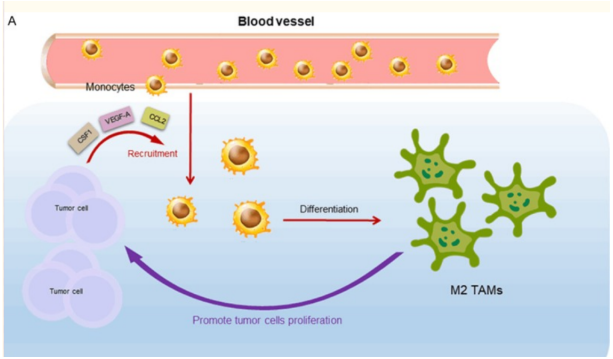
IMMUNOLOGY

Tumor associated macrophages (TAM) in the M1 phenotype allows for immune control over tumor cells. However, TAMs of the M2 phenotype inhibit antitumor activity[12]. M2 TAMs represent 50% of nucleated cells in ATC. This high density of M2 TAMs poses them as potential targets for ATC therapies. As seen in Figure 3, the M2 TAM variants arise from inflammatory molecules (i.e. CSF1, VEGF-A) recruiting monocytes, which then differentiate into M2. The amount of these molecules are correlated with the level of thyroid cancer malignancy.

Figure 3: Monocyte Differentiation into M2 TAM[12]



TAMs release the IL-10 cytokine. Upregulation of IL-10 results in increased BCL-2 and BCL-xL (anti-apoptosis molecules). Evidence has shown that for this reason, ATC is resistant to chemotherapy drugs[13].

Natural Killer cells are downregulated in ATC cells by the COX2 enzyme. This allows ATC to evade NK-targeted cancer cell destruction[14].

TREATMENTS

Upon diagnosis, 50% of ATC patients have experienced metastasis[2]. Given ATC's aggressiveness and chemotherapy resistance, the most common recommended procedure is surgical removal of the tumor[15]. This could include the removal of a part or the entire thyroid gland, in addition to surrounding tissue. Due to the location of the thyroid, ATC tumors most likely will have invaded a portion of the patient's voice box upon surgery. Thus, a patient will require vocal therapy afterwards. Furthermore, external beam radiation and chemotherapy are follow-up methods applied after surgery.

In 2019, there is a clinical trial to use Paclitaxel, a cytoskeletal drug that targets tubulin (component of cellular microtubules)[16]. The goal is to freeze ATC cells in metaphase, hindering proliferation. This drug has shown some degree of effectiveness for a small sample of patients, but further testing is required. Given that ATC only affects 2% of all thyroid cancer patients, in addition to a high mortality rate, it is hard to find an adequate sample size to test this drug, or any number of other novel treatments regarding ATC for that matter.

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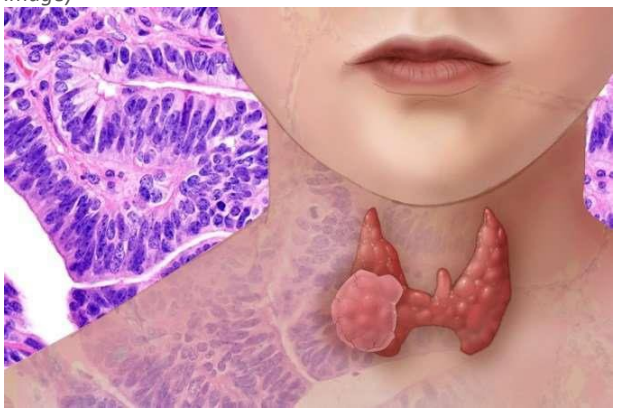
ANAPLASTIC THYROID CANCER

Figure 1: Thyroid Gland And Thyroid Cancer Growth (Left of Image)[1]



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INRODUCTION

Anaplastic thyroid cancer (ATC) is a highly aggressive form of thyroid cancer. ATC tumor cells have transformed to an extent where their phenotype is significantly deviated from their normal state. ATC affects the thyroid gland which is located at the lower front of the neck. It is responsible for creating various hormones that are crucial to regulating one's metabolism, growth, and maintaining homeostasis. This cancer proliferates faster than other common cancers (breast/colon/lung). It is likely that this cancer metastasizes into bones or surrounding lymph nodes, indicated by physical bumps around the affected regions.

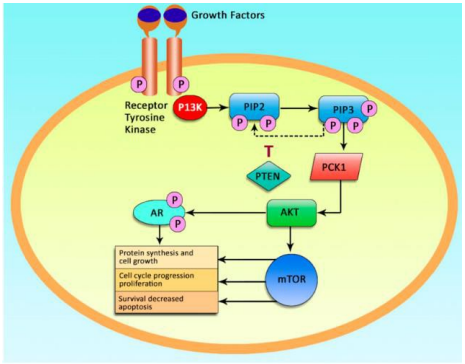
INCIDENCE RATE

ATC is relatively rare. Studies show a general trend of thyroid cancer increasing over a 14 year span from 8/100,000 affected to 15/100,000 affected[2]. ATC however, comprises 2% of those diagnosed with thyroid cancer. Women are twice as likely to be diagnosed with ATC, and it occurs mostly in those aged 60 or older.

GENETIC & CHROMOSOMAL ABNORMALITIES

In ATC, unregulated cell proliferation is a result of mutations in 2 pathways. The first is the MAP kinase pathway that plays a role in regulating apoptosis. A mutation of the BRAF V600E gene yields detrimental changes to the corresponding protein, crucial for MAP kinase activity[3]. Mutation of this protein causes reduction of p21kip1, a protein associated with cell cycle regulation. The second, and the more prevalent pathway in ATC is the PI3K receptor tyrosine kinase (phosphatidylinositol 3'-kinase) pathway shown in Figure 2. More specifically, the alpha subunit of this protein is mutated, leading to faulty cell cycle signaling along with deregulated cell growth, which contributes to ATC proliferation.

Figure 2: Normal PI3K Pathway For Cell Growth[3]



Coinciding mutations work along those above to promote ATC tumorigenesis. upregulation of mutated Ras coupled with inhibition of the tumor suppressor gene PTEN (causing Akt upregulation) results in uncontrolled cell growth via a compromised growth pathway[4]. Although normal cells use this pathway correctly, with assistance from Ras and tumor suppressor gene mutations, the PI3K gene converts into an oncogene.

ATC exhibits p53 inactivation, particularly de novo[7]. Ras mutations are low relative to other common cancers but are still apparent. Specifically, mutations of BRAF V600E is characterized as a missense mutation on exon15 of the 7q34 gene[5]. Respective point mutations in codons 12 and 13 of the H-Ras and K-Ras genes, in addition to codon 61 mutations for N-Ras results in upregulation of the Ras gene, contributing to the PI3KCA pathway deregulation.

Currently, there are no known tumor viruses associated with ATC.

TUMORIGENESIS

Further research on ATC proliferation is needed due to the significantly small proportion of ATC patients compared to those affected by other thyroid cancers. However, evidence suggests that ATC can arise from papillary thyroid cancer (PTC). From studies on PTC patients using ultrasound to measure tumor diameter and volume, results show 72% had tumors double in 5 years or greater[6]. In vitro experiments with ATC cells indicate a doubling time of 48 hours. Coupled with microRNA miR-146b (responsible for post transcription modification of RNA transcripts), doubling rate of ATC in vitro was 24 hours.

Upon severe cellular damage that leads to oncogenic mutations, cells can induce apoptosis. ATC prevents this by upregulating the PI3K/Akt pathway which promotes pro-survival signals and activates the Bcl-2 family proteins[7]. Bcl-2 proteins inhibit apoptosis by binding to the mitochondrial membrane to block cytochrome c release, an important molecule in initiating apoptosis. Furthermore, ATC's BRAF V600E gene mutation enhances cellular growth signals.

ATC uses a combination of TERT (telomere elongation reverse transcriptase) and the ALT mechanism to stabilize telomere ends. Evidence suggests that elevated TERT and ALT mutations in ATC do not result in overlengthening of telomeres in cancer cells, but rather, with the highly aggressive and replicative nature of the cancer, the TERT and ALT mutations are a way to maintain the telomere lengths, since each division cycle naturally shortens telomeres[8].

ATC MICROENVIRONMENT

MHC class 1 molecules associate with tumor antigens and act as an indicator for the body's T cells to activate and destroy the tumor cells[9]. ATC cells show signs of decreased levels of Beta-2-microglobulin, a component of MHC class 1 molecules and decreased levels of tumor infiltrating lymphocytes. This causes T cells to not recognize the tumors, allowing for ATC to evade an immune response.

ANGIOGENESIS & METASTASIS

ATC cells proliferate aggressively but lack optimal vasculature and lymphatic drainage, exposing them to hypoxic conditions[10]. Thus, they require higher than normal oxygen intake to proliferate. Hypoxic induction of HIF-1 alpha actiavtes VEGF and bFGF (growth factors) that promote blood vessel formation[9]. The ATC cells use these vessels as potential areas to invade proximal tissues and seep into the blood stream, potentially resulting in metastasis.

Regulatory T cells (Tregs) act to suppress immune responses. ATC patients have elevated levels of the CD4 Treg variant, particularly in the surrounding blood and tumor tissues[11]. This is emphasized at lymph node metastasis sites where Treg levels are high.

Furthermore, ATC tissue invasion, angiogenesis, and metastisis are all dependent on the gelatinase class of MMP (matrix metallopeptidases). Recruitment of inflammatory molecules such as cytokines and chemokines promote the MMP to rupture the ECM, allowing for the tumor cells to seep to nearby tissues[11].

Of all the thyroid cancer types, ATC has the highest levels of TAM (Tumor Associated Macrophages). TAMs suppress an immune response by producing various pro-inflammatory molecules including cytokines, chemokines, and growth factors[10]. Particularly, TAM-derived cytokines IL-23 and IL-27 promote inflammation, contributing to angiogenesis, and tumor growth[10]. Furthermore, ATC TAM secretes IL-8 such that experiments have shown that it promotes cancer invasion of nearby tissue[14].