Review

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Pathogenesis and Regulatory Mechanisms of Tumors—Insights From Thalassemia and Thyroid Cancer

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Thyroid carcinoma is the most common endocrine malignancy, with a rising global incidence. Simultaneously, the increased life expectancy of patients with transfusion-dependent thalassemia (TDT) has revealed new long-term complications, including an elevated risk of thyroid cancer. This epidemiological convergence raises the possibility of shared molecular mechanisms. In this review, we explore potential mechanistic associations between TDT and thyroid cancer, focusing on the oncogenic consequences of iron overload. Iron excess in TDT promotes a tumor-permissive environment via oxidative stress, chronic inflammation, and modulation of ferroptosis, a process with dual roles in tumor biology. These alterations contribute to DNA damage, genomic instability, and activation of oncogenic signaling cascades such as mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), while impairing immune surveillance. Iron-induced epigenetic remodeling and non-coding RNA dysregulation further support malignant transformation. Although a causal relationship remains unproven, the convergence of these pathways underscores the need for thyroid surveillance in thalassemia patients and supports targeted strategies addressing iron metabolism and ferroptotic vulnerability.

Keywords: β-thalassemia; thyroid carcinoma; iron overload; oxidative stress; ferroptosis; oncogenic signaling; inflammation; epigenetics

Introduction

Epidemiology and Clinical Background

Beta-thalassemia (β-thalassemia) is a hereditary disorder that consists of absent or reduced β-hemoglobin chain synthesis and results in chronic hemolytic anemia, ineffective erythropoiesis and iron overload. Three distinct clinical phenotypes of β-thalassemia exist, according to the type of mutations in the *β-globin* gene (silent, mild and severe), and these are thalassemia minor, thalassemia intermedia and thalassemia major. β-thalassemia can also be divided into transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) which reflects the difference in clinical management according to the degree of anemia [1].

The introduction of iron chelation treatment as well as vigilance in the appropriate frequency of transfusions, has increased longevity in β-thalassemia patients. As a consequence, the prevalence of several diseases in this population group is rising, including malignancies [2]. A study of the Taiwan population by Chung *et al.* [3] showed that thalassemia patients had increased risk of hematological and abdominal malignancies with hazard ratios of 5.32 and 1.96 respectively. The incidence was notably higher in patients with TDT [3].

Thyroid cancer is the most common malignancy of the endocrine glands, constituting 4.1% of newly diagnosed cancer cases worldwide [4]. Women appear to be at higher risk of being diagnosed compared to men by 3-fold [4]. The incidence of thyroid cancer has notably increased over the last years, which might be in part due to overdiagnosis [5], whereas the mortality remains low. Known risk factors for the development of thyroid cancer include age, gender, family history, ethnicity/race [6] as well as modifiable ones; ionizing radiation, especially during childhood [7] and obesity [8]. According to the 2022 WHO classification of endocrine tumors, the main histological types of thyroid cancer consist of differentiated thyroid carcinomas (DTC) (with papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) being the most common and least aggressive), poorly differentiated thyroid carcinoma (PDTC), anaplastic carcinoma (ACA) and medullary thyroid carcinoma (MTC) [9]. It is important to note that the terminology used in the literature to describe thyroid can-

cer subtypes are often inconsistent. Many earlier studies do not distinguish clearly between differentiated, medullary, or anaplastic thyroid carcinomas, and few adopt the current WHO 2022 classification. In this review, we use the term "thyroid cancer" to primarily refer to DTC unless otherwise specified in the source material.

Thyroid cancer is also one of the most frequent cancers in thalassemia patients, alongside hepatocellular carcinoma [10] and hematologic malignancies [11,12]. Since the first two patients with thyroid carcinoma and β-thalassemia were described by Poggi *et al.* in 2011 [13], more cases have emerged from different centers. An international survey of 3114 thalassemia major (TM) patients reported a prevalence of 0.41% for thyroid cancer. The respective prevalence for Italy and Greece was 1.57% and 1.3% [14]. A 15-year-old girl with β-thalassemia was diagnosed with papillary thyroid cancer being the youngest patient of this population presenting with the disease [15].

Rationale and Aim of the Review

Over the last decades, key genetic mutations and epigenetic alterations have been identified as drivers for tumorigenesis and progression in thyroid carcinomas. They offer insight into the biological behavior of the tumors and can guide treatment by enabling the development of targeted therapies [16]. In the pursuit of other molecular pathways or changes on a cellular level that are implicated in malignant transformation, the distinct pathophysiology of β-thalassemia as a disease could be hiding interesting clues.

Iron overload is a central feature in patients with β-thalassemia and is attributed to four main mechanisms: excessive iron intake through repeated transfusions, increased intestinal iron absorption in non-transfusion-dependent patients [17], hemolysis, and the suppression of hepcidin expression [18]. Hemolysis stems from ineffective erythropoiesis, leading to the release of iron from hemoglobin. Hepcidin, a peptide hormone that regulates iron homeostasis, normally binds to ferroportin on enterocytes and macrophages, reducing iron absorption and recycling. However, in thalassemia, hepcidin is suppressed due to elevated erythroferrone—produced in response to high erythropoietin levels—as well as through interference of transferrin receptor 1 (TfR1) with the homeostatic iron regulator (HFE) [19]. These interactions enhance systemic iron overload, potentially playing a role in carcinogenesis. While this review primarily focuses on TDT as a model of iron overload-associated pathology, we acknowledge the heterogeneity of thalassemia syndromes and the distinct mechanisms of iron accumulation across different clinical phenotypes.

The purpose of this review is to examine possible mechanisms that could connect the complex entity of TDT with thyroid cancer. In the following paragraphs we will discuss the available scientific evidence on oxidative stress, chronic inflammation, genetic and epigenetic changes as well as impaired ferroptosis and apoptosis in both diseases. In addition, we will identify areas where future research is required, in order to improve our understanding of the processes of malignant transformation and tumor progression in thyroid cancer.

Iron Overload, Oxidative Stress, and Thyroid Cancer: Mechanisms and Evidence

Mechanisms of Iron Overload in Thalassemia

Iron plays a central role in oxygen transport and cellular metabolism, yet in excess, it becomes a catalyst for cellular injury. In patients with thalassemia, chronic blood transfusions and ineffective erythropoiesis frequently lead to iron overload [20]. This disrupts redox homeostasis by increasing the levels of reactive oxygen species (ROS), thereby creating a pro-carcinogenic environment [21]. While the association between iron overload and hepatocellular carcinoma is well established, recent findings suggest a potential link with thyroid cancer, particularly DTC [22]. The thyroid gland's unique susceptibility to oxidative stress (OS), coupled with iron accumulation, raises the possibility that iron-induced OS may contribute to thyroid tumorigenesis [23]. In thalassemia, chronic transfusions and ineffective erythropoiesis frequently result in iron accumulation that surpasses transferrin's binding capacity. This leads to the formation of redox-active non-transferrin-bound iron (NTBI), an unbound iron fraction capable of catalyzing the Fenton reaction and generating highly ROS [24]. These ROS disrupt redox homeostasis and damage cellular components, particularly hematopoietic progenitor cells, as demonstrated in murine models [25] (Fig. 1). Clinically, this oxidative burden is reflected in elevated serum ferritin levels, a reliable surrogate marker of systemic iron overload, which has been shown to correlate significantly with oxidative stress markers such as malondialdehyde in patients with β-thalassemia major [26]. Importantly, the persistent generation of ROS contributes not only to tissue injury but also to a pro-tumorigenic microenvironment, characterized by chronic inflammation, DNA damage, and altered cellular signaling. Population-based studies have reported a higher incidence of malignancies, including DTC, in TDT patients, further implicating iron-induced oxidative stress in thyroid carcinogenesis [3]. While Chung *et al.* [3] report a 1.96 hazard ratio for thyroid cancer in TDT, the population-based design limits mechanistic inference. Additionally, case series such as Poggi *et al.* [13] describe thyroid cancer occurrence in TDT but lack control groups or sufficient statistical power. These limitations underscore the need for larger prospective studies focused on thyroid malignancy in thalassemia populations, particularly as these patients now live longer and age-related cancers become more prevalent.

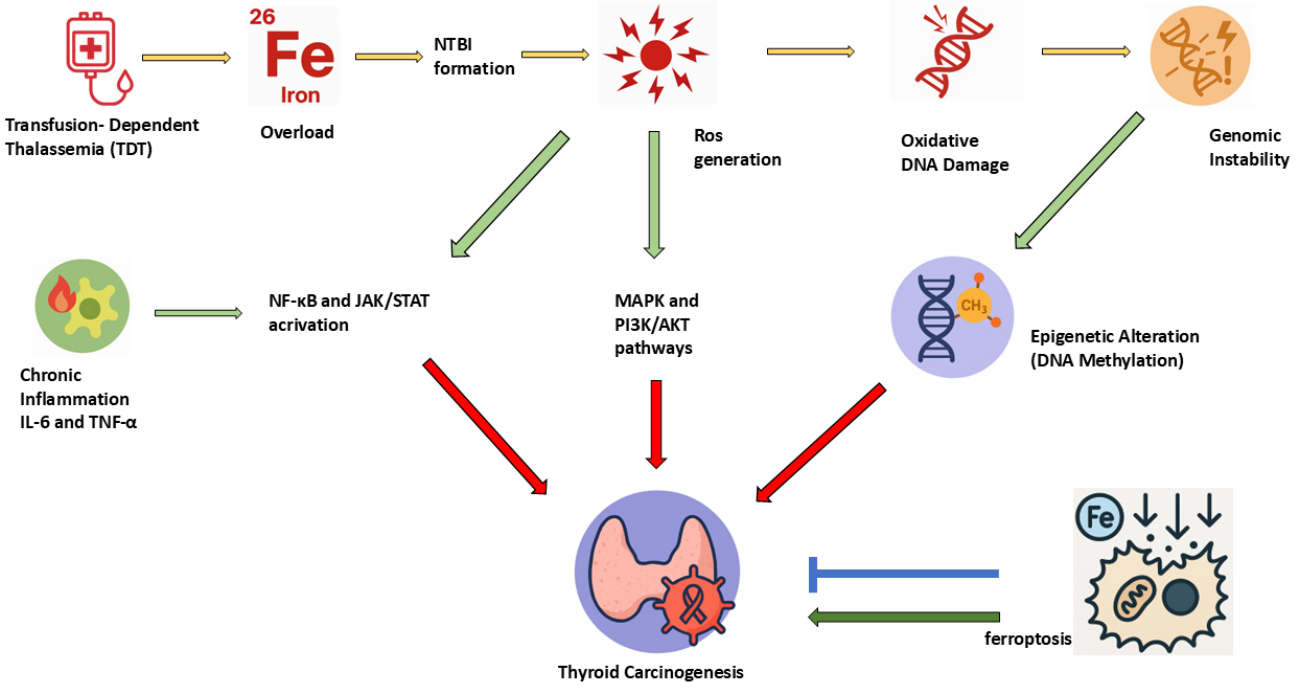

Fig. 1. Schematic representation of mechanistic links between transfusion-dependent thalassemia (TDT) and thyroid carcinogenesis. Chronic blood transfusions in TDT patients lead to systemic iron overload and the accumulation of non-transferrin-bound iron (NTBI). NTBI catalyzes the Fenton reaction, generating reactive oxygen species (ROS) that cause oxidative DNA damage and genomic instability. ROS also activate oncogenic pathways such as mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), promote chronic inflammation via interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), and induce epigenetic dysregulation. These mechanisms collectively contribute to thyroid carcinogenesis. Ferroptosis, an iron-dependent form of regulated cell death, plays a dual role in this context: it may suppress tumor initiation by eliminating damaged cells (tumor suppressive pathway, blue inhibition arrow), yet under chronic oxidative stress, it may also shape a tumor-promoting immune microenvironment (tumor-promoting pathway, dark green arrow). Figure created using ChatGPT (OpenAI, GPT-4.5 model, 28 April 2025, https://chat.openai.com/) along with Microsoft PowerPoint (Microsoft Office Professional Plus 2021, Microsoft Corporation, Redmond, WA, USA).

Iron-Induced ROS and DNA Damage

The molecular consequences of ROS overproduction are diverse and damaging. Oxidative stress induces DNA damage, promotes genomic instability, and impairs DNA repair mechanisms—fundamental steps in the initiation of cancer [27,28]. Specifically, hydroxyl radicals generated in iron-rich environments can directly modify nucleotides, fostering mutagenesis. ROS also alter protein structures, disrupting enzymatic and signaling functions, and activating oncogenic cascades such as the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathways, which are implicated in thyroid cancer progression [29]. Moreover, lipid peroxidation—another hallmark of oxidative stress—targets membrane-bound polyunsaturated fatty acids, leading to cellular dysfunction and the formation of reactive aldehydes. In thyroid cancer patients, increased markers of lipid peroxidation and elevated oxidative indices have been associated with aggressive features such as angioinvasion and metastasis [30].

Evidence Linking Iron to Thyroid Cancer

The thyroid gland is intrinsically vulnerable to oxidative stress due to its high metabolic activity and the physiologic use of hydrogen peroxide during thyroid hormone synthesis [31]. In the setting of iron overload, this vulnerability is exacerbated. Several clinical observations, as reviewed by Hodroj *et al.* [2], support an increased prevalence of papillary thyroid carcinoma in patients with thalassemia, suggesting that iron accumulation may be a contributing factor. ROS not only drive malignant transformation by damaging DNA but also enhance the activation of mitogenic signaling pathways such as mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and PI3K/AKT, which are frequently altered in thyroid cancer [32]. Interestingly, ROS at pharmacological doses—such as those generated by high-dose vitamin C—have been shown to inhibit these same pathways and induce apoptosis in thyroid cancer cells, revealing a dose-dependent duality in ROS function [29].

Recent research further supports the hypothesis that oxidative stress plays a central role in thyroid carcinogenesis. A study has reported significantly elevated total oxidant status (TOS) and oxidative stress index (OSI) in patients with DTC, reflecting a systemic redox imbalance [27]. While these findings are correlative, they suggest that ROS may synergize with genetic mutations—such as those in B-Raf proto-oncogene (*BRAF*) or Rat Sarcoma proto-oncogene (*RAS*)—to promote thyroid tumorigenesis. *In vitro* models have shown that increasing intracellular iron can trigger ROS production, leading to apoptosis in thyroid cancer cells, underscoring iron's potential cytotoxic role [33].

In this context, clinical and experimental data support the role of redox biomarkers and iron-dependent cell death mechanisms in thyroid cancer. In thyroid cancer specifically, the accumulation of ROS has been shown to increase levels of TOS and OSI, which correlate with advanced disease features such as angioinvasion and metastasis [27,28]. These indices serve as useful proxies for measuring redox imbalance in clinical settings.

Beyond mutational events, iron-induced oxidative stress may contribute to epigenetic alterations, including DNA methylation changes and deletion of tumor suppressor genes such as Cyclin-dependent kinase inhibitor 2A and 2B (*CDKN2A/2B*), both of which are implicated in various malignancies [34]. The interplay between iron metabolism and thyroid function is further complicated by iron deposition in endocrine tissues, including the thyroid, which has been linked to both hypothyroidism and tissue injury [35].

Despite compelling evidence, a direct causal relationship between iron overload and thyroid cancer has yet to be definitively established. Much of the available data derive from β-thalassemia populations, limiting broader applicability. Additionally, the confounding effects of other risk factors—such as radiation exposure, autoimmune thyroiditis, or viral infections like hepatitis C—have not been fully clarified. Nonetheless, the biological plausibility and growing body of clinical and experimental data warrant further investigation.

Therapeutic Implications

Although no direct evidence currently supports the use of iron chelators in thyroid cancer, their established ability to reduce oxidative damage in other malignancies suggests they may represent a promising therapeutic strategy, particularly in redox-sensitive thyroid pathologies [36,37]. Ferroptosis inducers that exploit iron's pro-oxidant properties, such as erastin, are also being explored as targeted cancer therapies [28]. Although vitamin E supplementation has been explored as a strategy to mitigate oxidative stress in TDT, clinical trials have shown no significant improvement in oxidative markers or quality of life following its use [38]. Given the heightened cancer risk among transfusion-dependent patients, routine thyroid screening has been proposed as a preventive strategy for early detection [3]. Although no clinical trials currently address iron chelators or ferroptosis inducers specifically in TDT-related thyroid disease, these agents merit further investigation. We also recommend annual thyroid ultrasound by experienced operators as a practical screening strategy in this high-risk group. In conclusion, iron overload, in conditions such as thalassemia, fosters oxidative stress, which may contribute to thyroid carcinogenesis through DNA damage, oncogenic signaling, and epigenetic modification. Although causality remains to be conclusively proven, the emerging evidence is strong and supports the development of targeted screening and therapeutic strategies aimed at modulating iron metabolism and oxidative stress in high-risk populations.

Chronic Inflammation and Thyroid Cancer in Thalassemia

Pro-Inflammatory Cytokines in the Tumor Microenvironment

Over the past decade, numerous studies have examined the role of inflammation in DTC, indicating a positive correlation between chronic inflammation and an increased risk of DTC development. The presence of an inflammatory microenvironment consisting of immune cells and proinflammatory molecules may play a role in the development and progression of thyroid cancer [39,40]. In particular, inflammatory mediators such as cytokines and chemokines in the tumor microenvironment (TME) promote cancer progression. Oxidative stress, described in detail in a previous section, may further intensify this process [39,41]. Additionally, a study indicates that oncoproteins expressed in PTC, such as REarranged during Transfection/papillary thyroid carcinoma (RET/PTC), RAS, and BRAF, can also trigger a pro-inflammatory response in thyroid cells [40].

Immune Cells and Tumor-Associated Macrophages (TAMs)

Increasing research highlights the presence of activated immune cells, proinflammatory cytokines, and a complex interaction between inflammatory and proliferative signaling pathways within the thyroid tumor microenvironment. A crucial component of this inflammatory microenvironment associated with thyroid cancer is the presence of tumor-associated macrophages (TAMs), which play a significant role in enhancing tumor proliferation and invasiveness [42,43]. Notably, studies have shown that TAM density is increased in advanced thyroid cancers, correlating with capsular invasion and extrathyroid extension, as well as decreased cancer-related survival [44,45]. Apart from TAMs it has been documented that proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), produced by inflammatory and epithelial cancer cells, are also

crucially involved in thyroid cancer inflammation. TNF-α is highly expressed in TME and impacts both tumor development and immune responses, playing a multifaceted role in the progression of PTC [46]. An *in vitro* study by Lv *et al*. [47] demonstrated that TNF-α could trigger epithelial-mesenchymal transition (EMT) in PTC cell lines, a process linked to enhanced tumor invasiveness and metastatic potential.

Interleukins play a pivotal role in thyroid cancer by regulating tumor cell proliferation and promoting epithelial-mesenchymal transition, as well as angiogenesis. Additionally, they influence the ability of thyroid cancer cells to resist apoptosis and evade immune surveillance. Through these pathways, interleukins significantly contribute to the tumorigenesis and progression of thyroid cancer [48]. Among interleukins, IL-6 has been demonstrated to promote proliferation and colony formation of thyroid cancer stem cells by activating the interleukin-6/Janus kinase 1/signal transducer and activator of transcription 3 (IL-6/JAK1/STAT3) pathway, thereby facilitating tumor growth and metastasis [49]. Additionally, in papillary thyroid cancer, IL-6 can downregulate thyroid-specific genes, such as those for the sodium/iodide symporter (NIS), thyroid peroxidase and thyroid-stimulating hormone receptor, as well as transcription factors, resulting in the dedifferentiation process. This, in turn, lowers the effectiveness of radioiodine therapy by reducing the expression of NIS [50].

Both thyroid cancer and thalassemia patients exhibit elevated levels of inflammatory cytokines. In β-thalassemia patients, levels of the inflammatory cytokines TNF-α and IL-6, as well as the anti-inflammatory cytokine IL-10 have been found to be significantly higher compared to healthy individuals, indicating an association with higher oxidative stress status in these patients [51]. In particular, elevated IL-6 levels seem to be related to factors such as the frequency of blood transfusions, splenectomy status, and ferritin levels [52]. Similarly, patients with papillary thyroid cancer exhibit increased IL-6 and IL-8 levels compared to healthy individuals, which tend to normalize after surgery [53]. Although IL-6 contributes significantly to thyroid cancer progression, there is no direct evidence linking it to thyroid cancer in thalassemia patients, highlighting the need for further studies to investigate any potential association. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling is involved in the link between inflammation and cancer, promoting tumor progression and immune evasion. Its specific role in thyroid carcinogenesis is discussed in the signaling pathways section below: JAK/STAT signaling, especially via IL-6-mediated STAT3 activation, contributes to thyroid cancer aggressiveness and resistance to therapy (a detailed analysis of this pathway follows in the section “Dysregulated Signaling Pathways”).

Autoimmunity and Hashimoto’s Thyroiditis

The link between thyroid cancer, especially the PTC subtype, and autoimmune thyroid diseases (AITD) has been documented in numerous studies. The incidence of well-differentiated papillary thyroid carcinomas is increased in autoimmune thyroid diseases like Hashimoto’s thyroiditis (HT) [40]. A systematic review by Resende de Paiva *et al*. (2017) [54] examining the association of Hashimoto’s thyroiditis and PTC found a relative risk of 2.36 for HT among PTC patients and 1.40 for PTC among HT patients. The inflammatory microenvironment in Hashimoto’s thyroiditis can trigger multiple signaling pathways, such as NF-κB and the STAT family, which are key regulators of tumor cell growth, survival, and immune escape [55]. While additional studies are needed to better understand the exact mechanisms underlying the coexistence of thyroid autoimmune and neoplastic conditions, current knowledge on the subject remains limited [56].

Inflammation in Thalassemia

Thalassemia, in both the transfusion-dependent and non-transfusion-dependent types, is characterized by chronic inflammation due to iron overload and anemia [57]. Excess iron accumulates in cells, triggering redox activity and resulting in cellular toxicity [2]. A recent study showed upregulation of toll-like receptors 3 and 9, correlating with increased proinflammatory cytokines [58]. While a direct association between thalassemia and thyroid cancer has not been established to date, emerging evidence highlights that both conditions involve chronic inflammation, a key factor in carcinogenesis.

Dysregulated Signaling Pathways

Tumorigenesis of thyroid tumors involves dysregulation of the signaling pathways of MAPK and phosphatidylinositol-3 kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathways. The most common oncogenic drivers of these pathways are *BRAF* and *RAS* point mutations [16,32]. However, we found no studies directly linking these thyroid-specific alterations to iron overload in the context of TDT. This represents a notable gap that warrants further mechanistic investigation.

MAPK Pathway

MAPK pathway is a critical signal transduction cascade in the Pathogenesis of thyroid carcinomas (TCs). Its constitutive activation drives tumorigenesis by regulating key cellular processes, including proliferation, differentiation, and survival [59]. This pathway involves multiple oncogenic proteins, notably receptor tyrosine kinases such as REarranged during Transfection (RET), Anaplastic Lymphoma Kinase (ALK), Vascular Endothelial Growth Factor Receptor (VEGFR), and Neurotrophic Receptor Tyrosine

Kinase 1 and 3 (NTRK1/3), as well as intracellular effectors such as RAS, Rapidly Accelerated Fibrosarcoma (RAF), Mitogen-activated protein kinase kinase (MEK), and extracellular signal-regulated kinase (ERK). Upon ligand binding, receptor tyrosine kinases initiate downstream signaling, promoting malignant transformation and tumor progression [16]. The concept of "mutual exclusivity" in mutations and rearrangements has been challenged, suggesting that these genetic alterations can coexist in PTCs. This co-occurrence is linked to more aggressive tumor behavior and progression to PDTCs and ACAs, often driven by additional mutational events [60,61].

PI3K/AKT/mTOR Pathway

The PI3K/AKT pathway plays a crucial role in thyroid tumorigenesis, involving key components such as Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA), AKT, Phosphatase and Tensin Homolog (PTEN), and the mTOR signaling complex [59]. Its activation occurs via RAS binding to PI3K catalytic subunits (notably PIK3CA and PIK3CB) or through receptor tyrosine kinase stimulation by growth factors, leading to AKT phosphorylation and downstream signaling. PTEN serves as a critical negative regulator by dephosphorylating Phosphatidylinositol (3,4,5)-Trisphosphate (PIP3), and its loss—either through mutations or deletions—results in constitutive pathway activation, particularly in PDTC and ACA [62–65].

Wnt/β-Catenin Pathway

The Wnt/β-catenin signaling pathway, regulated by Catenin beta 1 (*CTNNB1*), Axis Inhibition Protein 1 (*AXIN1*), and Adenomatous Polyposis Coli (*APC*) genes, plays a key role in cell adhesion and transcription [66]. Under normal conditions, β-catenin is phosphorylated by APC-bound kinases, including casein kinase I and Glycogen synthase kinase 3 (GSK3), leading to its ubiquitination and degradation [67]. Mutations in *APC* or *CTNNB1* disrupt the regulatory mechanism controlling β-catenin degradation, leading to pathway overactivation, uncontrolled proliferation, and tumor progression. In thyroid cancer, β-catenin pathway dysregulation is observed in approximately 25% of PDTCs and 65% of ACAs, often accompanied by nuclear β-catenin accumulation—a rare event in DTCs [16]. This process reflects the failure of the APC/AXIN/GSK3β complex, which normally promotes β-catenin phosphorylation and proteasomal degradation. When Wnt signaling is active or when this complex is genetically altered, β-catenin escapes degradation, accumulates in the cytoplasm, and translocates to the nucleus, where it functions as a transcriptional activator of genes promoting tumor growth [66,68]. Telomerase reverse transcriptase (TERT) enhances Wnt/β-catenin signaling by forming a transcriptional complex with β-catenin at target gene chromatin, thereby promoting transcriptional activation and contributing to tumor progression [69]. Loss of E-cadherin, a hallmark of PDTCs and anaplastic thyroid carcinomas (ATCs), facilitates dedifferentiation and invasion. These alterations converge on the β- catenin pathway, highlighting its activation as a critical driver of thyroid cancer aggressiveness [70,71].

Iron-Induced Modulation of Cellular Signaling

As previously discussed, iron overload disrupts redox homeostasis and contributes to cellular stress. In this section, we explore how these oxidative effects intersect with key oncogenic signaling pathways implicated in thyroid carcinogenesis. Specifically, in mesenchymal stem cells, iron-induced oxidative stress influences the MAPK, PI3K/AKT, and Wnt/β-catenin pathways, potentially promoting tumor progression.

There are numerous effects of iron overload in mesenchymal stem cells (MSC) components and MSC processes. For instance, the expansion of the labile iron pool (LIP) can elevate ROS production, which in turn can activate signaling pathways that induce MSC cycle arrest in the G0/G1 phase, promote apoptosis, and suppress MSC proliferation [72]. Excess iron has harmful effects on MSCs, disrupting their functionality, differentiation potential, hematopoiesis-supporting functions, and epigenetic regulation. It also alters key signaling pathways, including ROS, PI3K/AKT, MAPK, tumor protein p53 (p53), AMP-activated protein kinase/Mitochondrial fission factor/Dynamin-related protein 1 (AMPK/MFF/DRP1) and Wnt [73]. Although the impact of excess iron on Wnt/Ror2 signaling in MSCs remains unclear, it can be inferred that under iron- overloaded conditions, MSCs may facilitate cancer cell proliferation and accelerate cancer progression through Wnt signaling. Additionally, Wnt/β-catenin signaling can elevate ROS production, trigger MSC aging via p53 and p21 [74], and consequently impair the reparative functions of MSCs.

NF-κB Signaling Pathway

NF-κB is a key transcription factor regulating immune responses, inflammation, and cancer progression. In thyroid cancer, it promotes tumor growth, inhibits apoptosis, and enhances aggressiveness [75,76]. Its activation has been linked to more invasive forms of thyroid cancer [77], driven by oncogenic mutations (*BRAF*, *RET*) or chronic inflammatory states such as Hashimoto's thyroiditis. While direct evidence in thalassemia is limited, iron-induced inflammation may be a contributing factor.

JAK/STAT Pathway

The JAK/STAT pathway plays a critical role in thyroid cancer progression and therapeutic resistance. IL-6-mediated STAT3 activation promotes tumor cell proliferation, dedifferentiation, and immune evasion. Its activation is linked to shorter recurrence-free survival in differentiated

thyroid cancer and poor outcomes in anaplastic subtypes [78]. Notably, this pathway also drives resistance to BRAF inhibitors in BRAF(V600E)-positive tumors, supporting the rationale for combined therapeutic targeting [49,79]. The iron-induced activation of the PI3K/AKT/Forkhead box O (FOXO) pathway, combined with inactivation of the PI3K/AKT/mTOR pathway in MSCs, may have significant implications for iron-overloaded patients [73]. These alterations could contribute to increased cancer susceptibility, as observed in hereditary hemochromatosis [80].

Other Pathways

Iron overload in rat bone marrow-derived mesenchymal stem cells (BM-MSCs) has been shown to increase the phosphorylation of ERK1/2 and c-Jun N-terminal kinase (JNK) [81], while in mice BM-MSCs, it elevated ERK levels [82]. Since increased intracellular ROS can activate ERKs, JNKs, or p38-MAPKs [83], the iron-induced activation of MAPK/ERK and MAPK/JNK pathways in rat BM-MSCs may be mediated through iron-induced ROS. However, in human BM-MSCs, although iron enhanced the phosphorylation of nuclear ERK1/2, this activation occurred without apoptotic signals or ROS elevation [84]. This suggests that, beyond ROS, other mediators may contribute to pathway activation under iron-overloaded conditions.

Epigenetic Regulation in Thyroid Cancer: Emerging Links to Iron Overload

Epigenetic Modifications in Thyroid Cancer

In recent years, the focus in cancer biology has expanded beyond genetic mutations to encompass a spectrum of epigenetic and post-transcriptional regulatory mechanisms. Particular attention has been directed toward the epigenetic landscape of thyroid cancer, including the roles of non-coding RNAs and the potential influence of systemic factors such as iron overload on epigenomic integrity.

DNA Methylation and Promoter Silencing

Recently, in addition to genetic alterations leading to cancer progression, including cell growth, survival and metastasis, other mechanisms such as epigenetic alterations, microRNA and long non-coding RNAs have received attention [85,86]. Methylation of certain tumor suppressor genes or promoters of essential genes is known to assist in tumorigenesis and dedifferentiation [87]. Specifically, in thyroid carcinomas, methylation of the TSH-receptor gene promoter is associated with reduced iodine uptake which renders treatment with radioactive iodine less effective. Additionally, methylation of the thyroid hormone receptor β gene causes reversible enhancement of tumor cell proliferation and migration [32,88]. RNA transcripts that do not encode for a protein are called non-coding RNAs. Small (under 200 bps) and long non-coding RNAs (greater than 200 bps) can be distinguished [89]. Emerging evidence suggesting that long non-coding RNAs play an important role in cancer biology is gaining popularity. These molecules may interact with chromatin-modifying enzymes as well as with histones [90]. Thus, DNA methylation not only plays a diagnostic and prognostic role but may also guide therapeutic strategies, particularly in radioiodine- resistant thyroid tumors. These methylation changes play a role in tumor dedifferentiation and treatment resistance, notably impacting radioiodine therapy.

Non-Coding RNAs in Thyroid Cancer

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are now recognized as key regulators in thyroid cancer biology. miRNAs can function either as tumor suppressors or oncogenes, depending on their expression profiles, while lncRNAs influence chromatin remodeling, modulate gene transcription, and promote processes such as epithelial-to-mesenchymal transition. These molecules often show differential expression between malignant and benign thyroid tissues and are increasingly investigated as prognostic biomarkers and potential therapeutic targets. Micro-RNAs have been extensively studied in the context of cancer pathogenesis, revealing two distinct types: miRNAs that act as tumor-suppressors which have been found downregulated in certain cancers, and miRNAs with oncogenic properties that are overexpressed in others [91]. Dysregulation of RNA is implicated in disease progression [81] and may be useful as an independent prognostic factor for the patient's outcome [92]. Research has shown that lncRNAs induce epithelial-to-mesencymal transition, through PI3K-AKT as well as Wnt/β-catenin pathways, promoting metastasis [93]. Furthermore, lncRNAs are potent biomarkers and highly specific for a given cancer type. In thyroid cancer, the level of tumor-suppressive lncRNAs is considerably lower compared to non-neoplastic tissue. Additionally, oncogenic lncRNAs are found to be over-expressed in malignant thyroid tissue [94]. Non-coding RNAs are emerging as key players in thyroid cancer biology, with strong potential as both biomarkers and therapeutic targets.

Iron Overload and Epigenetic Alterations

Systemic iron overload—prominent in thalassemia—may also influence the epigenome, potentially predisposing to malignancy. Iron-induced oxidative stress has been shown to affect methylation patterns, histone function, and chromatin remodeling [95]. In hereditary hemochromatosis, hypermethylation of tumor suppressor genes has been reported [96], suggesting that excess iron may trigger early epigenetic reprogramming. A genome-wide methylation study by Zhang *et al.* [97] demonstrated significant differences in thalassemia patients compared to healthy controls. Whether such changes involve thyroid-specific genes

remains unknown, but this represents a promising direction for future research. Epigenetic dysregulation, via promoter methylation and non-coding RNAs, underlies key processes in thyroid cancer progression and offers translational potential. Iron overload—particularly in thalassemia—may further shape the epigenome, promoting tumor heterogeneity. These molecular–metabolic intersections warrant integrative studies to define thyroid-specific epigenetic signatures and inform precision oncology. To date, no studies have directly examined methylation changes in thyroid-specific genes in thalassemic patients. This represents an important area for future investigation.

Ferroptosis in Thalassemias and Thyroid Cancer

Ferroptosis in Thalassemia

As discussed earlier, iron overload in thalassemia arises from chronic transfusions, increased absorption, hemolysis, and hepcidin suppression [18]. These mechanisms are key drivers of ROS accumulation and ferroptosis susceptibility. Ferroptosis is an iron- dependent form of regulated cell death, triggered by the accumulation of lipid peroxides and reactive oxygen species (ROS) to cytotoxic levels, first proposed in 2012 [98], and is characterized by the iron-dependent, overwhelming accumulation of lipid reactive oxygen species to lethal levels. Polyunsaturated fatty acids (PUFAs) in cellular membranes are vulnerable to peroxidation and subsequent disruption and lipid peroxides are responsible for the inactivation of enzymes and proteins [99]. Ferroptosis is tightly related to iron metabolism, even though a study has shown that another metal, copper, is implicated in the same pathophysiological mechanisms that lead to ferroptosis [100]. In addition, ROS accumulation, which is the initial signal to induce ferroptosis, is also generated by the mitochondrial electron transport chain and the NADPH oxidase protein family [101]. Nevertheless, the main causes of ROS production (and subsequent ferroptosis) in β-thalassemia are the accumulation of α-globin and iron overload [18]. In the case of iron overload, there is an increase of ROS production via Fenton chemistry (the formation of hydroxyl radicals through the reaction between Fe^{2+} and hydrogen peroxide) as well as increased transport of iron to several enzymes involved in lipid peroxidation [102].

A study has revealed that ferroptosis is an important regulatory factor in the development of many diseases, such as cancer, neurodegenerative and inflammatory diseases [103]. Research on the specific mechanisms implicated in ferroptosis has rapidly increased, but our understanding in this field is still incomplete. However, it is undeniable that it is a distinct form of cell death, different from apoptosis, autophagy and others, in terms of biological, morphological and genetic characteristics [98].

Understanding ferroptosis pathways could reveal its role in cancer biology and guide the development of targeted therapies. Erastin is the prototype ferroptosis inducer [98]; it directly inhibits antitransporter system X_c^- an important antioxidant system consisted of two membrane subunits, solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2). Through this system extracellular cysteine is inserted into the cell and is involved in the synthesis of glutathione (GSH), which functions as a cofactor for glutathione peroxidases (GPXs). GPX4 catalyzes the conversion of lipid peroxides (L-OOH) to corresponding alcohols (L-OH), thus inhibiting ROS generation and subsequent ferroptosis [104]. Hence, GPX4 functions as the gatekeeper of ferroptosis and depletion of cysteine or/and glutathione leads to excessive lipid peroxidation and cell death. Moreover, insufficiency of other important cellular substances can lead to ferroptosis; Selenium is an important component of selenocysteine-containing enzymes, including GPX4, and its deficiency leads to ferroptotic damage. Coenzyme Q10 (CoQ) is a key lipophilic antioxidant involved in mitochondrial respiration and defense against ferroptosis. It is well-known that it reduces cell sensitivity in ferroptosis [105]. Ferritin, which is the main iron storage protein, is obviously important in preventing iron-mediated oxidative cell damage. The release of iron stored in ferritin through ferritinophagy mediated by nuclear receptor coactivator 4 (NCOA4) [106] as well as ferritin degradation by the activation of the ubiquitin- proteasome system (UPS) [107], induce ferroptosis.

Tumor protein p53 (*TP53*), a fundamental tumor suppressor gene, downregulates the expression of *SLC7A11*, thus inhibiting cystine uptake through system X_c^-, resulting in accumulation of lipid ROS and ferroptosis [108]. However, the overall role of *TP53* in ferroptosis is still unclear and may depend on cell type and target gene. Furthermore, nuclear transcription factor E2 (Nfr2), which induces the expression of the antioxidant protein heme oxygenase 1 (HO-1), is another important inhibitor of ferroptosis, because it governs several downstream genes implicated in the regulation of iron metabolism, intermediary metabolism and glutathione synthesis [109].

Ferroptosis and Thyroid Cancer

Ongoing research is exploring ferroptosis in thyroid cancer, and there is strong evidence suggesting a correlation between ferroptotic regulators and pathophysiological mechanisms in this malignancy. *GPX4* expression has been found to be elevated in thyroid cancer [110] and was correlated with poor prognosis [111]. On the other hand, inhibition of *GPX4* led to reduced viability in thyroid cancer [110]. SLC7A11, a transmembrane protein which plays an important role in ferroptosis, has also been found to be elevated in thyroid cancer tissues [112] and its downregulation hindered the development of PTC [113]. Furthermore, the high activity of Nfr2 in PTC cells [114] and the consequent inhibition of ferroptosis is also linked to increased viability of these cells and poor prognosis. Sirt6 is a chromatin

associated protein required for DNA repair and is overexpressed in thyroid cancer [115]. A recent study showed that Sirt6 induces the autophagy degradation of ferritin through NCOA4, thereby increasing the sensitivity of cancerous cells in ferroptosis [116]. Another important component of the ferroptotic mechanism, TfR1, also known as CD71, which is involved in the insertion of iron into the cells, has been found to be downregulated in cell lines of anaplastic thyroid cancer. As a result, these cells maintain their viability against ferroptotic inducers, a mechanism that seems to contribute to the aggressiveness of anaplastic thyroid cancer [117].

There is a continuously growing amount of evidence extrapolated from recent studies which demonstrates that ferroptosis plays an important role in the pathophysiology of thyroid cancer and that novel agents inducing ferroptosis emerge as promising therapeutic methods. The induction of ferroptotic mechanisms due to iron overload in thalassemias could function as a protective mechanism against the occurrence of thyroid and other malignancies. On the other hand, iron is an important nutrient for cells and cofactor for several enzymatic reactions, so it could enhance the occurrence and progression of tumors. Of note, tumor cells have an increased ability to absorb iron since their iron requirements are higher than normal cells [118]. Another important issue is the impact of ferroptosis on the tumor microenvironment of malignancies. It has been claimed that ferroptosis may play a binary role in tumorigenesis. Ferroptosis in immune cells seems to be in favor of cancer progression and may result to the modification of immune response against malignancies; cancer-associated fibroblasts have been shown to induce ferroptosis in Natural Killer cells, thus limiting their cytotoxic action [119]. In another research, autophagy-related ferroptosis resulted in the modification of macrophage-mediated function in certain tumors, favoring tumor development [120]. The interplay between ferroptosis and the immune system is further complicated by the release of damage-associated molecular patterns (DAMPs), that can promote inflammation and immune responses [121,122]; ferroptotic death of tumor cells thus leads to remodeling of the immune microenvironment. The specific interactions need to be further investigated.

Ferroptosis represents a critical interface between iron metabolism and cancer progression. In thalassemia, chronic iron overload predisposes cells to ferroptosis but may also induce resistance mechanisms such as *GPX4* upregulation. In thyroid cancer, ferroptosis resistance markers like SLC7A11 and nuclear factor erythroid 2-related factor (NRF2) are associated with aggressiveness, while ferroptosis inducers show promise as therapeutic tools. Exploring the dual role of ferroptosis—as both a tumor suppressor mechanism and a modulator of immune responses—may unlock novel treatment strategies for iron-related malignancies.

Conclusion

The rising incidence of thyroid cancer in TDT highlights a potential mechanistic link centered on iron overload. Excess iron induces oxidative DNA damage, promotes chronic inflammation, and disrupts oncogenic signaling pathways—including MAPK, PI3K/AKT, Wnt/β-catenin, and NF-κB—while impairing ferroptosis and apoptosis. These processes contribute to genomic instability, immune evasion, and tumor progression. Concurrently, epigenetic remodeling and non- coding RNA dysregulation modulate gene expression profiles conducive to malignant transformation. Although causality remains to be confirmed, the mechanistic overlap is compelling. While these mechanisms are well described in conditions such as hemochromatosis and hepatocellular carcinoma, direct evidence linking TDT to thyroid cancer remains limited. This review aims to highlight a potentially novel association, encouraging further investigation in this underexplored area. Routine thyroid surveillance in high-risk thalassemia populations and exploration of iron- or ferroptosis-targeted interventions may offer novel preventive and therapeutic avenues. This paradigm provides a valuable framework for studying iron-mediated oncogenesis across endocrine and hematologic contexts.

Availability of Data and Materials

Not applicable.

Author Contributions

CS, EKa and II conceived and designed this work. CS, EKa, DR, EKou, VT, SP, KB and II performed the literature research. CS, EKa, DR, EKou, VT, SP, KB and II drafted the manuscript, revised it critically for important intellectual content and wrote its final version. All authors gave final approval of the version to be submitted/published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and all agreed to be accountable for all aspects of the work relating to its accuracy and integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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