Published in final edited form as:

Endocrine. 2020 October ; 70(1): 24–35. doi:10.1007/s12020-020-02453-8.

Progression and Dormancy in Metastatic Thyroid Cancer: Concepts and Clinical Implications

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Abstract

Distant metastasis classically has been defined as a late stage event in cancer progression. However, it has become clear that metastases also may occur early in the “lifetime” of a cancer and that they may remain stable at distant sites. This stability of metastatic cancer deposits has been termed “metastatic dormancy” or, as we term it, “metastatic progression dormancy” as the progression either may reflect growth of already existing metastases or new cancer spread. Biologically, dormancy is the presence of non-growing, static metastatic cells that survive over time. Clinically, dormancy is defined by stability in tumor markers, imaging, and clinical course. Metastatic well-differentiated thyroid cancer offers an excellent tumor-type to understand these processes for several reasons: 1) primary therapy often includes removal of the entire gland with ablation of residual normal tissue thereby removing one source for new metastases; 2) the presence of a sensitive biochemical and radiographic monitoring tests enabling monitoring of metastasis throughout the progression process; and 3) its tendency toward prolonged clinical dormancy that can last for years or decades be followed by progression. This latter factor provides opportunities to define therapeutic targets and/or markers of progression. In this review, we will discuss concepts of metastatic progression dormancy and the factors that drive both long-term stability and loss of dormancy with a focus on thyroid cancer.

Keywords

metastasis; dormancy; progression; thyroid cancer

Brief Clinical Case

In 1991, a 40 year old woman was diagnosed with a 2.2x1.3x1.4 cm intrathyroidal well-differentiated papillary thyroid cancer (PTC). She was treated with total thyroidectomy and

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Conflicts of interest/Competing interests: None

Ethics approval, Consent to participate. Availability of data, material, and code: N/A Consent for publication: All authors have agreed to the final version of the publication Authors' contributions NR, TK, MDR all contributed to the writing of this manuscript

81 mCi of I-131 following levothyroxine withdrawal. Pre and post-therapy scans demonstrated thyroid bed uptake. Thyroglobulin (Tg) level on levothyroxine with TSH ~ 0.1 mU/L was < 2 ng/ml (undetectable) after initial therapy. Radioiodine (RAI) scan was negative in 1993 but TSH-stimulated Tg level was 12 ng/ml. Chest CT had a 4 mm left lobe lung nodule. Over the following 10 years, Tg remained undetectable on L-T4. Following rhTSH-stimulation in 1994, and 1998, Tg was 10 and 12 ng/ml, respectively with negative RAI scans. In 2003, with changes in Tg assay, Tg was 0.7 ng/ml with a TSH < 0.1 mU/L. Chest CTs in 1994, 1998, 2003, and 2005 were stable. Tg increased to 2.2 with a TSH < 0.1 mU/L in 2005. She received 154 mCi I-131 with a TSH-stimulated Tg of 13 ng/ml, had a negative post-therapy scan, and was referred for “thyroglobulin, scan negative” thyroid cancer.

Serial Tg levels and annual chest CTs were stable until 2011 when Tg increased to 8 ng/ml with TSH < 0.1 and the lung nodule increase to 9 mm. PET/CT was positive in the lung nodule (SUV 3.3) but not in other locations. CT-guided FNA of the lung nodule confirmed well-differentiated PTC. In 2013, Tg increased to 620 ng/ml with a suppressed TSH. PET/CT had new bone metastases in the left scapula and left iliac crest; the lung nodule increased in size to 14 mm. Molecular analysis of the primary tumor using a 248 gene panel identified a BRAF^{V600E} mutation and biopsy of the scapula bone metastasis showed PTC with no additional pathogenic mutations. The bone lesions were treated with external beam radiation that achieved pain control and stabilization. In 2017, the lung lesions grew $> 50\%$ in size and increased in number. She was started on Sorafenib and after initial period of stable disease, the lung nodules increased in size. Since 2018 she has been managed on Lenvatinib with stable disease, albeit with side effects that require occasional “drug holidays.”

Introduction

Classical cancer models describe metastatic progression as a late stage event in the “lifetime” of a malignancy, and that when it occurs it leads to rapid growth that results in patient mortality [1]. The development of more sensitive biochemical markers, such as Tg in thyroid cancer; PSA in prostate cancer, circulating tumor cell detection, circulating free DNA assays, and more sensitive imaging tests have challenged this model [1-6]. Data from multiple tumor-types demonstrate that some cancer cells have the ability to circulate, survive, and survive in a metastatic tissue environment while maintaining stability or growing slowly, demonstrating that metastatic progression also can be an early event. Because many cancers display specific patterns of distant metastases it was hypothesized that primary cancers secrete factors such as microvesicles, cytokines, or chemokines that enable metastasis early in the cancer process. This “seed and soil” relationship for cancer metastasis, where the location of metastatic progression has tissue specificity, was suggested more than a century ago by Paget [7-9]. In thyroid cancer, the specificity of location of metastases for the different thyroid cancer subtypes was affirmed in a recent 25 year autopsy study that included more than 650 cases from the Netherlands [10]. Additionally, primary cancers are now recognized to be comprised from a non-uniform heterogeneous group of cancer cells along with stromal and immune cells that can both constrain and promote progression depending on their cell type [11]. Resistant populations further can be selected

for surviving treatment and environmental challenges. Thus, different populations of cells may have metastatic and/or invasive potential while others may not have such properties, or they may be located in a sub-environment that does not support this behavior [11].

Recurrent vs Residual Thyroid Cancer

With this evolution in our understanding of the timing of metastatic progression, it is important to recognize that from a clinical perspective, “recurrence”, or the new identification of cancer after a period remission, may reflect instead the growth of preexisting small metastatic lesions to a detectable volume. This concept is particularly evident in thyroid cancer in which often the entire primary organ is removed and residual normal tissue is ablated with I-131. Per this model, if the primary source of metastatic cells has been removed and ablated, the later-identified metastases either must have predated the initial therapy or are secondary metastases from other subclinical sites. The concept of clinically silent early metastasis in thyroid cancer is incorporated into the American Thyroid Association Guidelines in which Tg levels are used in the response criteria and incorporated into the concept of “risk of structural recurrence” [12]. Importantly, the rate of progression after metastasis has occurred often reflects the aggressiveness of the primary tumor. Thus, it is slower typically for well-differentiated thyroid cancers and faster for poorly differentiated or anaplastic thyroid cancers. This high frequency of silent metastases is supported by the aforementioned autopsy series in which 15.6% of the 359 patients diagnosed with thyroid cancer incidentally at autopsy also had distant metastases [10]. Thus, in thyroid cancer, it seems likely that the majority of “recurrence” at distant sites represents growth of pre-existing metastases occurring as early stage events that are **biologically dormant** (i.e. not growing at the molecular level) or growing at a pace and volume below the threshold of detection (i.e. **clinically dormant**).

Once growth is detected in a metastatic site either biochemically or radiographically, well-differentiated thyroid cancer metastases tend to progress at a consistent log-linear rate over time [13,14]. This information has led to utilization of “doubling times” to monitor the pace of progression even for radiographically silent disease. The likelihood of radiographic detection increases concordantly with the Tg levels that can result in changes in clinical care [12,15]. Thus, not only the pace of progression, but also the size of lesions and Tg levels are used to determine the frequency of monitoring and the timing of initiation of therapies, even if “doubling times” are constant. For example, the clinical response to a tumor that doubles from 3 to 6 mm may not be the same as one that doubles 3 to 6 cm over the same period of time, despite a stable “doubling time.” Indeed, measurement increases of 20% when tumor masses are >1 cm defines progression in most clinical trials (e.g. RECIST criteria), thereby emphasizing the dual importance of progression and tumor volume. In these cases, TSH suppression to levels <0.1 mU/L is recommended to avoid TSH-induced growth of thyroid cancers that still maintain expression of the TSH receptor [12,15]. TSH suppression is less relevant for anaplastic thyroid cancers that lose TSH receptor expression. Importantly, in some cases, as exemplified in the case report, the doubling time decreases and new and/or more rapidly growing metastases are identified. These changes in growth rate represent changes in biological behavior that serve as “inflection points” in the progression of the cancer. Such alterations imply that secondary biological changes have occurred in the

metastatic deposits and lead typically to more extensive imaging and often more therapy not always targeting the secondary changes. On imaging, the growth may be limited to one or several lesions or may be consistent for all deposits. The molecular events that lead to changes in the biological behavior in metastases include the development of new driver events or loss of progression restraining events in the cancer cells that enhance their intrinsic growth rate and/or induce changes in the tumor microenvironment that facilitate progression [16]. In addition, the identification of metastasis in a new anatomic site may be due to loss of dormancy in metastatic deposits already present or could represent secondary metastases arising from another metastatic site [17]. As more information becomes available from both molecular analysis of human metastatic tumors and mouse models, it will be critical to fully define the mechanisms behind late stage progression to identify new therapeutic targets and biomarkers. Pathways that are currently targeted and those that may be exploited in the future are highlighted in this review.

Overview of Metastatic Spread, Dormancy, and Progression

Metastatic spread

The ability of cancer cells to metastasize often is linked to tumor growth, but because it may occur even in small tumors, growth is not necessary for metastasis. By distinction, progression of metastatic cancer more broadly includes both metastasis and subsequent growth of metastatic lesions over time. The ability of cancer cells to metastasize requires invasion and intravasation into the vascular and/or lymphatic systems, the ability to survive in circulation, extravasation and invasion in a new microenvironment, and subsequent survival (Figure 1). Intravasation is essential to the metastatic process [18]. Access to lymphatic vessels allows cancer cell spread to local and regional nodes while vascular invasion allows for distant metastases. Intravasation can occur as individual cells, which express enzymes to degrade local stromal elements such as metalloproteinases and collagenases, or can occur through collective migration where a subset of outer cells form a leading edge with those properties [19]. The process also can involve angiogenesis, or the formation of new blood vessels around these clusters of cells. Circulating individuals or clusters of cells can be identified and isolated from blood samples by genetic signatures and cell isolation methods and serve predictors for metastatic progression [4-6]. It has been demonstrated that the number of circulating cancer cells is much higher than previously thought, suggesting that the metastatic process is relatively inefficient [1]. Metastasis is regulated further by elements derived from the cancer cells and factors derived from the stroma [20]. The cancer-derived factors can contribute to metastasis both by affecting the invasive capacity of the cancer cells through paracrine interactions and by influencing how the cancer cells and the local and target organ micro-environments interact [20]. They can be subdivided into two groups; 1) factors that regulate extracellular environments such as those that induce angiogenesis, facilitate a prometastatic local immune environment and/or that regulate the pre-metastatic niche in target organs and 2) factors that regulate cancer cell biology including those that result in epithelial – to – mesenchymal transition (EMT) to enable local invasion and those that enable survival of cancer stem cell (CSC) populations [20]. EMT is one of the hallmarks of invasive cancers and is the transition of cancer cells from an organ tissue-type morphology (e.g. polarized epithelial cuboidal thyroid follicular

cells) to a fibroblastoid morphology that enables invasive capacity [21,22]. Cancer stem cells (CSC's) are a slowly dividing, relatively treatment-resistant population of cells that exhibit plasticity in response to therapeutic or environmental challenges and express genes and surface markers [21,23-25]. Cells that have undergone EMT and CSCs are critical in all components of the metastatic cascade and demonstrate the considerable "plasticity" of cancer cells.

Metastatic Dormancy

In both primary and metastatic environments, cancer dormancy is governed by a complex interplay between cancer cells and host factors that regulate angiogenesis, the immunologic response to the cancer, and cancer cell proliferation and apoptosis [26]. Angiogenic dormancy occurs when there is sufficient blood supply to support cell survival, but insufficient blood supply to support proliferation. Angiogenic responses are regulated largely by tissue hypoxia leading to secretion of growth factors from cancer and stromal cells with angiogenic and anti-angiogenic functions [27]. Dormancy is also maintained by immune-surveillance whereby immune cells, such as tumor infiltrating lymphocytes (TILs) are recruited that suppresses progression (e.g. cytotoxic CD8+ T cells) [28]. By contrast, subsets of TILs can suppress immune surveillance, and non-lymphocyte immune cell population such as tumor-associated macrophages (TAMs) can either inhibit or promote cancer progression depending on the subtype [29,30]. Tumor promoting TAMs have been shown to be highly prevalent in poorly differentiated and anaplastic thyroid cancer and play a functional role in progression in mouse models [31,32]. In addition, programmed death-ligand 1 (PD-L1) expression on cancer cells allows for avoidance of host immune system T cells and its overexpression predicts therapeutic response to checkpoint inhibitors that target either PD-L1 or its receptor [33,34].

Intrinsic cellular dormancy, which can be maintained by MPS genes, allows for cell survival in nutrient and oxygen-limiting environments whereby cells are pushed into the G0 phase of cell cycle, where they remain in a quiescent state until enough oxygen or other nutrients are provided to allow for growth [35,36]. Additional microenvironment factors also constrain or activate progression, including the tissue modulus (hardness), collagens and other protein complexes in the stroma, and other stromal cell types, such as cancer associated fibroblasts (CAFs) [37-39]. These processes are described in more detail later in this manuscript.

Metastatic Progression

In addition to loss of MPS gene expression, thyroid cancer growth rate in metastatic tissues often can be predicted by the histology and genotype of the primary tumor. For example, in papillary thyroid cancer the combination of a BRAF^{V600E} mutation with a mutation in the promoter of hTERT is associated with a more aggressive clinical course [40-42]. Similarly, the loss of P53, or co-occurrence of a BRAFV600E MAPK pathway activating mutation with PI3K pathway activation together lead to dedifferentiation, rapid growth, and poor prognosis [43-47]. FTCs, that more frequently have activation of the PI3K pathway, tend to metastasize hematogenously while PTCs tend to metastasize to regional nodes [10,12,48-50]. In general, metastatic lesions tend to retain clonal expression of driver mutations present in the primary cancer. However, in some cases, additional mutations such

as those in the SWI/SNF and DNA Damage Repair pathways are identified uniquely in metastatic lesions [51,52]. Thus, in some cases the progression is predicted by the mutation profile of the primary tumor, but in other cases, new genetic mutations can be identified in the metastatic lesions that may be important in late-stage progression. Because most of the available data have focused on analysis of DNA (i.e. identification of mutations), changes in gene expression and the roles of DNA hypermethylation and microRNAs are incompletely defined. Finally, similar to primary tumors, metastatic lesions are also comprised of subpopulations of thyroid cancer cells, immune cells, and stromal elements, all of which contribute to the growth or stability of metastatic lesions [53].

Regulation of Metastasis

Both stimulatory and inhibitory pathways regulate cancer progression. We will focus on inhibitory and activated pathways in cancer cells that modulate metastatic potential and changes in the microenvironment that restrain or facilitate metastatic progression. Although we are considering them separately, these features are closely linked and dynamically regulate one another. In addition, rates of growth of metastatic lesions may be influenced by specific features of metastatic sites, such as the blood-brain barrier, bone marrow vs bone cortex, and lung inflammatory responses. General mechanistic concepts relevant to thyroid cancer are reviewed below.

Tumor Cell Factors

Metastasis Progression Suppressors and Pathways—The term “metastasis suppressor” describes genes whose loss is sufficient to enable metastatic spread of cancer cells but not sufficient for cellular transformation [2,54]. They are distinct from tumor suppressor genes whose loss is sufficient to induce cellular transformation but may or may not regulate metastasis. Because these genes often inhibit many facets of cancer cell behavior, including proliferation, invasion, and EMT, we propose the term “**metastasis progression suppressors**” (MPS). More than 20 MPS genes have been described [55]. MPSs are typically expressed (or overexpressed) in primary cancers and function as intrinsic “brakes” to slow cancer cell growth. Reduced expression in progressive metastatic lesions and and/or in subcomponents of primary tumors are hallmarks of these genes, thus loss of expression is a potential biomarker for aggressive disease [56]. Moreover, it is possible that their re-expression, or inhibition of the consequently activated downstream pathways, represent potential therapeutic approaches [57]. Because metastatic dormancy is typical for thyroid cancer, it serves as an excellent model to study pathways that regulate dormancy in cancer cells.

Several of the known MPSs, and their functions, have been studied in thyroid cancer, including KiSS1, RCAN1.4, and NM23 [2,57-60]. The KiSS1 gene products, termed “kisspeptins”, are the endogenous ligands for G-protein coupled receptor (GPR) 54. In the hypothalamus, mutations in GPR54 or KiSS-1 cause infertility due to reduced development and function of the gonadotropin-releasing cells [61,62]. In addition to this function, KiSS-1-activated GPR54, and KiSS-1 activation of other pathways, together reduce the proliferative, invasive, and metastatic capacities of melanoma, breast and thyroid cancer

cells [58,59,63-65]. In addition, in solid tumors, KiSS1 expression follows the typical expression pattern of a MPS [66,60,67,68]. The inducibility of GPR54 by kisspeptins created a system to identify downstream metastasis suppression pathways. Subsequent studies demonstrated that GPR54 activity resulted in an increase expression and function of the regulator of calcineurin isoform 4 (RCAN1.4) leading to reduced calcineurin signaling in thyroid cancer, colon cancer, and melanoma cells [56,58]. RCAN 1.4 overexpression and activity were shown to be necessary for GPR54 effects in vitro, RCAN 1.4 overexpression was sufficient independently to inhibit cell motility and invasion, and its loss increased cell invasion and proliferation but was not for transformation, consistent with MPS activity [56,58,60]. The mechanisms by which RCAN 1.4 levels are reduced include promoter hypermethylation and increased protein degradation following phosphorylation by MAPK and TGF beta-activated-kinase -1 (TAK1) [59,69]. *In vivo* studies confirmed that RCAN 1.4 is a bonafide MPS in thyroid cancer. This MPS function required the transcription factor NFE2L3 (Nrf3) which is overexpressed in metastatic thyroid cancer lesions [60]. Similar data ascribing cancer progression activity to NFE2L3 was demonstrated in gastric and hepatic cancers [70].

Interestingly, RCAN 1.4 is known to be important in the biology of Down's syndrome, or trisomy 21, which is associated with a markedly reduced frequency of solid tumors [71]. RCAN 1.4 is the primary inducible transcribed mRNA of the RCAN1 gene located on chromosome 21 that was originally identified as the Down's Syndrome Critical Region 1 (DSCR1) gene [67]. The low frequency of cancer is recapitulated in mice that are engineered to have three copies of most chromosome 16 (the mouse homolog of human chromosome 21) and this feature is dependent on expression of three copies of RCAN 1 [71]. Promoter expression studies demonstrate that this effect is driven by RCAN 1.4 via NFAT-mediated regulation vascular endothelial growth factor (VEGF) release and angiogenesis [59,67,72]. Thus, it appears that RCAN 1.4 regulates cancer progression both by impacting cancer cells and, in the context of Down's syndrome, on host cell biology.

Oncogene Signaling and Metastatic Progression—Early stage well-differentiated thyroid cancers typically are genomically stable compared with other tumors [73]. Early thyroid oncogenic drivers include constitutively active forms of BRAF and translocations that involve RET that both display MAPK-dependent transformation for PTC; and RAS and PI3K activation for FTC. Hürthle Cell cancers appear to be driven by mTOR signaling and are characterized by chromosomal loss [74-77]. When these genomically stable tumors metastasize, they typically progress slowly while more genomically complex poorly differentiated tumors often progress more rapidly [52,78]. Targeting oncogenic drivers such as BRAFV600E, RET/PTC, ALK, NTRK, and others can result in robust initial anti-tumor responses in metastatic sites, although long-term disease control is rare [79].

As noted above, thyroid cancers display tumor specific patterns of distant metastases [10]. The reasons for these tissue distributions are uncertain but likely are driven by the oncogenic drives or the primary tumors through the release of factors that create a “premetastatic niche” in particular locations (Figure 1). For example, it has been shown that tumor-derived secreted factors, such as extracellular vesicles (EVs) (exosomes and microvesicles) carry DNA, RNA, proteins, cell surface receptors and other “cargo” that contribute to the

development of the premetastatic niche [80-82]. In thyroid and breast cancer cells, the components of secreted exosomes are regulated by MAPK and PI3K pathways [83,84]. In addition to microvesicles, cancer cells secrete a number of chemical factors (TGF β , VEGF, MMP9, LOX, CCL2, etc.) and RNA species that can regulate the premetastatic niche [81]. The factors together influence the host environment to regulate metastatic progression (Figure 1) [85,86].

To better target the more rapidly growing metastatic lesions with specificity, it is important to identify changes in those tissues that result in escape from biological and/or clinical dormancy [87]. Several groups have examined the genomics of growing metastatic lesions and in some cases, compared them with the primary tumors [51,52,88-91] and themes are beginning to emerge from these data: 1) there is continued expression of the initial driver oncogenes, 2) Mutations in genes involved in DNA Damage Repair are common and 3) Mutational loss of members of the SWI/SNF chromatin-remodeling complex are common. These data suggest the abnormal DNA repair and regulation of transcription may be crucial to late stage thyroid cancer progression [51,52,88,92]. Ongoing studies using RNA sequencing, methylation profiling, and single cell analyses are still required to more fully characterize the metastatic lesions.

Host Factors

Angiogenesis—Angiogenesis, or the process by which new blood vessels form, is a vital function, required for growth, development, wound healing, and in the tissue response to nutrient deprivation and hypoxia. Hypoxia is a potent “angiogenic switch” that signals quiescent endothelium to proliferate and migration leading to tube formation and the subsequent development of new blood vessels [93,94]. Limitations in the formation of new blood vessels is known to be one of the key features used to promote dormancy in cancer [1]. In addition to being needed for growth and metastasis at the primary tumor sites, angiogenesis also is required for the survival and growth of metastatic deposits [95]. The vascular endothelial growth factor (VEGF) is one of the critical hypoxia-stimulated angiogenic signals that has been targeted to treat thyroid cancer [96]. Higher levels of VEGF expression have been associated with tumor development, size, progression, and invasiveness [97-101]. The FDA-approved drugs for progressive metastatic thyroid cancer, Sorafenib and Lenvatinib, share VEGF receptors as targets and both reduce tumor vascularity, thus anti-angiogenesis is felt to be critical to the efficacy of these agents [102,103].

Extracellular matrix and Cancer-Associated Fibroblasts—The extracellular matrix (ECM) is the non-cellular tissue network that maintains tissue architecture by providing both structural and chemical support. It serves as a natural barrier to cell movement. Cancer cells, particularly those that have undergone EMT, secrete proteins that enzymatically degrade ECM to enable invasion by either individual cells or cluster of cells (i.e. individual or collective invasion) [104-106]. The biochemical and biophysical properties of the ECM also provides signals that promote cellular proliferation, migration and invasion [107,108]. Collagen is a principle component of the ECM. Changes in the balance between collagen deposition or degradation can result in the loss of homeostasis and enable intravasation

[109,110]. For example, degradation of the ECM by matrix metalloproteinases (MMPs) is critical and perhaps necessary for cancer cell invasion [111]. MMP over-expression is associated with increased cancer aggressiveness [112] and have been therapeutically targeted [112,113]. Matrix stiffness affects intracellular and intercellular mechanical interactions through signals transmitted by integrins and other receptor/signaling pathways [114]. In papillary thyroid cancer, activation of integrin signaling is associated with local invasion and EMT, and inhibition of key downstream effectors, including PAK, AKT, SRC kinase, and FAK reduce cancer invasion and metastasis in vitro and in vivo [25,78,115-117].

Cancer associated fibroblasts (CAFs) are stromal cells that modulate the ECM and also can facilitate cancer progression. Studies in genetically engineered mice have demonstrated that loss of Pten only in fibroblasts, can increase invasiveness of breast cancer [118-120] and that CAF-derived platelet derived growth factor beta (PDGF β) increases brain metastases in breast cancer [121]. In thyroid cancer, the role of CAFs in metastasis has been less well defined. It has been demonstrated; however, that BRAF V600E in mouse thyroid facilitates collagen expression, deposition, and CAF recruitment suggesting an important role for collagen in PTC development and progression [122].

Immune surveillance—Over the past decade, the concepts of immune surveillance to limit cancer progression, immune exhaustion whereby cancer cells evade the immune response, and the development of a prometastatic immune environment have greatly expanded [123]. Clinical studies have long implicated improved outcomes for patients co-existent Hashimoto's thyroiditis in PTC papillary thyroid cancer [124] and worse outcomes for patients with both thyroid cancer Graves' disease [125]. While a full review of this topic is beyond the scope of this manuscript, in thyroid cancer, there is evidence that as cancer progress, the immune environment progresses from an inhibitory environment to an exhausted or facilitating environment. Natural killer (NK) cells, cytotoxic T-lymphocytes, and mature dendritic cells all are essential in maintaining immune surveillance of cancers [126]. Several metastasis progression inhibitors have been shown to induce or maintain this immune response including KiSS-1 and RCAN1.4 [60,127]. By contrast, cancer progression is associated with a higher percentage of regulatory T-cells (Tregs), enrichment in lymphocyte expression of programmed death-1 (PD-1) and the PD-1 ligand 1 (PDL1), and enhanced infiltration of tumor associated macrophages (TAM) and immature dendritic cell infiltration that together facilitate cancer progression [128]. One interesting related phenomenon is the "abscopal effect" in which radiation therapy in one location induces an anti-tumor immune response that leads to metastasis regression outside of the radiation field [129]. In thyroid cancer, there is strong evidence that the development of an immune exhausted signature is associated with progressive disease and that TAMs are critical for progression [31,32,130-132]. The role of individual thyroid oncogenes in inducing an immune exhausted environment has been less clear. RET/PTC expression has been associated with lymphocytic infiltration in PTC. BRAFV600E expression has not been associated with an increase in PD1 and PDL1 expression in melanoma or PTC, suggesting that secondary changes and later stage events may be required for PD1/PDL1 overexpression [133]. Interestingly, correlations have been reported between overexpression of NFE2L3 with both a tumor promoting immune environment and distant metastases in thyroid cancer

[60,126]. Thus, dormant distant metastases likely are maintained in part by a balance in the cancer:immune interface, and changes in that balance functionally regulates cancer progression.

Summary

Thyroid cancer provides an outstanding model to study regulation of dormancy, as prolonged dormancy is common in the tumor type, but late progression also occurs. Based on biomarker and autopsy studies, it is likely that clinical “recurrence” of metastatic thyroid cancer often represents progression of pre-existing radiographically undetectable lesions. The growth rate of the metastases tends to mirror growth rates in the primary tumors and they are genomically similar. Factors that drive late stage progression include loss of expression of metastasis progression suppressors, gain of new mutations in genes that regulate DNA damage repair and chromatin remodeling, and potentially the expansion of resistant cells with increased proliferation, angiogenesis, invasion, and escape from immune surveillance. Further study and a deeper mechanistic understanding of the biology in progressive distant metastases is needed to improve the outcome for patients with progressive metastatic thyroid cancer.

Acknowledgments

Funding: Funding from NIH to MDR (R01CA102572, and R01CA227847).

References

1. Welch DR, Hurst DR: Defining the Hallmarks of Metastasis. *Cancer Research* 79(12), 3011–3027 (2019). doi:10.1158/0008-5472.CAN-19-0458 [PubMed: 31053634]
2. Ringel MD: Metastatic Dormancy and Progression in Thyroid Cancer: Targeting Cells in the Metastatic Frontier. *Thyroid* 21(5), 487–492 (2011). doi:10.1089/thy.2011.2121 [PubMed: 21476892]
3. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Hurwitz M, Ippolito JE, Kane CJ, Kuettel MR, Lang JM, McKenney J, Netto G, Penson DF, Plimack ER, Pow-Sang JM, Pugh TJ, Richey S, Roach M, Rosenfeld S, Schaeffer E, Shabsigh A, Small EJ, Spratt DE, Srinivas S, Tward J, Sheard DA, Freedman-Cass DA: Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *JNCCN* 17(5), 479–505 (2019). doi:10.6004/jnccn.2019.0023 [PubMed: 31085757]
4. Paoletti C, Hayes DF: Circulating Tumor Cells. *Novel Biomarkers in the Continuum of Breast Cancer* 882, 235–258 (2015). doi:10.1007/978-3-319-22909-6_10
5. Yang JD, Liu MC, Kisiel JB: Circulating Tumor DNA and Hepatocellular Carcinoma. *Seminars in Liver Disease* 39(4), 452–462 (2019). doi:10.1055/s-0039-1688503 [PubMed: 31226727]
6. Ehlers M, Allelein S, Schwarz F, Hautzel H, Kuebart A, Schmidt M, Haase M, Dringenberg T, Schott M: Increased Numbers of Circulating Tumor Cells in Thyroid Cancer Patients. *Hormone and Metabolic Research* 50(8), 602–608 (2018). doi:10.1055/a-0651-4913 [PubMed: 30081408]
7. Paget S: The distribution of secondary growths in cancer of the breasts. *The Lancet* 133(3421), 571–573 (1889). doi:10.1016/S0140-6736(00)49915-0
8. Hadfield G: The Dormant Cancer Cell. *British Medical Journal* 2(4888), 607–610 (1954). doi:10.1136/bmj.2.4888.607 [PubMed: 13190204]
9. Akhtar M, Haider A, Rashid S, Dakhilalla A: Paget's “Seed and Soil” Theory of Cancer Metastasis - An Idea Whose Time has Come. *Advances in Anatomic Pathology* 26(1), 69–74 (2019). doi:10.1097/PAP.0000000000000219 [PubMed: 30339548]

10. Hugen N, Sloot YJE, Netea-Maier RT, Water C.v.d., Smit JWA, Nagtegaal ID, Grunsven I.C.H.v.E.-v.: Divergent Metastatic Patterns Between Subtypes of Thyroid Carcinoma Results From the Nationwide Dutch Pathology Registry. *JCEM* 105(3), 299–306 (2020). doi:10.1210/clinem/dgz078
11. Wick MR: Metastases of malignant neoplasms: Historical, biological, & clinical considerations. *Seminars in Diagnostic Pathology* 35(2), 112–122 (2018). doi:10.1053/j.semdp.2017.11.009 [PubMed: 29198586]
12. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 26(1), 1–133 (2016). doi:10.1089/thy.2015.0020 [PubMed: 26462967]
13. Sabra MM, Sherman EJ, Tuttle RM: Tumor Volume Doubling Time of Pulmonary Metastases Predicts Overall Survival and Can Guide the Initiation of Multikinase Inhibitor Therapy in Patients With Metastatic, Follicular Cell-Derived Thyroid Carcinoma. *Cancer* 123(15), 2955–2964 (2017). doi:10.1002/cncr.30690 [PubMed: 28369717]
14. Miyauchi A, Kudo T, Kihara M, Higashiyama T, Ito Y, Kobayashi K, Miya A: Relationship of Biochemically Persistent Disease and Thyroglobulin-Doubling Time to Age at Surgery in Patients With Papillary Thyroid Carcinoma. *Endocrine Journal* 60(4), 415–421 (2013). doi:10.1507/endocrj.EJ12-0363 [PubMed: 23182919]
15. Nabhan F, Ringel MD: Thyroid Nodules and Cancer Management Guidelines: Comparisons and Controversies. *Endocrine Related Cancer* 24(2), 13–26 (2016). doi:10.1530/ERC-16-0432
16. Neophytou CM, Kyriakou T-C, Papageorgis P: Mechanisms of Metastatic Tumor Dormancy and Implications for Cancer Therapy. *International Journal of Molecular Sciences* 20(24), 1–21 (2019). doi:10.3390/ijms20246158
17. Reeves MQ, Kandyba E, Harris S, Rosario RD, Balmain A: Multicolour Lineage Tracing Reveals Clonal Dynamics of Squamous Carcinoma Evolution From Initiation to Metastasis. *Nature Cell Biology* 20(6), 699–709 (2018). doi:10.1038/s41556-018-0109-0 [PubMed: 29802408]
18. Zavyalova MV, Denisov EV, Tashireva LA, Savelieva OE, Kaigorodova EV, Krakhmal NV, Perelmuter VM: Intravasation as a Key Step in Cancer Metastasis Biochemistry (Moscow) 84(7), 762–772 (2019). doi:10.1134/S0006297919070071 [PubMed: 31509727]
19. Janiszewska M, Primi MC, Izard T: Cell adhesion in cancer: Beyond the migration of single cells. *JBC* 295(8), 2495–2505 (2020). doi:10.1074/jbc.REV119.007759
20. Liu Q, Zhang H, Jiang X, Qian C, Liu Z, Luo D: Factors involved in cancer metastasis: a better understanding to “seed and soil” hypothesis. *Molecular Cancer* 16(176), 1–19 (2017). doi:10.1186/s12943-017-0742-4 [PubMed: 28093071]
21. Dongre A, Weinberg RA: New insights into the mechanisms of epithelial–mesenchymal transition and implications for cancer. *Nature Reviews - Molecular Cell Biology* 20, 69–84 (2018). doi:10.1038/s41580-018-0080-4
22. Bhatia S, Wang P, Toh A, Thompson EW: New Insights Into the Role of Phenotypic Plasticity and EMT in Driving Cancer Progression. *Frontiers in Molecular Biosciences* 7(71), 1–18 (2020). doi:10.3389/fmolb.2020.00071 [PubMed: 32039235]
23. Peiris-Pagès M, Martinez-Outschoorn UE, Pestell RG, Sotgia F, Lisanti MP: Cancer stem cell metabolism. *Breast Cancer Research* 18(1), 1–10 (2016). doi:10.1186/s13058-016-0712-6 [PubMed: 26728744]
24. Cho J-M, Lee HJ, Chung JH, Kim WY, Kang MH, Ha KS, Woo SU, Lee JB: Papillary Thyroid Cancer Tumor Spheres Cultured by Passaging Without Sorting Exhibit Cancer Sternness. *Anticancer Research* 40(7), 3801–3809 (2020). doi:10.21873/anticancer.14369 [PubMed: 32620619]
25. Vasko V, Espinosa AV, Scouten W, He H, Auer H, Liyanarachchi S, Larin A, Savchenko V, Francis GL, Chapelle A.d.l., Saji M, Ringel MD: Gene expression and functional evidence of epithelial-to-mesenchymal transition in papillary thyroid carcinoma invasion. *PNAS* 104(8), 2803–2808 (2007). doi:10.1073/pnas.0610733104 [PubMed: 17296934]

26. Yeh AC, Ramaswamy S: Mechanisms of Cancer Cell Dormancy—Another Hallmark of Cancer? *Cancer Research* 75(23), 5014–5022 (2015). doi:10.1158/0008-5472.CAN-15-1370 [PubMed: 26354021]
27. Jahanban-Esfahlan R, Seidi K, Manjili MH, Jahanban-Esfahlan A, Javaheri T, Zare P: Tumor Cell Dormancy: Threat or Opportunity in the Fight against Cancer. *Cancers* 11(8), 1–23 (2019). doi:10.3390/cancers11081207
28. Endo H, Inoue M: Dormancy in cancer. *Cancer Science* 110(2), 474–480 (2018). doi:10.1111/cas.13917
29. Lee RS, Schlumberger M, Caillou B, Pages F, Fridman WH, Tartour E: Phenotypic and functional characterisation of tumour infiltrating lymphocytes derived from thyroid tumours. *European Journal of Cancer* 32(7), 1233–1239 (1996). doi:10.1016/0959-8049(96)00017-2
30. Bastman JJ, Serracino HS, Zhu Y, Koenig MR, Mateescu V, Sams SB, Davies KD, Raeburn CD Jr., R.C.M., Haugen BR, French JD: Tumor-Infiltrating T Cells and the PD-1 Checkpoint Pathway in Advanced Differentiated and Anaplastic Thyroid Cancer. *JCEM* 101(7), 2863–2873 (2016). doi:10.1210/jc.2015-4227 [PubMed: 27045886]
31. Ryder M, Gild M, Hohl TM, Pamer E, Knauf J, Ghossein R, Joyce JA, Fagin JA: Genetic and Pharmacological Targeting of CSF-1/CSF-1R Inhibits Tumor-Associated Macrophages and Impairs BRAF-induced Thyroid Cancer Progression. *PloS One* 8(1), 1–10 (2013). doi:10.1371/journal.pone.0054302
32. Ryder M, Ghossein RA, Ricarte-Filho JCM, Knauf JA, Fagin JA: Increased Density of Tumor-Associated Macrophages Is Associated With Decreased Survival in Advanced Thyroid Cancer. *Endocrine Related Cancer* 15(4), 1069–1074 (2008). doi:10.1677/ERC-08-0036 [PubMed: 18719091]
33. Sun C, Mezzadra R, Schumacher TN: Regulation and Function of the PD-L1 Checkpoint. *Immunity* 48(3), 434–452 (2018). doi:10.1016/j.immuni.2018.03.014 [PubMed: 29562194]
34. Moretti S, Menicali E, Nucci N, Guzzetti M, Morelli S, Puxeddu E: THERAPY OF ENDOCRINE DISEASE Immunotherapy of advanced thyroid cancer: from bench to bedside. *European Journal of Cancer* 183(2), 41–55 (2020). doi:10.1530/EJE-20-0283
35. Toom E.E.v.d., Verdone JE, Pienta KJ: Disseminated tumor cells and dormancy in prostate cancer metastasis. *Current Opinion in Biotechnology* 40, 9–15 (2016). doi:10.1016/j.copbio.2016.02.002 [PubMed: 26900985]
36. Pradhan S, Sperduto JL, Farino CJ, Slater JH: Engineered In Vitro Models of Tumor Dormancy and Reactivation. *Journal of Biological Engineering* 12(37), 1–19 (2018). doi:10.1186/s13036-018-0120-9 [PubMed: 29339972]
37. Ishii G, Ochiai A, Neri S: Phenotypic and functional heterogeneity of cancer-associated fibroblast within the tumor microenvironment. *Advanced Drug Delivery Reviews* 99, 186–196 (2015). doi:10.1016/j.addr.2015.07.007 [PubMed: 26278673]
38. Arneth B: Tumor Microenvironment. *Medicina* 56(1), 1–21 (2019). doi:10.3390/medicina56010015
39. MacDonald L, Jenkins J, Purvis G, Lee J, Franco AT: The Thyroid Tumor Microenvironment: Potential Targets for Therapeutic Intervention and Prognostication. *Hormones and Cancer*, 1–13 (2020). doi:10.1007/s12672-020-00390-6 [PubMed: 32016820]
40. Estrada-Flórez AP, Bohórquez ME, Vélez A, Duque CS, Donado JH, Mateus G, Panqueba-Tarazona C, Polanco-Echeverry G, Sahasrabudhe R, Echeverry M, Carvajal-Carmona LG: BRAF and TERT mutations in papillary thyroid cancer patients of Latino ancestry. *Endocrine Connections* 8(9), 1310–1317 (2019). doi:10.1530/EC-19-0376 [PubMed: 31454788]
41. Xing M, Liu R, Liu X, Murugan AK, Zhu G, Zeiger MA, Pai S, Bishop J: BRAF V600E and TERT Promoter Mutations Cooperatively Identify the Most Aggressive Papillary Thyroid Cancer With Highest Recurrence. *Journal of Clinical Oncology* 32(25), 2718–2727 (2014). doi:10.1200/JCO.2014.55.5094 [PubMed: 25024077]
42. Liu R, Zhang T, Zhu G, Xing M: Regulation of Mutant TERT by BRAF V600E/MAP Kinase Pathway Through FOS/GABP in Human Cancer. *Nature Communications* 9(1), 1–13 (2018). doi:10.1038/s41467-018-03033-1

43. Nikitski AV, Rominski SL, Condello V, Kaya C, Wankhede M, Panebianco F, Yang H, Altschuler DL, Nikiforov YE: Mouse Model of Thyroid Cancer Progression and Dedifferentiation Driven by STRN-ALK Expression and Loss of p53: Evidence for the Existence of Two Types of Poorly Differentiated Carcinoma. *Thyroid* 29(10), 1425–1437 (2019). doi:10.1089/thy.2019.0284 [PubMed: 31298630]
44. Xing M: Genetic Alterations in the Phosphatidylinositol 3-Kinase/Akt Pathway in Thyroid Cancer. *Thyroid* 20(7), 697–706 (2010). doi:10.1089/thy.2010.1646 [PubMed: 20578891]
45. Koifman G, Aloni-Grinstein R, Rotter V: p53 balances between tissue hierarchy and anarchy. *Journal of Molecular Cell Biology* 11(7), 553–563 (2019). doi:10.1093/jmcb/mjz022 [PubMed: 30925590]
46. Ricarte-Filho JC, Ryder M, Chitale DA, Rivera M, Heguy A, Ladanyi M, Janakiraman M, Solit D, Knauf JA, Tuttle RM, Ghossein RA, Fagin JA: Mutational Profile of Advanced Primary and Metastatic Radioactive Iodine-Refractory Thyroid Cancers Reveals Distinct Pathogenetic Roles for BRAF, PIK3CA, and AKT1. *Cancer Research* 69(11), 4885–4893 (2009). doi:10.1158/0008-5472.CAN-09-0727 [PubMed: 19487299]
47. Saji M, Ringel MD: The PI3K-Akt-mTOR Pathway in Initiation and Progression of Thyroid Tumors. *Molecular and Cellular Endocrinology* 321(1), 20–28 (2009). doi:10.1016/j.mce.2009.10.016 [PubMed: 19897009]
48. Kim CS, Vasko VV, Kato Y, Kruhlak M, Saji M, Cheng S-Y, Ringel MD: AKT Activation Promotes Metastasis in a Mouse Model of Follicular Thyroid Carcinoma. *Endocrinology* 146(10), 4456–4463 (2005). doi:10.1210/en.2005-0172 [PubMed: 16002527]
49. Jang EK, Song DE, Sim SY, Kwon H, Choi YM, Jeon MJ, Han JM, Kim WG, Kim TY, Shong YK, Kim WB: NRAS Codon 61 Mutation Is Associated with Distant Metastasis in Patients with Follicular Thyroid Carcinoma. *Thyroid* 24(8), 1275–1281 (2014). doi:10.1089/thy.2014.0053 [PubMed: 24820091]
50. Sabra MM, Dominguez JM, Grewal RK, Larson SM, Ghossein RA, Tuttle RM, Fagin JA: Clinical Outcomes and Molecular Profile of Differentiated Thyroid Cancers With Radioiodine-Avid Distant Metastases. *JCEM* 98(5), 829–836 (2013). doi:10.1210/jc.2012-3933 [PubMed: 23322817]
51. Justiniano SE, McElroy JP, Yu L, Yilmaz AS, Coombes KR, Senter L, Nagy R Jr., P.W., Volinia S, Vinco M, Giordano TJ, Croce CM, Saji M, Ringel MD: Genetic Variants in Thyroid Cancer Distant Metastases. *Endocrine-Related Cancer* 23(10), 33–36 (2016). doi:10.1530/ERC-16-0351
52. Landa I, Ibrahimipasic T, Boucai L, Sinha R, Knauf JA, Shah RH, Dogan S, Ricarte-Filho JC, Krishnamoorthy GP, Xu B, Schultz N, Berger MF, Sander C, Taylor BS, Ghossein R, Ganly I, Fagin JA: Genomic and Transcriptomic Hallmarks of Poorly Differentiated and Anaplastic Thyroid Cancers. *The Journal of Clinical Investigation* 126(3), 1052–1066 (2016). doi:10.1172/JCI85271 [PubMed: 26878173]
53. Prasetyanti PR, Medema JP: Intra-tumor heterogeneity from a cancer stem cell perspective. *Molecular Cancer* 16(41), 1–9 (2017). doi:10.1186/s12943-017-0600-4 [PubMed: 28093071]
54. Bodenstine TM, Welch DR: Metastasis Suppressors and the Tumor Microenvironment. *Cancer Microenvironment* 1(1), 1–11 (2008). doi:10.1007/s12307-008-0001-8 [PubMed: 19308680]
55. Stafford LJ, Vaidya KS, Welch DR: Metastasis Suppressors Genes in Cancer. *International Journal of Biochemistry and Cell Biology* 40(5), 874–891 (2008). doi:10.1016/j.biocel.2007.12.016 [PubMed: 18280770]
56. Ringel MD, Hardy E, Bernet VJ, Burch HB, Schuppert F, Burman KD, Saji M: Metastin Receptor Is Overexpressed in Papillary Thyroid Cancer and Activates MAP Kinase in Thyroid Cancer Cells. *JCEM* 87(5), 2399–2402 (2002). doi:10.1210/jcem.87.5.8626 [PubMed: 11994395]
57. Wong KM, Song J, Saini V, Wong YH: Small Molecules as Drugs to Upregulate Metastasis Suppressors in Cancer Cells. *Current Medical Chemistry* 26(32), 5876–5899 (2019). doi:10.2174/0929867325666180522090842
58. Stathatos N, Bourdeau I, Espinosa AV, Saji M, Vasko VV, Burman KD, Stratakis CA, Ringel MD: KiSS-1/G Protein-Coupled Receptor 54 Metastasis Suppressor Pathway Increases Myocyte-Enriched Calcineurin Interacting Protein 1 Expression and Chronically Inhibits Calcineurin Activity. *JCEM* 90(9), 5432–5440 (2005). doi:10.1210/jc.2005-0963 [PubMed: 15998767]

59. Espinosa AV, Shinohara M, Porchia LM, Chung YJ, McCarty S, Saji M, Ringel MD: Regulator of calcineurin 1 modulates cancer cell migration in vitro. *Clinical and Experimental Metastasis* 26, 517–526 (2009). doi:10.1007/s10585-009-9251-1 [PubMed: 19306109]
60. Wang C, Saji M, Justiniano SE, Yusof AM, Zhang X, Yu L, Fernández S Jr., P.W., Perle KL, Nakanishi H, Pohlman N, Ringel MD: RCAN1-4 is a thyroid cancer growth and metastasis suppressor. *JCI insight* 2(5), 1–15 (2017). doi:10.1172/jci.insight.90651
61. Seminara SB, Messenger S, Chatzidaki EE, Thresher RR Jr., J.S.A., Shagoury JK, Bo-Abbas Y, Kuohung W, Schwinof KM, Hendrick AG, Zahn D, Dixon J, Kaiser UB, Slaugenhaupt SA, Gusella JF, O'Rahilly S, Carlton MBL Jr., W.F.C., Aparicio SAJR, Colledge WH: The GPR54 Gene as a Regulator of Puberty. *The New England Journal of Medicine* 349(17), 1614–1627 (2003). doi:10.1056/NEJMoa035322 [PubMed: 14573733]
62. Topaloglu AK, Tello JA, Kotan LD, Ozbek MN, Yilmaz MB, Erdogan S, Gurbuz F, Temiz F, Millar RP, Yuksel B: Inactivating KISS1 mutation and hypogonadotropic hypogonadism. *N Engl J Med* 366(7), 629–635 (2012). doi:10.1056/NEJMoa1111184 [PubMed: 22335740]
63. Beck BH, Welch DR: The KISS1 metastasis suppressor: A good night kiss for disseminated cancer cells. *European Journal of Cancer* 46(7), 1283–1289 (2010). doi:10.1016/j.ejca.2010.02.023 [PubMed: 20303258]
64. Arab K, Smith LT, Gast A, Weichenhan D, Huang JP-H, Claus R, Hielscher T, Espinosa AV, Ringel MD, Morrison CD, Schadendorf D, Kumar R, Plass C: Epigenetic deregulation of TCF21 inhibits metastasis suppressor KISS1 in metastatic melanoma. *Carcinogenesis* 32(10), 1467–1473 (2011). doi:10.1093/carcin/bgr138 [PubMed: 21771727]
65. Lee JH, Miele ME, Hicks DJ, Phillips KK, Trent JM, Weissman BE, Welch DR: KiSS-1, a Novel Human Malignant Melanoma Metastasis-Suppressor Gene. *Journal of the National Cancer Institute* 88(23), 1731–1737 (1996). doi:10.1093/jnci/88.23.1731 [PubMed: 8944003]
66. Trevisana CM, Montagna E, Oliveira R.d., Christofolini DM, Barbosa CP, Crandall KA, Bianco B: Kisspeptin/GPR54 System: What Do We Know About Its Role in Human Reproduction? *Cellular Physiology and Biochemistry* 49(4), 1259–1276 (2018). doi:10.1159/000493406 [PubMed: 30205368]
67. Minami T, Yano K, Miura M, Kobayashi M, Suehiro J.-i., Reid PC, Hamakubo T, Ryeom S, Aird WC, Kodama T: The Down syndrome critical region gene 1 short variant promoters direct vascular bed-specific gene expression during inflammation in mice. *JCI* 119(8), 2257–2270 (2009). doi:10.1172/JCI35738 [PubMed: 19620774]
68. Iizumi M, Bandyopadhyay S, Watabe K: Interaction of Duffy Antigen Receptor for Chemokines and KAI1: A Critical Step in Metastasis Suppression. *Cancer Research* 67(4), 1411–1414 (2007). doi:10.1158/0008-5472.CAN-06-3801 [PubMed: 17308076]
69. Liu Q, Busby JC, Molkentin JD: Interaction between TAK1–TAB1–TAB2 and RCAN1–calcineurin defines a signalling nodal control point. *Nature Cell Biology* 11, 154–161 (2009). doi:10.1038/ncb1823 [PubMed: 19136967]
70. Chowdhury AMMA, Katoh H, Hatanaka A, Iwanari H, Nakamura N, Hamakubo T, Natsume T, Waku T, Kobayashi A: Multiple Regulatory Mechanisms of the Biological Function of NRF3 (NFE2L3) Control Cancer Cell Proliferation. *Scientific Reports* 7(1), 1–14 (2017). doi:10.1038/s41598-017-12675-y [PubMed: 28127051]
71. Baek K-H, Zaslavsky A, Lynch RC, Britt C, Okada Y, Siarey RJ, Lensch MW, Park I-H, Yoon SS, Minami T, Korenberg JR, Folkman J, Daley GQ, Aird WC, Galdzicki Z, Ryeom S: Down's syndrome suppression of tumour growth and the role of the calcineurin inhibitor DSCR1. *Nature* 459, 1126–1130 (2009). doi:10.1038/nature08062 [PubMed: 19458618]
72. Ryeom S, Baek K-H, Rioth MJ, Lynch RC, Zaslavsky A, Birsner A, Yoon SS, McKeon F: Targeted Deletion of the Calcineurin Inhibitor DSCR1 Suppresses Tumor Growth. *Cancer Cell* 13(6), 420–431 (2008). doi:10.1016/j.ccr.2008.02.018 [PubMed: 18455125]
73. Consortium, T.I.T.P.-C.A.o.W.G.: Pan-cancer analysis of whole genomes. *Nature* 578, 82–93 (2020). doi:10.1038/s41586-020-1969-6 [PubMed: 32025007]
74. Covach A, Patel S, Hardin H, Lloyd RV: Phosphorylated Mechanistic Target of Rapamycin (p-mTOR) and Noncoding RNA Expression in Follicular and Hürthle Cell Thyroid Neoplasm. *Endocrine Pathology* 28(3), 207–212 (2017). doi:10.1007/s12022-017-9490-7 [PubMed: 28660408]

75. Ganly I, Filho JR, Eng S, Ghossein R, Morris LGT, Liang Y, Socci N, Kannan K, Mo Q, Fagin JA, Chan TA: Genomic Dissection of Hurthle Cell Carcinoma Reveals a Unique Class of Thyroid Malignancy. *The Journal of Clinical Endocrinology and Metabolism* 98(5), 962–972 (2013). doi:10.1210/jc.2012-3539
76. Ganly I, Makarov V, Deraje S, Dong Y, Reznik E, Seshan V, Nanjangud G, Eng S, Bose P, Kuo F, Morris LGT, Landa I, Blecua P, Albornoz C, Riaz N, Nikiforov YE, Patel K, Umbricht C, Zeiger M, Kebebew E, Sherman E, Ghossein R, Fagin JA, Chan TA: Integrated Genomic Analysis of Hürthle Cell Cancer Reveals Oncogenic Drivers, Recurrent Mitochondrial Mutations, and Unique Chromosomal Landscapes. *Cancer Cell* 34(2), 256–270 (2018). doi:10.1016/j.ccell.2018.07.002 [PubMed: 30107176]
77. Gopal RK, Kübler K, Calvo SE, Polak P, Livitz D, Rosebrock D, Sadow PM, Campbell B, Donovan SE, Amin S, Gigliotti BJ, Grabarek Z, Hess JM, Stewart C, Braunstein LZ, Arndt PF, Mordecai S, Shih AR, Chaves F, Zhan T, Lubitz CC, Kim J, lafrate AJ, Wirth L, Parangi S, Leshchiner I, Daniels GH, Mootha VK, Dias-Santagata D, Getz G, McFadden DG: Widespread Chromosomal Losses and Mitochondrial DNA Alterations as Genetic Drivers in Hürthle Cell Carcinoma. *Cancer Cell* 34(2), 242–255 (2018). doi:10.1016/j.ccell.2018.06.013 [PubMed: 30107175]
78. Papp S, Asa SL: When Thyroid Carcinoma Goes Bad: A Morphological and Molecular Analysis. *Head and Neck Pathology* 9(1), 16–23 (2015). doi:10.1007/s12105-015-0619-z [PubMed: 25804379]
79. Cabanillas ME, Ryder M, Jimenez C: Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond. *Endocrine Reviews* 40(6), 1573–1604 (2019). doi:10.1210/er.2019-00007 [PubMed: 31322645]
80. Qin J, Zhang Z, Fu Z, Ren H, Liu M, Qian M, Du B: The UDP/P2y6 axis promotes lung metastasis of melanoma by remodeling the premetastatic niche. *Cellular & Molecular Immunology*, 1–3 (2020). doi:10.1038/s41423-020-0392-0 [PubMed: 31611651]
81. Liu Y, Cao X: Characteristics and Significance of the Pre-metastatic Niche. *Cancer Cell* 30(5), 668–681 (2016). doi:10.1016/j.ccell.2016.09.011 [PubMed: 27846389]
82. Høye AM, Erler JT: Structural ECM components in the premetastatic and metastatic niche. *American Journal of Physiology - Cell Physiology* 310(11), 955–967 (2016). doi:10.1152/ajpcell.00326.2015
83. Agarwal K, Saji M, Lazaroff SM, Palmer AF, Ringel MD, Paulaitis ME: Analysis of Exosome Release as a Cellular Response to MAPK Pathway Inhibition. *Langmuir* 31(19), 5440–5448 (2015). doi:10.1021/acs.langmuir.5b00095 [PubMed: 25915504]
84. Guzman N, Agarwal K, Asthagiri D, Yu L, Saji M, Ringel MD, Paulaitis ME: Breast Cancer–Specific miR Signature Unique to Extracellular Vesicles Includes “microRNA-like” tRNA Fragments. *Molecular Cancer Research* 13(5), 891–901 (2015). doi:10.1158/1541-7786.MCR-14-0533 [PubMed: 25722304]
85. Ghouse SM, Vadrevu SK, Manne S, Reese B, Patel J, Patel B, Silwal A, Lodhi N, Paterson Y, Srivastava SK, Karbowiczek M, Markiewski MM: Therapeutic Targeting of Vasculature in the Premetastatic and Metastatic Niches Reduces Lung Metastasis. *The Journal of Immunology* 204(4), 990–1000 (2020). doi:10.4049/jimmunol.1901208 [PubMed: 31900334]
86. Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, Psaila B, Kaplan RN, Bromberg JF, Kang Y, Bissell MJ, Cox TR, Giaccia AJ, Erler JT, Hiratsuka S, Ghajar CM, Lyden D: Pre-metastatic niches: organ-specific homes for metastases. *Nature Reviews Cancer* 17, 302–317 (2017). doi:10.1038/nrc.2017.6 [PubMed: 28303905]
87. Bible KC, Cote GJ, Demeure MJ, Elisei R, Jhiang S, Ringel MD: Correlative Studies in Clinical Trials: A Position Statement From the International Thyroid Oncology Group. *JCEM* 100(12), 4387–4395 (2015). doi:10.1210/jc.2015-2818 [PubMed: 26418285]
88. Ibrahimipasic T, Xu B, Landa I, Dogan S, Middha S, Seshan V, Deraje S, Carlson DL, Migliacci J, Knauf JA, Untch B, Berger MF, Morris L, Tuttle RM, Chan T, Fagin JA, Ghossein R, Ganly I: Genomic Alterations in Fatal Forms of Non-Anaplastic Thyroid Cancer: Identification of MED12 and RBM10 as Novel Thyroid Cancer Genes Associated With Tumor Virulence. *Clinical Cancer Research* 23(19), 5970–5980 (2017). doi:10.1158/1078-0432.CCR-17-1183 [PubMed: 28634282]

89. Masoodi T, Siraj AK, Siraj S, Azam S, Qadri Z, Albalawy WN, Parvathareddy SK, Al-Sobhi SS, Al-Dayel F, Alkuraya FS, Al-Kuraya KS: Whole-Exome Sequencing of Matched Primary and Metastatic Papillary Thyroid Cancer. *Thyroid* 30(1), 42–56 (2020). doi:10.1089/thy.2019.0052 [PubMed: 31668133]
90. Lan X, Bao H, Ge X, Cao J, Fan X, Zhang Q, Liu K, Zhang X, Tan Z, Zheng C, Wang A, Chen C, Zhu X, Wang J, Xu J, Zhu X, Wu X, Wang X, Shao Y, Ge M: Genomic Landscape of Metastatic Papillary Thyroid Carcinoma and Novel Biomarkers for Predicting Distant Metastasis. *Cancer Science* 111(6), 2163–2173 (2020). doi:10.1111/cas.14389 [PubMed: 32187423]
91. Iñiguez-Ariza NM, Jasim S, Ryder MM, Chintakuntlawar AV, Morris JC, Hilger CR, Menefee ME, Smallridge RC, Karlin NJ, Alcaino C, Bible KC: Foundation One Genomic Interrogation of Thyroid Cancers in Patients With Metastatic Disease Requiring Systemic Therapy. *Journal of Clinical Endocrinology and Metabolism* 105(7), 1–12 (2020). doi:10.1210/clinem/dgaa246
92. Gupta GP, Massagué J: Cancer Metastasis: Building a Framework. *Cell* 127(4), 679–695 (2006). doi:10.1016/j.cell.2006.11.001 [PubMed: 17110329]
93. Baeriswyl V, Christofori G: The angiogenic switch in carcinogenesis. *Seminars in Cancer Biology* 19(5), 329–337 (2009). doi:10.1016/j.semcancer.2009.05.003 [PubMed: 19482086]
94. Indraccolo S: Insights Into the Regulation of Tumor Dormancy by Angiogenesis in Experimental Tumors. *Advances in Experimental Medicine and Biology* 734, 37–52 (2013). doi:10.1007/978-1-4614-1445-2_3 [PubMed: 23143974]
95. Li D-Q, Shao Z-M: Emerging Therapeutic Targets for Cancer Metastasis: From the Perspective of Embryo Implantation. *Introduction to Cancer Metastasis*, 353–337 (2017). doi:10.1016/B978-0-12-804003-4.00019-0
96. Backer MV, Hamby CV, Backer JM: Inhibition of Vascular Endothelial Growth Factor Receptor Signaling in Angiogenic Tumor Vasculature. *Advances in Genetics* 67, 1–27 (2009). doi:10.1016/S0065-2660(09)67001-2 [PubMed: 19914448]
97. Sherman SI, Wirth LJ, Droz J-P, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun Y-N, Juan T, Stepan DE, Schlumberger MJ: Motesanib Diphosphate in Progressive Differentiated Thyroid Cancer. *The New England Journal of Medicine* 359(1), 31–42 (2008). doi:10.1056/NEJMoa075853 [PubMed: 18596272]
98. Cheng S-P, Liu C-L, Chen M-J, Chien M-N, Leung C-H, Lin C-H, Hsu Y-C, Lee J-J: CD74 expression and its therapeutic potential in thyroid carcinoma. *Endocrine-Related Cancer* 22(2), 179–190 (2015). doi:10.1530/ERC-14-0269 [PubMed: 25600560]
99. I., L.-T., A., W.-L.: Expression of vascular endothelial growth factor (VEGF) in human thyroid tumors. *Polish Journal of Pathology* 53(3) (2002).
100. Bunone G, Vigneri P, Mariani L, Butó S, Collini P, Pilotti S, Pierotti A, M., Bongarzone, I.: Expression of Angiogenesis Stimulators and Inhibitors in Human Thyroid Tumors and Correlation with Clinical Pathological Features. *The American Journal of Pathology* 155(6), 1967–1976 (1999). doi:10.1016/S0002-9440(10)65515-0 [PubMed: 10595926]
101. Rajabi S, Dehghan MH, Dastmalchi R, Mashayekhi FJ, Salami S, Hedayati M: The roles and role-players in thyroid cancer angiogenesis. *Endocrine Journal* 66(4), 277–293 (2019). doi:10.1507/endocrj.EJ18-0537 [PubMed: 30842365]
102. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, Fouchardiere C.d.l., Pacini F, Paschke R, Shong YK, Sherman SI, Smit JWA, Chung J, Kappeler C, Peña C, Molnár I, Schlumberger MJ, investigators, D.: Sorafenib in Radioactive Iodine-Refractory, Locally Advanced or Metastatic Differentiated Thyroid Cancer: A Randomised, Double-Blind, Phase 3 Trial. *Lancet* 384(9940), 319–328 (2014). doi:10.1016/S0140-6736(14)160421-9 [PubMed: 24768112]
103. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim S-B, Krzyzanowska MK, Dutcus CE, Heras B.d.l., Zhu J, Sherman SI: Lenvatinib Versus Placebo in Radioiodine-Refractory Thyroid Cancer. *The New England Journal of Medicine* 372(7), 621–630 (2015). doi:10.1056/NEJMoa1406470 [PubMed: 25671254]
104. Stuelten CH, Parent CA, Montell DJ: Cell Motility in Cancer Invasion and Metastasis: Insights From Simple Model Organisms. *Nature Reviews Cancer* 18(5), 296–312 (2018). doi:10.1038/nrc.2018.15 [PubMed: 29546880]

105. Zijl F, Krupitza G, Mikulits W: Initial steps of metastasis: Cell invasion and endothelial transmigration. *Mutation Research/Reviews in Mutation Research* 728(1-2), 23–24 (2011). doi:10.1016/j.mrrev.2011.05.002
106. Chen B-J, Wu J-S, Tang Y-J, Tang Y-L, Liang X-H: What makes leader cells arise: Intrinsic properties and support from neighboring cells. *Journal of Cellular Physiology*, 1–14 (2020). doi:10.1002/jcp.29828
107. Walker C, Mojares E, Hernández Ad.R.: Role of Extracellular Matrix in Development and Cancer Progression. *International Journal of Molecular Sciences* 19(10), 1–31 (2018). doi:10.3390/ijms19103028
108. Gritsenko PG, Ilina O, Friedl P: Interstitial guidance of cancer invasion. *The Journal of Pathology* 262(2), 185–199 (2011). doi:10.1002/path.3031
109. Fang M, Yuan J, Peng C, Li Y: Collagen as a double-edged sword in tumor progression. *Tumor Biology* 35(4), 2871–2882 (2013). doi:10.1007/s13277-013-1511-7 [PubMed: 24338768]
110. Provenzano PP, Eliceiri KW, Campbell JM, Inman DR, White JG, Keely PJ: Collagen reorganization at the tumor-stromal interface facilitates local invasion. *BMC Medicine* 4(38), 1–16 (2006). doi:10.1186/1741-7015-4-38 [PubMed: 16412236]
111. Young D, Das N, Anowai A, Dufour A: Matrix Metalloproteases as Influencers of the Cells' Social Media. *International Journal of Molecular Sciences* 20(16), 1–20 (2019). doi:10.3390/ijms20163847
112. Gonzalez-Avila G, Sommer B, Mendoza-Posada DA., Ramos C, Garcia-Hernandez AA, Falfan-Valencia R: Matrix metalloproteinases participation in the metastatic process and their diagnostic and therapeutic applications in cancer. *Critical Reviews in Oncology/Hematology* 137, 57–83 (2019). doi:10.1016/j.critrevonc.2019.02.010 [PubMed: 31014516]
113. Winer A, Adams S, Mignatti P: Matrix Metalloproteinase Inhibitors in Cancer Therapy: Turning Past Failures Into Future Successes. *Molecular Cancer Therapeutics* 17(6), 1147–1155 (2018). doi:10.1158/1535-7163.MCT-17-0646 [PubMed: 29735645]
114. Baker EL., Bonnecaze RT, Zaman MH: Extracellular Matrix Stiffness and Architecture Govern Intracellular Rheology in Cancer. *Biophysical Journal* 97(4), 1013–1021 (2009). doi:10.1016/j.bpj.2009.05.054 [PubMed: 19686648]
115. Schweppe RE, Kerege AA, French JD, Sharma V, Grzywa RL, Haugen BR: Inhibition of Src with AZD0530 Reveals the Src-Focal Adhesion Kinase Complex as a Novel Therapeutic Target in Papillary and Anaplastic Thyroid Cancer. *JCEM* 94(6), 2199–2203 (2009). doi:10.1210/jc.2008-2511 [PubMed: 19293266]
116. McCarty SK, Saji M, Zhang X, Jarjoura D, Fusco A, Vasko VV, Ringel MD: Group I p21-activated kinases regulate thyroid cancer cell migration and are overexpressed and activated in thyroid cancer invasion. *Endocrine-Related Cancer* 17(4), 989–999 (2010). doi:10.1677/ERC-10-0168 [PubMed: 20817787]
117. McCarty SK, Saji M, Zhang X, Knippler CM, Kirschner LS, Fernandez S, Ringel MD: BRAF activates and physically interacts with PAKto regulate cell motility. *Endocrine Related Cancer* 21(6), 865–877 (2014). doi:10.1530/ERC-14-0424 [PubMed: 25228413]
118. Jones CE, Hammer AM, Cho Y, Sizemore GM, Cukierman E, Yee LD, Ghadiali SN, Ostrowski MC, Leight JL: Stromal PTEN Regulates Extracellular Matrix Organization in the Mammary Gland. *Neoplasia* 21(1), 132–145 (2019). doi:10.1016/j.neo.2018.10.010 [PubMed: 30550871]
119. Sizemore GM, Balakrishnan S, Thies KA, Hammer AM, Sizemore ST, Trimboli AJ, Cuitiño MC, Steck SA, Tozbikian G, Kladney RD, Shinde N, Das M, Park D, Majumder S, Krishnan S, Yu L, Fernandez SA, Chakravarti A, Shields PG, White JR, Yee LD, Rosol TJ, Ludwig T, Park M, Leone G, Ostrowski MC: Stromal PTEN Determines Mammary Epithelial Response to Radiotherapy. *Nature Communications* 9(1), 1–14 (2018). doi:10.1038/s41467-018-05266-6
120. Wallace JA, Li F, Leone G, Ostrowski MC: Pten in the Breast Tumor Microenvironment: Modeling Tumor–Stroma Coevolution. *Cancer Research* 71(4), 1203–1207 (2011). doi:10.1158/0008-5472.CAN-10-3263 [PubMed: 21303970]
121. Thies KA, Hammer AM, Hildreth BE, Steck SA, Spehar JM, Kladney RD, Geisler JM, Das M, Russell LO, Bey JF, Bolyard CM, Pilarski R, Trimboli AJ, Cuitiño MC, Koivisto CS, Stover DG, Schoenfield L, Otero J, Godbout J, Chakravarti A, Ringel MD, Ramaswamy B, Li Z, Kaur B,

- Leone G, Ostrowski MC, Sizemore ST, Sizemore GM: Stromal platelet-derived growth factor receptor- β signaling promotes breast cancer metastasis in the brain. *Cancer Research* (2020). doi:10.1158/0008-5472.CAN-19-3731
122. Jolly LA, Novitskiy S, Owens P, Massoll N, Cheng N, Fang W, Moses HL, Franco AT: Fibroblast-Mediated Collagen Remodeling Within the Tumor Microenvironment Facilitates Progression of Thyroid Cancers Driven by BrafV600E and Pten Loss. *Cancer Research* 76(7), 1804–1813 (2016). doi:10.1158/0008-5472.CAN-15-2351 [PubMed: 26818109]
 123. Vinaya DS, Ryan EP, Pawelec G, Talib WH, Stagg J, Elkord E, Lichtor T, Decker WK, Whelan RL, Kumara HMCS, Signori E, Honoki K, Georgakilas AG, Amin A, Helfericho WG, Boosani CS, Guha G, Ciriolo MR, Chen S, Mohammed SI, Azmi AS, Keith WN, Bilsland A, Bhakta D, Halicka D, Fujii H, Aquilano K, Ashraf SS, Nowsheen S, Yang X, Choi BK, Kwon BS: Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Seminars in Cancer Biology* 35, 185–198 (2015). doi:10.1016/j.semcancer.2015.03.004
 124. Jankovic B, Le KT, Hershman JM: Hashimoto's Thyroiditis and Papillary Thyroid Carcinoma: Is There a Correlation? *JCEM* 98(2), 474–482 (2013). doi:10.1210/jc.2012-2978 [PubMed: 23293329]
 125. Medas F, Erdas E, Canu GL, Longheu A, Pisano G, Tuveri M, Calò PG: Does hyperthyroidism worsen prognosis of thyroid carcinoma? A retrospective analysis on 2820 consecutive thyroidectomies. *Journal of Otolaryngology - Head and Neck Surgery* 47(6), 1–6 (2018). doi:10.1186/s40463-018-0254-2 [PubMed: 29301560]
 126. Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, Nair VS, Xu Y, Khuong A, Hoang CD, Diehn M, West RB, Plevritis SK, Alizadeh AA: The prognostic landscape of genes and infiltrating immune cells across human cancers. *Nature Medicine* 21, 938–945 (2015). doi:10.1038/nm.3909
 127. Nash KT, Phadke PA, Navenot J-M, Hurst DR, Accavitti-Loper MA, Sztul E, Vaidya KS, Frost AR, Kappes JC, Peiper SC, Welch DR: Requirement of KISS1 Secretion for Multiple Organ Metastasis Suppression and Maintenance of Tumor Dormancy. *JNCI* 99(4), 309–321 (2007). doi:10.1093/jncj/djk053 [PubMed: 17312308]
 128. Ribatti D: The concept of immune surveillance against tumors: The first theories. *Oncotarget* 8(4), 7175–7180 (2017). doi:10.18632/oncotarget.12739 [PubMed: 27764780]
 129. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC: Using Immunotherapy to Boost the Abscopal Effect. *Nature Reviews Cancer* 18(5), 313–322 (2018). doi:10.1038/nrc.2018.6 [PubMed: 29449659]
 130. French JD, Kotnis GR, Said S, Raeburn CD, Robert C McIntyre J, Klopper JP, Haugen BR: Programmed Death-1+ T Cells and Regulatory T Cells Are Enriched in Tumor-Involved Lymph Nodes and Associated with Aggressive Features in Papillary Thyroid Cancer. *JCEM* 97(6), 934–943 (2012). doi:10.1210/jc.2011-3428
 131. Scarpino S, Stoppacciaro A, Ballerini F, Marchesi M, Prat M, Stella MC, Sozzani S, Allavena P, Mantovani A, Ruco LP: Papillary Carcinoma of the Thyroid: Hepatocyte Growth Factor (HGF) Stimulates Tumor Cells to Release Chemokines Active in Recruiting Dendritic Cells. *The American Journal of Pathology* 156(3), 831–837 (2000). doi:10.1016/S0002-9440(10)64951-6 [PubMed: 10702399]
 132. Qing W, Fang W-Y, Ye L, Shen L-Y, Zhang X-F, Fei X-C, Chen X, Wang W-Q, Li X-Y, Xiao J-C, Ning G: Density of Tumor-Associated Macrophages Correlates with Lymph Node Metastasis in Papillary Thyroid Carcinoma. *Thyroid* 22(9), 905–910 (2012). doi:10.1089/thy.2011.0452 [PubMed: 22870901]
 133. Rodi N, Anders RA, Eshleman JR, Lin M-T, Xu H, Kim JH, Beierl K, Chen S, Lubner BS, Wang H, Topalian SL, Pardoll DM, Taube JM: PD-L1 expression in melanocytic lesions does not correlate with the BRAF V600E mutation. *Cancer Immunology Research* 3(2), 110–115 (2015). doi:10.1158/2326-6066.CIR-14-0145 [PubMed: 25370533]

Figure 1. Model of Thyroid Cancer Metastatic Progression.

Primary tumors release factors (blue circles) that include chemokines and cytokines, nucleic acids, and exosomes and other microvesicles to create a receptive environment for cancer cells. The cancer cells (red pentagons) along with stromal cells invade locally and also into blood vessels and follow the chemokines to metastatic sites with relative specificity for different subtypes. Once in the metastatic sites, the cancer deposits can remain dormant influenced by MPSs (such as KiSS-1, NM23, and RCAN 1.4 in thyroid cancer) and a tumor growth inhibiting microenvironment characterized by absent angiogenesis, the inability to degrade tissue matrix, and immune surveillance. Progression in the metastatic sites is enhanced by loss of MPSs, the development of new growth promoting changes, and the development of a tumor growth promoting microenvironment with enhanced angiogenesis, the development of invasive properties (e.g EMT), and a tumor promoting immune environment.