lines.(*36*) Our investigations show that human thyroid cancer cell lines express PPARγ variably; chromosomal translocations involving PPARγ are, however, uncommon. Troglitazone induced antiproliferation in papillary, follicular, Hurthle cell, and anaplastic thyroid cancer cell lines. Its action can be explained in part by cell cycle arrest in the G0/1 phase and apoptotic cell death. Troglitazone also down-regulated CD97, a thyroid dedifferentiation marker, in thyroid cancer cell lines.(*37*) Treatment with PPARγ agonists might become a useful new medical therapy for patients who have poorly differentiated thyroid cancers and differentiated thyroid cancers that fail to respond to convetional therapy by inducing growth inhibition and redifferentiation.

4) Histone deacetylase inhibitor

Histone acetylation and deacetylation can modulate chromatin structure and regulate gene expression relating to DNA replication, transcription, differentiation, and apoptosis.(*38*) Reversible acetylation of e-amino groups of lysine residues in the N-terminal of histone is controlled by histone acetyltransferases

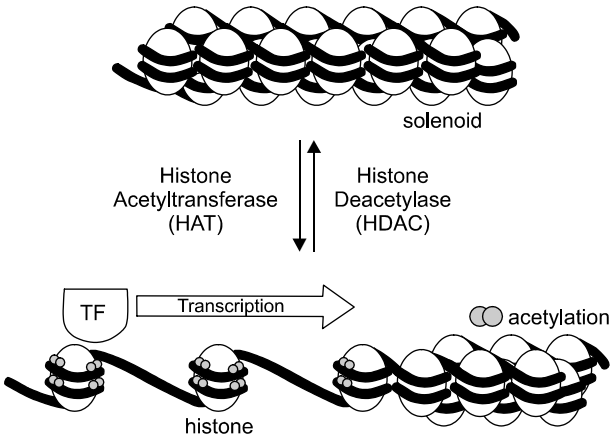

Fig. 2. Reversible acetylation of histones by histone acetyltransferases (HAT) and histone deacetylases (HDAC). Acetylation status affects transcriptional activity of specific genes via a transcriptional factor (TF).

(HATs) and histone deacetylases (HDACs) (Fig. 2). HATs lead to the relaxation of chromatin structure and transcriptional activation, whereas HDACs lead to the chromatin condensation and transcriptional repression of target genes.(*39*) There is increasing evidence that abnormalities in histone acetylation can be associated with tumor development.(*40*)

HDAC inhibitors such as depsipeptide (FR901228), trichostatin A, and suberoylanilide hydroxamic acid (SAHA) are promising new anticancer agents. HDAC inhibitors induce hyperacetylation of chromatin and activate genes that are related with differentiation and apoptosis in cancer cells.(*41,42*) Depsipeptide (FR901228) is currently in phase I clinical studies and the results of treatments are promising.(*43*)

In thyroid cancer cells, HDAC inhibitors inhibit cell proliferation by inducing apoptosis through the activation of the caspase cascade and cell cycle arrest at G1 and G2/M via a reduction in cdk2- and cdk1-associated kinase activities.(*44*) In addition to the antiproliferative effects, HDAC inhibitors can modulate expression of several genes. Thyroid specific genes can be transcriptional targets controlled by acetylation status of histones. In particular, Kitazona et al reported that depsipeptide markedly increased mRNA level of sodium/iodide symporter (NIS) and resultant radioiodine uptake in low concentrations.(*45*) Zarnegar et al demonstrated NIS expression in different thyroid diseases.(*46*) They also demonstrated that trichostatin A dramatically increases NIS expression and resltant radioiodine uptake in low concentrations. Trichostatin A also inhibits cell proliferation by inducing apoptosis and cell cycle arrest at G2/M phase in a dose-dependent manner.(*46*) Methylation is another mechanism of

transcriptional repression of certain genes. Combination of these inhibitors might have synergistic effects because these two epigenetic processes are closely linked.(*47*)

Gene Therapy

Cancer gene therapy is the transfer of nucleic acids that can replace defective genes or introduce suicide or immune modulator genes. Recently, there have been considerable technical advances in terms of gene transfection efficiency and tissue specificity. Gene therapy for cancer has moved from the success in laboratory animals to clinical trials. Several genes have been considered as candidates for gene therapy in patients with thyroid cancer. Differentiation related genes such as p53, TTF-1, PAX-8, and sodium/iodide symporter (NIS) genes were introduced to retard cancer cell growth or induce redifferentiation. Recently thyroid specific promoters and HDAC inhibitors have been used to increase transcriptional activity and tissue specificity in thyroid cancer cell lines.(*48,49*) Investigators continue to improve the efficiency of tissue specific, multi-gene, transfection therapy.

1) p53, TTF-1, PAX-8

Most well differentiated thyroid cancers do not have p53 gene mutations, whereas some poorly differentiated thyroid cancers, most anaplastic thyroid cancers and established thyroid cancer cell lines have p53 mutations.(*50*) Several investigations suggest that undifferentiated thyroid carcinomas originate from differentiated ones. It therefore appears that p53 mutations occur as a late genetic event associated with de-differentiation of thyroid tumor cells and immortalization of cell lines.

Gene therapy with wild type p53 in thyroid carcinoma cells in culture that had a p53 mutation showed that it (a) induced growth arrest (not apoptosis),(*51*) (b) increased thyroid specific gene expression,(*52*) (c) enhanced the response to chemotherapy and radiation therapy,(*53,54*) and (d) down-regulated TSP (thrombospondin)-1 expression (not VEGF).(*55,56*) However, it seems unlikely that gene therapy with wild type p53 gene alone will become an effective treatment in patients who have poorly differentiated thyroid cancer or anaplastic thyroid cancer, because it induced growth arrest rather than apoptotic cell death and it rarely induced thyroid specific gene expression, especially for radioiodine uptake. To be an effective treatment, co-transfection of differentiation related genes or other effective genes might be needed. In addition to the role of wild type p53 in dedifferentiation of thyroid cancers, thyroid specific transcriptional factors, such as TTF-1, TTF-2 and PAX-8 are closely related with thyroid specific differentiated functions such as radioiodine uptake.(*57-59*) Induction of overexpression of TTF-1 and PAX-8 restored thyroglobulin gene promoter activity in thyroid cancer cell lines.(*60*) Further investigations are necessary to determine whether co-transfection of wild type p53 and thyroid specific genes will be more effective in inducing redifferentiation than when used separately.

2) Sodium/iodide symporter (NIS) gene

After total or near total thyroidectomy for patients with differentiated thyroid cancer of follicular cell origin, regional or distant metastases are often effectively ablated with 131-I. Iodide uptake by thyrocytes is mediated by the sodium/iodide symporter (NIS). Most differentiated thyroid carcinomas express NIS and NIS expression correlates with clinical radioiodine uptake.(*61*) However, some differentiated and most undifferentiated thyroid carcinomas fail to express NIS. These tumors lack the ability to uptake iodide and are thereby refractory to radioiodine therapy.(*62,63*)

Investigators have tried to restore NIS expression in thyroid cancer cells.(*9,23,57*) There are two remarkable advances in this field i.e. histone deacetylase inhibitors and gene therapy using NIS gene. Cloning and characterization of the sodium/iodide symporter (NIS) gene made it possible to try gene therapy using this gene in both thyroidal and non-thyroidal malignancies. Several clinical trials using NIS gene transfection for triggering significant iodide uptake in non-thyroid tumors are currently underway.(*64-66*) In thyroid cancer, transduction of hNIS in a follicular thyroid cancer cell line (FTC-133) induced high uptake of radioiodine *in vitro* and also *in vivo* in a xenograft model.(*67*) Although the transduction of the hNIS gene can induce radioiodine influx, it is followed by rapid efflux. Inhibition of iodide efflux has to be added for a therapeutic application of the hNIS gene. Iodide efflux could be inhibited by co-transfection of thyroperoxidase (TPO) gene, decreasing Pendrin (PDS) gene activity, or combination with lithium treatment.(*68,69*) Of interest, treatment of thyroid cancer cell lines with trichostatin A both increased NIS expression and decreased PDS expression. (*46*)

For transcriptionally targeted gene therapy, the thyroglobulin (Tg) promoter can be used. Thyroid specific transcription factors such as TTF-1, TTF-2, or PAX-8 closely interact with the TG promoter. TG promoter activity in poorly differentiated and anaplastic thyroid cancer cells, however, may not be enough because of other defects in these transcriptional factors. Cotransfection of these genes may enhance TG promoter activity.(*70*)

CONCLUSION

In vitro and *in vivo* investigations as well as preclinical trials suggest that new medical treatments will improve the care of patients with thyroid cancer. More basic science research and clinical trials are necessary. We hope that these new therapies will become available for patients who fail to respond to conventional therapy.

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