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Novel Approaches in Anaplastic Thyroid Cancer Therapy

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Abstract

Anaplastic thyroid cancer (ATC), accounting for less than 2% of all thyroid cancer, is responsible for the majority of death from all thyroid malignancies and has a median survival of 6 months. The resistance of ATC to conventional thyroid cancer therapies, including radioiodine and thyroid-stimulating hormone suppression, contributes to the very poor prognosis of this malignancy. This review will cover several cellular signaling pathways and mechanisms, including RET/PTC, RAS, BRAF, Notch, p53, and histone deacetylase, which are identified to play roles in the transformation and dedifferentiation process, and therapies that target these pathways. Lastly, novel approaches and agents involving the Notch1 pathway, nuclear factor κB, Trk-fused gene, cancer stem-like cells, mitochondrial mutation, and tumor immune microenvironment are discussed. With a better understanding of the biological process and treatment modality, the hope is to improve ATC outcome in the future. ***The Oncologist*** 2014; 19:1148–1155

Implications for Practice: Because of its aggressive phenotype and poor prognosis, anaplastic thyroid cancer (ATC) is automatically classified as TNM stage IV regardless of tumor burden, and survival has shown minimal improvement in the last decades. The purpose of this review is to summarize the promising preclinical and clinical studies in ATC treatment, as well as reveal new preclinical studies with novel approaches at genetic, organelle, cellular, and microenvironment levels. Because of the poor prognosis, all ATC patients should be referred to centers that participate in current clinical trials with new agents and delivery systems.

Introduction

Anaplastic thyroid carcinoma (ATC), contrary to the well differentiated thyroid cancer (DTC), is one of the most aggressive human malignancies. This undifferentiated thyroid cancer is responsible for more than half of all thyroid cancer deaths, with an overall survival rate as low as 13%, despite only accounting for <2% of thyroid cancer incidence [1–4]. Clinical presentation is frequently characterized by a rapidly growing neck mass with associated compressive symptoms [5]. ATC also displays highly invasive behavior, with extrathyroid extension and lymph node metastasis affecting 40% of ATC patients, whereas the remaining 60% of patients have distant metastases [6]. The aggressive phenotype and poor prognosis associated with ATC form the basis for its automatic classification as TNM stage IV regardless of tumor burden [7].

Unlike DTC, which can often be cured by surgical resection, radioiodine ablation, and thyrotropin (thyroid-stimulating hormone [TSH])-suppressive therapy, treatment options for ATC are mainly palliative because of the aggressive and resilient nature of the disease. Gross resection is recommended in nearly all cases [8], and thyroidectomy can relieve airway compression, but curative resection is often impossible [9]. Lacking the sodium-iodide symporter (NIS), ATC is resistant to therapeutic radioiodine, whereas radiotherapy and chemotherapy alone have shown limited efficacy, contributing to the limited survival improvement over the last decades [3, 10, 11]. Current recommendations support multimodal interventions that use adjuvant and neoadjuvant therapy in combination with surgery to improve control of locoregional and metastatic disease [8]. Despite these measures, ATC continues to carry a median survival of less than 6 months and a 1-year survival of less than 20% [7, 12]. Therefore, investigation of novel antiproliferative, redifferentiation, immunological, and gene therapies has been an ongoing interest [13].

Markers and Signal Pathways

During the dedifferentiation process, the thyroid carcinoma loses thyroid-specific gene expression, contributing to the lack of response to radioiodine ablation therapy in ATC [14].

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Specifically, NIS, which mediates the active iodide uptake at the basolateral membrane of the thyroid follicular cell, plays a crucial role in the success of radioiodine therapy [15, 16]. In addition to RAS, BRAF, RET/PTC, and p53, the Notch family receptors and ligands were recently found to be involved in the proliferation and differentiation of thyroid cancer [17, 18]. We will cover the main pathways to date that are known to contribute to thyroid oncogenesis, tumorigenesis, and dedifferentiation, including RET-RAS-RAF, Notch1, and histone deacetylase (HDAC).

Markers

The gene mutations in DTC and ATC were found to be different; thus, the progression of indolent to aggressive thyroid cancer was thought to be a multistep tumorigenesis [19, 20]. Interestingly, ATC can develop from 1% of patients with DTC [14]. Normal thyrocytes initially undergo early mutations of *ret*, *ras*, *BRAF*, or a paired box homeotic gene 8 (PAX8)-peroxisome proliferator activated receptor γ (PPARγ) to transform into DTCs [21–24]. Further dedifferentiation into poorly differentiated thyroid cancer (PDTC), and ATCs were found to be due to inactivation mutation of *p53* [25–27]. p53 tumor suppressor gene is critical in regulating cell cycle and apoptosis in response to DNA and is one of the most frequently found mutation in human malignancy. In thyroid cancer, p53 mutation appeared to be a late event responsible for transformation and dedifferentiation into more aggressive types. This is evident by the low frequency of p53 mutation in DTC but a high detection rate, up to 95%, in ATC [11]. The thyroid-specific transcription factor (TTF-1) and PAX-8 expression levels are decreased in less-differentiated papillary and follicular carcinomas and are lost in ATC, with comparable level changes of thyroglobulin (Tg), thyroperoxidase (TPO), thyrotropin receptor (TSH-R), and NIS [28–31].

RET/PTC-RAS-RAF

RET/PTC is a chimeric oncogene between RET, located at chromosome 10q11.2, and the promoter of an unrelated gene, resulting in constitutive activation of the RET gene [32, 33]. To date, 13 different types of RET/PTC rearrangements have been reported [34]. RAS is the next direct downstream effector in this cascade. RAS mutation, although most significant in the diagnosis of follicular thyroid cancer (FTC), is also reported in papillary thyroid cancer (PTC) and ATC [35, 36]. From studies of different histological types of thyroid cancer, up to 60% of ATC was found to harbor RAS mutation [36–38]. In a stepwise process, RAS appeared to be an "early-stage" mutation. Furthermore, RAS mutation was proposed to initiate dedifferentiation of DTC into ATC, because RAS mutation predisposes the cell to more genetic and molecular derangement, likely because of chromosome instability [39, 40].

BRAF, a member of the RAF serine/threonine-kinase family and a downstream effector of RAS, has been shown to be an important regulator in normal thyroid cell proliferation, apoptosis, and thyroid-specific gene expression [41, 42]. Liu et al. [43] showed that BRAF mutation and the subsequent activation of MAPK pathway in rat thyroid cells could silence expression of NIS, and removal of BRAF with siRNA restore the expression of thyroid-specific genes. BRAF mutation, specifically BRAFV600E mutation, was demonstrated to impede both NIS gene expression and NIS membrane localization, whereas inhibition of BRAF by smad7 reversed NIS transcription repression [44–46]. In addition to promoting dedifferentiation, BRAF is also responsible in promoting migration and invasive growth [41, 47, 48]. Based on the significance of BRAF mutation in PTC and the potential of PTC to transform into ATC, BRAF is a target of investigation in treatment of ATC [49, 50].

Another translocation event underlying PTC involves a fusion between Trk-fused gene (TFG) and the receptor tyrosine kinase NTRK1 [51]. Analogous to chromosomal rearrangements involving RET, several TFG fusion proteins have been shown to result in the hyperactivation of MAPK kinase signaling [52–55]. Endogenous TFG localizes to specialized subdomains of the endoplasmic reticulum that are responsible for the biogenesis of vesicles that carry secretory cargoes out of cells [55]. The TFG-NTRK1 fusion protein similarly localizes to these sites, and this distribution is key to its transforming activity [55]. Although direct targets of TFG-NTRK1 activity have yet to be defined, these studies highlight the possibility that alterations in the secretory pathway may contribute to cell transformation or oncogenesis in the thyroid.

Notch1

Notch receptors (Notch1–4) and ligands (δ-like 1, 3, and 4 and Jagged-1 and -2) were reported to regulate cell proliferation, migration, adhesion, and differentiation in various situations [56]. Depending on the cell type, Notch can function as either an oncogene or a tumor suppressor [18, 57–62]. Ferretti et al. [17] first demonstrated that the expression of Notch was decreased in DTC and further in ATC when compared with normal thyroid tissue. The effect of Notch1 on cell growth and differentiation is exerted via transcription regulation [63]. Although Notch1 was studied in many other tissues and cancers, the role of Notch1 in thyroid cancer has only recently being explored. As a downstream effector of Notch1, Hes1 plays a central role in thyrocyte proliferation and differentiation, evident by a 34%–65% decrease in thyroid surface area and 69% decrease in NIS protein expression in *Hes1*$^{-/-}$ mouse embryo [64].

HDAC

Acetylation of histone lysine residue induces changes in the nucleosomal conformation caused by decreased affinity for the negatively charged DNA [65, 66]. Inhibition of HDAC was shown to induce expression of NIS, TPO, and Tg in thyroid carcinoma cell lines [67–69]. Thyroid-specific gene induction resulted in increased radioiodine uptake, organification, and intratumoral radioiodine accumulation. The HDAC inhibitor induced re-expression of NIS, but TPO or Tg were not mediated by newly produced transcription factor [68]. Zhang et al. [70] found that HDAC was the link between BRAF mutation and NIS silencing. The BRAF mutation upregulates HDAC, causing an epigenetic modification via constitution histone acetylation at the NIS promoter site. The significance of HDAC in thyroid cancer resistance was demonstrated by Hou et al. [31] with a potent HDAC inhibitor, suberanilohydroxamic (SAHA or vorinostat), which restored thyroid-specific gene expression, including NIS, TSH-R, TPO, Tg, and TTF-1, as well as radioiodine uptake. Therefore, therapies that can move the balance toward histone acetylation should be able to restore thyroid gene

expression and ultimately induce radioiodine avidity to improve the effectiveness of radioiodine therapy.

NF-κB

Nuclear factor κB (NF-κB) is a family of transcription factors that is held inactive in the cytoplasm of resting cells, including thyroid cancer cells, and its activation is induced by multiple proinflammatory cytokines, chemotherapeutic agents, and ionizing radiation [71]. Many NF-κB target genes are prosurvival genes and are critical for intrinsic cancer cell resistance to chemo- and radiation therapy, and therefore inhibition of NF-κB activity could lead to apoptosis or sensitization to chemo- and radiotherapy in various cancer cell, including thyroid cancer cells, in vitro and in vivo [72–74]. Activation of NF-κB was observed in PTC and FTC, as well as aggressive ATC [75–78]. Moreover, recent findings demonstrate that NF-κB significantly contributes to the establishment and maintenance of protumorigenic microenvironment [79, 80]. Therefore, inhibition of NF-κB activation is thought to enforce antitumorigenic effects of chemo- and radiation therapy through cancer cell-intrinsic and -extrinsic mechanisms.

Therapeutic Approach

Recent developments of treatment modalities in advance thyroid cancers include investigation of kinase inhibitors, redifferentiation therapy, statins, and gene transfer [81].

Kinase Inhibitors

Epidermal growth factor receptor (EGFR) mutation was described in thyroid cancer and contributes to RET activation [82]. Therefore, gefitinib, an EGFR inhibitor, is a drug of interest. In a phase II trial with a mixed cohort of thyroid cancer patients, including 19% as ATC, gefitinib did not induce any tumor response, but 12% of patients had stable disease at 12 months and median progression-free survival (PFS) was 16 weeks for ATC patients [83]. Other receptors are also therapeutic targets under investigation. Rugo et al. [84] established the safety and clinical activity of axitinib, an inhibitor vascular endothelial growth factor receptors 1, 2, and 3, in various advanced solid tumor, including thyroid tumor. A subsequent phase II trial from the University of Chicago with a mixed cohort of 60 patients, including 3 patients with ATC, showed that 1 ATC patient had a partial response, whereas the rest of the patients had stable disease [85]. Sorafenib is a multikinase inhibitor that targets BRAF, which showed growth inhibition in ATC xenografts and improves survival in vivo [86–88]. An early phase II trial with a mixed cohort with metastatic, radioiodine-refractory disease, including one patient with PDTC and one patient with ATC, showed an overall clinical benefit rate of 77% with a median PFS of 79 weeks and a 70% mean decrease of serum Tg level [89]. However, both patients with PDTC and ATC had progressive disease despite treatment, and the treatment for the ATC patients was discontinued 4 days after initiation because of medical complications. A randomized controlled trial by Brose et al. [90], including 10% PDTC but no ATC patients, demonstrated that sorafenib elicited 12.2% partial response and was superior in prolonging PFS when compared with placebo. A recent multi-institutional phase II clinical trial with all ATC patients showed a 35% of partial response or stable disease rate in 20 patients who failed previous treatments with tolerable adverse events [91]. Because BRAF mutation was shown to be partly responsible for dedifferentiation and depressed expression of NIS [43], a combination therapy of BRAF inhibition and radioiodine therapy provides a potential future approach. Other phase II trials with various BRAF inhibitors, including vemurafenib (NCT01524978), dabrafenib (NCT02034110), and LGX818 (NCT01981187), are underway [92].

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HDAC Inhibitors

Depsipeptide was able to induce re-expression of NIS, TPO, and Tg in vitro and in vivo but had no effect on re-expression of TSH-R [68]. Unfortunately, clinical experience in other cancers showed that patients treated with depsipeptide experienced severe gastrointestinal, cardiac, and cutaneous adverse events [93]. On the other hand, SAHA was shown to restore NIS, TPO, and Tg, as well as TSH-R in ATC cell lines [31]. Valproic acid (VPA), a safe and widely used anticonvulsant and mood stabilizer, was found to act as a HDAC inhibitor in addition to enhancing the apoptotic activity of paclitaxel [94, 95]. A study by Catalano et al. [96] found that when used in combination with imatinib, VPA induced cell cycle arrest via G1 cell cycle arrest by decreasing AKT phosphorylation without affecting apoptosis. Although VPA showed promise in inducing expression of NIS gene, NIS membrane localization, and radioiodine accumulation in PDTC at a safe dose, it failed to show effects in ATC beyond re-expression of NIS gene [97]. Another novel molecule, LBH589, is under phase II clinical trial at University of Wisconsin-Madison for patients with metastatic MTC and radioiodine-resistant DTC [92]. The potential of applying the results to ATC patients is promising with the inclusion of radioiodine-resistant patients in the study.

Gene Therapy

There have been many types of promising gene therapies, including corrective gene therapy, cytoreductive gene therapy, and immunomodulatory gene therapy [11]. Spitzweg et al. [10] first proposed the potential cytoreductive gene therapy to transfer NIS gene followed by radioiodine therapy. Unfortunately, transfection of the NIS gene alone does not appear sufficient in cells lacking other thyroid-specific proteins, including Tg, TPO, and TSH-R, because of efflux of radioiodine that is not organified and retained in the cells [98, 99]. Means to increase efficacy of NIS gene therapy include introducing other thyroid-specific genes to enhance radioiodine retention by organification, increasing NIS gene transduction efficiency to maximize uptake, blocking iodide efflux to minimize lose, and application of alternative radionuclides to maximize energy deposit [11, 15, 100–102].

Another application for gene therapy is to allow the innate immune system to recognize and destroy the tumors via

immunomodulation. Cotransfection of human interleukin-2 and the HSV-tk gene in ATC cells, showing complete elimination in ATC xenograft [103]. In a pilot study of combined suicide and cytokine gene therapy in two patients with end-stage ATC, Barzon et al. [104] discovered some promise in immune response and local tumor destruction with application of the therapy.

In a study with corrective gene therapy, Lee et al. [105] showed that neither NIS gene nor wild-type p53 gene transfer alone affect ATC cell survival in vitro or tumor growth in vivo after radionuclide treatment but found a decrease in tumor volume of 80% with NIS, wild-type p53, and radionuclide treatment. Furthermore, wild-type p53 restoration in p53 mutant ATC was associated with redifferentiation and promotes induction of thyroid-specific genes [104, 106].

Natural Compounds

Natural compounds often have relatively low toxicity and may eventually play a supporting role in drug treatments targeting ATC. We have previously shown that the plant polyphenol resveratrol suppresses ATC cell growth in a dose-dependent manner for both HTh7 and 8505C cell lines via S-phase cell-cycle arrest and apoptosis [63]. In vivo experiments showed reduced growth of ATC tumors derived from both cell lines when administered i.p. at 10 mg/kg. The expression of thyroid-specific genes including TTF1, TTF2, Pax8, and NIS was upregulated in both ATC cell lines with resveratrol treatment, and Notch1 siRNA interference abrogated the induction of some of these genes. Thus, this study links resveratrol treatment, activation of Notch1 signaling, and redifferentiation. We have also shown that chrysin (a plant flavone) treatment of ATC cells leads to induction of messenger RNA levels of Notch1 and a dose-dependent inhibition of cellular growth. Oral administration of chrysin suppressed the growth of ATC xenografts by an average of 59% compared with the vehicle control group [107]. Recently, Kang et al. [108] have shown growth-inhibiting and redifferentiation effects of several plant phytochemicals in thyroid cancer cell lines. Although the clinical experience with natural compounds in thyroid cancer is limited, these animal studies suggest potential benefits.

Other Agents and Approaches

Bortezomib, approved for treatment of advanced multiple myeloma [109], can effectively control canonical and non-canonical NF-κB signaling, and such effects are thought to contribute to antimyeloma effects [110]. Although bortezomib alone had a modest effect on advanced thyroid cancers [111], when combined with other chemotherapy agent for thyroid cancer in preclinical studies, there was some synergy, indicating the promise of bortezomib in combination therapy [112]. Inhibition of NF-κB activity in different thyroid cancer contexts, including aggressive forms of thyroid cancers, is uniformly reported to cause chemo- or radiosensitization [73, 74, 76, 113–119] and is associated with reduced metastatic potential [78]. These observations provide the scientific rationale for targeting NF-κB for treatment in resistant, aggressive thyroid malignancies.

Thiazolidinediones, known most commonly for antidiabetic therapy, is a potent agonist for the PPARγ, which is a ligand-activated transcription factor responsible for cell proliferation and growth [120–122]. Although ATC cell has high level of PPARγ, troglitazone was unable to inhibit cell proliferation of ATC cells until a concentration of 20 μM [121]. A later study by Antonelli et al. [123] showed that both rosiglitazone and pioglitazone inhibited ATC cells at a level of 20 μM as early as 1 hour after administration, regardless of BRAF mutation. Another study demonstrated that thiazolidinediones, with troglitazone having the greater effect, not only inhibited transformed thyroid cell proliferation but also induced redifferentiation, evident by re-expression of NIS and radioiodide uptake [122].

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, antagonists of the rate-limiting step of cholesterol production, are frequently used for treatment of hypercholesterolemia and reducing cardiovascular morbidity and mortalities [124–127]. The main effect of statin on ATC is proliferation inhibition by apoptosis via different proposed mechanisms, including inhibition of geranylgeranylation of ρ, lamin B proteolysis, and cytochrome c release from mitochondria [128–131]. In an in vivo study, Wang et al. [132] demonstrated that lovastatin was able to decreased ATC tumor growth rate in xenograft by 73% at a concentration of 10 mg/kg per day. Furthermore, lovastatin exerted either apoptotic or cytomorphological differentiation effects on ATC cells at concentration [130]. However, radioiodine uptake was largely unaffected [133].

In addition to focusing on the thyroid cancer as a whole, the existence of subsets of cancer stem-like cells (CSCs) with the ability for self-renewal and unlimited growth has been postulated [134–137]. Higher percentages of CSCs may be responsible for the resistance to radiation and chemotherapy, as well as the aggressive behavior of ATC [136, 138]. The inability to differentiate beyond CSC is due to genomic alterations in RET/PTC, PAX8-PPARγ rearrangement, and BRAF mutation [139]. Epithelial-mesenchymal transition is thought to be the mechanism that allows the more well-differentiated cancer cells to transform into CSCs [136, 140]. Further understanding of this mechanism and characterization of CSCs may lead to more effective therapies for more aggressive and lethal thyroid cancers [139].

Finally, modifying the tumor immune microenvironment from pro- to antitumorigenic has been an approach sought after by many [141]. It has been recently shown that thyroid inflammation affects thyroid cancer outcomes [142]. An inflammatory immune microenvironment seems to be protumorigenic, whereas an autoimmune microenvironment seems to be antitumorigenic [142, 143]. T-cell progenitors present in thyroid cancer inflammatory immune microenvironment seem to facilitate tumor development [143]. Driving these T-cell progenitors to maturity may become a therapeutic strategy in itself or in combination with other approaches.

T-cell progenitors present in thyroid cancer inflammatory immune microenvironment seem to facilitate tumor development. Driving these T-cell progenitors to maturity may become a therapeutic strategy in itself or in combination with other approaches.

Conclusion

ATC is an aggressive malignancy with extremely poor prognosis, partly because of the resistance to radioiodine uptake, which is one of the mainstay therapies besides surgery for thyroid cancer. The re-expression of thyroid-specific genes, specifically NIS, has the potential to restore the radioiodine uptake ability of the cancer. Furthermore, the ability of cells to take up radioiodine can be enhanced by TSH, which necessitates the re-expression of TSH-R. Many studies have demonstrated that redifferentiation can be achieved by modifying various pathways, including Notch1, RET/PTC-RAS-RAF-MEK, HDAC, and NF-κB with different agents or gene therapy. Clinical trials so far have only shown no or slight improvement in survival. Although a small case series from Mayo Clinic demonstrated the beneficial potential of aggressive multimodal therapy [144], further prospective trials with multimodal or multitarget approach should be performed in hopes of improving the clinical outcome of ATC. Lastly, emerging targets and approaches can not only provide better understanding of the tumor biology but also more optimistic outcome in the future.

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For Further Reading:

Ligy Thomas, Stephen Y. Lai, Wenli Dong et al. Sorafenib in Metastatic Thyroid Cancer: A Systematic Review. ***The Oncologist*** 2014;19:251–258.

Implications for Practice:

This meta-analysis of 219 patients treated with sorafenib for metastatic thyroid cancers demonstrated that 81% of patients had either partial response or stable disease, and none had a complete response. The partial response rate was best for medullary thyroid cancer, followed by differentiated thyroid cancer. Responses in anaplastic thyroid cancer were low. The overall median progression-free survival was 18 months for all histologies. There were significant dose reductions and discontinuations as a result of toxicities, which need to be considered when treating patients who may otherwise be asymptomatic and have reasonable overall survival.