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Trends Cell Biol. Author manuscript; available in PMC 2014 December 01.

Published in final edited form as:
Trends Cell Biol. 2013 December ; 23(12): . doi:10.1016/j.tcb.2013.06.001.

Transcriptional control of cancer metastasis

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Abstract

Transcriptional regulation is an essential component of tumor progression and metastasis. During cancer progression, dysregulation of oncogenic or tumor suppressive transcription factors, as well as master cell fate regulators and tumor microenvironment-induced factors, collectively influence multiple steps of the metastasis cascade, including local invasion, dissemination, and eventual colonization of the tumor to distant organs. Furthermore, epigenetic alterations in tumor cells, including DNA methylation, as well as activation or suppression of histone deacetylases (HDACs), histone acetyltransferases (HATs), and other chromatin modifying enzymes can further distort the transcriptional network to influence metastasis. We focus here on recent research advances in transcriptional control of metastasis and highlight the therapeutic potential of targeting such transcriptional regulatory networks.

Keywords

transcription factors; metastasis; epithelial-mesenchymal transition; tumor microenvironment; epigenetics

A central role of transcriptional regulation in metastasis

Gene regulation is dependent on the interplay between numerous factors acting in concert to produce cell- and tissue-specific expression patterns. Transcription is tightly choreographed through temporal and spatial interactions between transcriptional machinery, including RNA polymerase II, transcription factors and associated cofactors, and regulatory elements within the DNA. Proper regulation of gene expression is essential for normal cellular development, with aberrant expression leading to improper cell growth and differentiation, and resulting in diseases including the development and progression of cancer. Several layers of altered transcriptional regulation can occur during tumor progression to affect metastasis, including the gain-or loss-of-function of transcription factors related to oncogenesis and altered signaling by misexpression of cell fate regulators or through the influence of the tumor microenvironment (Figure 1). Additionally, epigenetic modifications can produce broad transcriptional changes that can also influence metastasis. Here we summarize different modes of transcriptional regulation in metastatic cancer cells, which have important implications for therapeutic targeting of metastasis.

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Transcription factors with dual roles in oncogenesis and metastasis

The misregulation of oncogenes and tumor suppressors is associated with increased cellular growth and survival during early tumorigenesis. Beyond their well established role in primary tumor formation, multiple oncogenic transcription factors (TFs) are now known to also regulate metastasis. For example, c-Myc is a basic helix-loop-helix leucine zipper transcription factor that is dysregulated in 30% of all human cancers [1]. Within the genes regulated by c-Myc, comprising up to 15% of the genome, are mediators of cell cycle control, stem cell maintenance, and apoptosis [2]. In addition, Myc has been linked to elevated invasion and migration through increased expression of OPN and RhoA and the induction of epithelial-mesenchymal transition [3]. Thus, Myc represents a class of oncogenes that functions in both primary tumor formation and metastasis [4]. Conversely, tumor suppressors can also functions as metastasis suppressors. For example, Krüppel-like factor 4 (KLF4), a zinc finger transcription factor, functions as an inhibitor of cell growth by increasing transcription of *p21*$^{WAF1/Cip1}$ and inhibiting *cyclin D1* [5]. KLF4 also enhances E-cadherin (CDH1) expression in breast cancer cells [6] and suppresses *Slug/Snail2* expression in prostate cancer cells [7] to enforce an epithelial phenotype and suppress metastatic behavior [6].

The ETS family of TFs is commonly dysregulated during tumorigenesis, and has more recently been tied to metastasis. Overexpression of several ETS family TFs, including Pea3, promotes metastasis in pre-clinical models [8]. Pea3 is associated with HER2/neu-overexpressing breast cancer, and has been shown to transcriptionally increase HER2/Neu expression [9]. Additionally, Pea3 induces the expression of Osteopontin (OPN) and various matrix metalloproteases (MMPs) [8], and is correlated with increased aggressiveness in human breast cancer patients. Similarly, Ets1 has been linked to metastasis through the upregulation of uPA and MMPs [10]. Other ETS family TFs are known to be tumor- and metastasis-suppressors. Elf5 is essential for mouse embryogenesis and mammary alveolar expansion during pregnancy and lactation [11] and suppresses mammary gland stem cell activity by repressing the Notch signaling pathway [12]. In breast cancer, Elf5 is often lost during tumorigenesis, even in early hyperplasia, and was recently shown to inhibit epithelial-mesenchymal transition (EMT) and metastasis by transcriptionally repressing *Snail2* expression [13]. Similarly, ectopic expression of the ETS transcription factor Pdef reduced invasion, migration, and cellular growth in breast cancer cells [14], while knockdown of Pdef enhanced migration [15]. Pdef promotes the expression of the metastasis suppressor Maspin [14], which has been shown to inhibit cellular adhesion and migration [15].

Gain-of-function mutations in tumor suppressors can likewise regulate the transcription of metastasis associated genes. p53, a prototypical tumor suppressor, is mutated in approximately half of all human cancers, leading to unrestrained proliferation and resistance to apoptosis [2]. p53 knockout mice develop tumors which are not typically metastatic, while gain-of-function mutant isoforms of p53 have been shown to give rise to tumors with higher metastatic capabilities [16]. Gain-of-function p53 mutations typically result in alterations to the DNA binding domain or give rise to conformational mutants with larger structural changes [16]. The functional consequences of these gain-of-function mutants are widespread, with mutant p53 inactivating the p63 and p73 tumor suppressors [16]. Additionally, mutant p53 can amplify SP1 and ETS1 activity, as opposed to the inhibitory effect that wild-type p53 has on the transcription factors [17]. Wild-type and mutant p53 also show different responses to TGFβ signaling; mutant p53 can function downstream of TGFβ signaling to form a complex with Smad2 and inhibit p63, resulting in the promotion of invasion and metastasis [18]. The expression of mutant-p53 and TGFβ can inhibit TAp63-dependent expression of *SHARP1*, an inhibitor of HIF-1α and HIF-2α mediated invasion

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and metastasis [19]. Additionally, mutant p53 can inhibit miR-130b, leading to increased ZEB1 expression and tumor invasion in endometrial cancer [20]. Gain-of-function p53 has also been shown to enhance migration and invasion by promoting the recycling of β1 integrins in a Rab-coupling protein (RCP)-dependent manner [21].

Cell fate determinants

The formation of adult tissues is driven by a number of lineage-specific transcriptional factors. Misregulation of such cell fate determinants has been increasingly linked to the development of metastatic characteristics [22]. Homeobox transcription factor Nkx2-1 plays an essential role in transcription during embryonic lung morphogenesis [23]. Within Kras-induced development of mouse lung adenocarcinoma, Nkx2-1 controls tumor differentiation and limits metastatic potential by repressing the embryonically restricted chromatin regulator Hmga2 [24]. Similarly, GATA3 and PDX1 function to regulate mammary gland and pancreatic development, respectively, and their loss in tumor cells is connected to increased metastasis proclivity. GATA3 is required for luminal differentiation in the mammary gland and is lost during tumor progression; forced expression of *GATA3* was sufficient to induce differentiation within primary tumors, and significantly reduced pulmonary dissemination [25]. GATA3 was shown to directly induce the expression of miR-29b, which can itself promote differentiation and can inhibit the expression of pro-metastasis genes including VEGFA, ANGPTL4, and TGFβ, thereby inhibiting breast cancer lung metastasis [26]. PDX1 is essential for pancreatic development, and its loss correlates with increased invasion and lymph node metastasis from gastric carcinomas [27]. Thus, dysregulation of lineage-specific TFs represents an important feature of metastatic progression in multiple cancers.

The transition between an epithelial and mesenchymal morphology, first discovered as a feature of embryogenesis, is another powerful example of a developmental process that is utilized during tumor progression [28]. During EMT, cells lose apical-basal polarity and cell-cell contacts, and acquire migratory and invasive phenotypes [29]. In the framework of metastasis, EMT is thought to be an important, if transient, feature of invasive tumor cells that allows them to escape from the primary tumor and disseminate into distant organs [29]. EMT has also been shown to induce cancer stem cell features, another enabling property for cancer metastasis [30]. A number of important signaling pathways are involved in stimulating EMT, including Wnt/β-catenin, Notch, Hedgehog, and transforming growth factor β (TGFβ) [29]. These pathways in turn regulate a number of essential EMT master transcription factors such as Snail, Slug, ZEB1/2, and Twist (Table 1) that either directly or indirectly suppress E-cadherin transcription and regulate other hallmarks of EMT [28, 29, 31, 32].

Microenvironment induced transcription factor regulatory network

The microenvironments that tumor cells encounter during metastatic progression are responsible for significant changes in gene transcription. Indeed, although the majority of TFs are not frequently mutated in cancer, they often exhibit altered expression during tumor progression. The tumor microenvironment often strongly influences the activity of metastasis TFs, leading to context specific expression or repression of genes with functional important consequences in metastasis. The TGFβ family of cytokines control EMT, cell growth and differentiation, while also possessing stage-specific roles of tumor suppression and metastasis promotion [33]. TGFβ is often secreted by cancer cells themselves, but can also be expressed by stromal cells, including macrophages and fibroblasts, or released from bone matrix during osteolytic bone metastasis. Canonical TGFβ signaling occurs through the phosphorylation of Smad2/3 TFs by the ligand-activated TGFβ receptors, leading to the

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activation or repression of downstream genes [34]. TGFβ has been shown to limit proliferation in multiple cell types, and thus many cancers show mutations in components of the TGFβ signaling cascade [35]. During cancer progress, TGFβ plays an active role in promoting metastasis through regulating many of its downstream target genes in cancer cells (Table 2). TGFβ-induced EMT promotes migration and invasion of tumor cells through the downstream induction of Snail and Slug, which are well established zinc-finger EMT transcription factors [31]. TGFβ has been shown to mediate immune evasion through the downregulation of perforin, Fas ligand, interferon α, and granzme A and B [36] and can regulate angiogenesis through the direct activation of VEGF and CTGF. Additionally, TGFβ has been implicated in regulating bone metastasis through the induction of PTHrP, Jagged1, IL11 and CTGF [37–39], as well as in the seeding of breast cancer cells in the lung through the induction of ANGPTL4 [40].

Inflammation has been long known to associate with an increased occurrence of cancer, with inflammation-related events contributing to every stage of metastatic progression. Tumor cells can induce inflammation in the surrounding tissue through the aberrant expression of TFs including NF-κB, and the STAT family of proteins [41–43]. While the expression of these TFs can be associated with cell-intrinsic amplifications, mutations, and deletions, the tumor microenvironment plays an important role in their induction through secreted cytokines from tumor-infiltrating stromal cells [42]. In this way, cytokine production from tumor-associated immune cells, including T cells and macrophages, can induce the expression of NF-κB and STAT3, which can in turn stimulate additional immune cell invasion into the tumor through the release of downstream inflammatory cytokines including TNF-α and IL-1β [44]. Immune cells are important mediators of tumor invasion during the early stages of metastasis, with macrophages, granulocytes, and lymphocytes inducing EMT through the secretion of cytokines that activate TGF-β, TNF-α, NF-κB, Notch, and additional EMT pathways [43]. In addition, recruited myeloid cells have been shown to promote invasiveness through the secretion of MMP2 and MMP9, and direct association between tumor cells and macrophages promotes invasion [41, 44]. It has also been suggested that an association between tumor cells and macrophages might additionally protect the metastatic cells during circulation [43]. Thus, inflammation and inflammation related pathways play an important role in metastasis and might provide important therapeutic targets.

Survival in hypoxic conditions is an additional trademark of cancer progression and serves as another example of microenvironment-induced transcriptional regulation of metastasis. Hypoxic cancer cells utilize a number of mechanisms to survive in hypoxic conditions, including induction of autophagy, suppression of apoptosis, and increased angiogenesis [45]. Many of these effects are mediated by the hypoxia-inducible factors (HIFs), a family of transcription factors that regulate cellular responses to changing oxygen levels. HIF-1α expression is capable of inducing MMP-2, uPAR, and CTSD, prompting disruption of the basement membrane, and increasing angiogenesis through the induction of VEGF and PDGF (Table 2). Indeed, HIF-1α is correlated with poor prognosis and has been functionally linked to metastasis in breast cancer [46]. Lysyl oxidase (LOX), a HIF-1α target that can in turn potentiate HIF-1α expression via the activation of PI3K signaling [47], promotes breast cancer invasion and metastasis [48]. HIF-1α also activates the expression of the collagen lysyl hydroxylase PLOD2, an enzyme required for proper collagen cross-linking with an important functional role in promoting breast cancer invasion and metastasis [49]. Similar to HIF-1, the activator protein (AP)-1 transcription factor complex is overexpressed in a variety of different tumor cells in response to hypoxia [50]. Pre-clinical studies have exposed a role for AP-1 proteins in invasion and metastasis, survival, and angiogenesis, although in a highly context-dependent manner [51].

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Epigenetic regulators

Although cancer has been traditionally portrayed as a genetic disease, it is now well accepted that epigenetic changes, including DNA methylation and histone modifications, play a key role in tumor progression [52]. These epigenetic changes are thought to result in the altered expression of numerous genes during tumorigenesis, well in excess of changes due to genetic mutation alone [52]. Importantly, unlike genetic changes, epigenetic changes are reversible upon treatment with pharmacological drugs.

DNA methylation occurs at CpG islands, which are commonly found within the regulatory region of genes throughout the genome. Methylation has been shown to silence gene expression within these promoter regions, while methylation in the transcribed region is less well understood [53]. Altered methylation is frequently associated with tumorigenesis, and has been more recently linked to metastasis [52]. Studies in metastatic prostate cancer samples demonstrate a similar pattern of methylation as seen in primary lesions, which differs greatly from that seen in healthy tissues [54]. Interestingly, the index of methylation increased greatly in the metastatic samples. Analysis of esophageal squamous cell carcinoma patient samples revealed that downregulation of *CDH*1 is tightly associated with hypermethylation of the *CDH1* promoter region [55]. [0]Furthermore, while genetic mutations in *CDH1* have been reported for certain cancers, including diffuse gastric cancer and certain cases of breast cancer, *CDH1* mutations are rare in most breast cancer patients and therefore loss of CDH1 function is more likely to be caused by epigenetic silencing [56]. In addition to methylation of metastasis-suppressing genes, there is strong evidence for the methylation-mediated silencing of microRNAs (miRNAs). MiR-10b, which is hypermethylated in gastric cancer, has been shown to play an important, context specific role as either a tumor-suppressor [57] or pro-metastatic miRNA [58]. Similar promoter hypermethylation can be seen in a number of metastasis-suppressing miRNAs from a methylation signature derived from multiple human metastases [59]. Taken together, these results illustrate the compounding nature of aberrant DNA methylation, with methylation-induced silencing potentially leading to the misexpression of dozens of downstream metastasis genes.

In addition to DNA methylation, histone modifications are powerful epigenetic mediators of transcriptional regulation in both normal and oncogenic tissues. Histones possess unobstructed N-terminal “tail” regions which contain numerous residues capable of being modified [60]. The most frequently observed modifications involve acetylation and mono-, di-, or tri-methylation of lysine residues, and mono- or di-methylation of arginine residues, although multiple alternative modifications exist [60]. Together, these modifications influence chromatin structure and activate or repress the expression of local genes.

Histone deacytlases (HDACs) have been shown to play a role in tumor development through the specific removal of acetyl groups, allowing for the reorganization of chromatin and, typically, transcriptional repression [61]. HDACs may regulate many genes during tumor initiation and subsequent progression, namely by repressing transcription of tumor- and metastasis-suppressor genes [61]. SIRT1, a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetlyase, regulates EMT through repression of CDH1 [62]. Accordingly, SIRT1 knockdown reverted the cancer cells to an epithelial phenotype, reduced invasion and inhibited lung metastasis. Histone methylation is regulated through the combined activity of histone methyltransferases and demethylases, which function to either activate or repress transcription in a context specific manner [60]. Importantly, histone methyltransferases display a significant degree of specificity, both to a specific histone and to a specific lysine or arginine residue [60]. This specificity allows for precise mapping of transcriptional output after the methylation of individual histones, and has the potential to

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streamline the development of targeted therapeutics. For example, EZH2, the catalytic component of the PRC2 complex, is essential for the tri-methylation of histone H3 and promotes metastasis through the silencing of metastasis suppressing genes such as *CDH1* and *FOXC1* [63]. G9a similarly methylates histone H3 to silence *Ep-Cam*, increasing invasion and metastasis [64]. Conversely, histone demethylases specifically remove methyl groups in a histone and residue context-specific manner. In this way, the lysine demethylase KDM4A promotes AP1 recruitment to the promoter region of downstream genes, including *JUN*, *FOSL1/2*, *VEGFA*, enhancing squamous cell carcinoma metastasis [65]. Thus, histone modifications represent important regulatory features during metastasis.

Although progress has been made in identifying specific epigenetic markers that correlate with tumor progression, it is not yet known exactly how the epigenetic alterations are specified during metastasis. Epigenetic patterns are highly dependent upon neighboring marks, leading to regional changes in the epigenetic landscape [61]. In this way it is possible that improper regulation of individual DNA or histone modifying enzymes could lead to broad changes in the epigenetic landscape during tumor progression. Analysis of metastasis samples from patients with lethal metastatic prostate cancer revealed strong intra-patient maintenance of both DNA copy number alterations and methylation status, particularly in areas of hypermethylation, with substantially reduced correlation across patients [66]. It is not yet known if the areas of hypermethylation in these prostate metastases represent driver events during metastasis, or simply passenger alterations.

Interconnected multi-layer regulation of transcription in metastasis

Individual transcription factors are capable of regulating the expression of numerous downstream genes. Unfortunately, the identification of functional TF targets is complicated by the presence of functional TF binding sites located at relatively long-range distances from the promoter. In fact, it is possible for TFs to mediate enhancer-promoter pairing over hundreds of bases by facilitating DNA looping [83]. It is not known how many TFs function in this way, nor how many genes might be directly regulated by long-range TF binding-sites, further convoluting target identification. With the advent of gene expression profiling technology, a reverse strategy has been applied for the identification of the less apparent candidate TFs as master regulators of metastasis (Box 1).

Box 1

Identifying Master transcriptional regulators of metastasis gene signatures

Research on cancer related genes and signaling pathways has led to the discovery of several TFs as regulators of metastasis, and has facilitated the analysis of their targets as direct functional effectors in metastasis. Unfortunately, traditional methods of identifying TF mediators of metastasis are frequently unable to identify less apparent master regulators. Recently, genomic profiling of clinical tumor samples and animal models of cancer metastasis has led to the identification of gene expression signatures with prognostic values for metastatic relapses and organ-tropic metastasis gene signatures [84–86]. The regulatory networks within some of these signatures have subsequently been computationally de-convoluted to allow for the identification of candidate TF drivers of metastasis.

Bioinformatic approaches have allowed for network reverse engineering, which analyzes target gene-expression changes and then maps these changes to their potential upstream transcription factors. In one such application [87], microarray data was clustered into gene expression bi-clusters showing concurrent expression patterns in a large group of sublines of MDA-MB-231 breast cancer cell line featuring different metastatic potentials

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to various organs. Gene set enrichment analysis of such clusters led to the identification of clusters featuring significant association with bone-tropic metastasis. Finally, promoter motif analysis was employed to identify enriched transcription factor binding sites among the promoters of genes in the same cluster. Using these methods, BACH1 was identified as a master regulator of breast cancer bone metastasis with direct bone metastasis gene targets such as *MMP1* and *CXCR4*[87]. A complimentary study examining the downstream transcriptional network of the metastasis suppressor RKIP also identified BACH1 as a functional target of RKIP, and a direct activator of *MMP1* expression [88], showing the convergence of two different bioinformatic approaches in the identification of metastasis TFs.

Gene signatures can also be mapped to DNA copy number to create a list of candidate regulators that can predict the entire signature. This approach produced MYC and CSN5 as essential TF drivers of a wound response signature consisting of 512 genes [86], with ectopic expression of the two factors mirroring the prognostic value of the entire signature [89]. Thus, it is possible to use multiple computational de-convolution approaches to identify functional transcription factors that mediate metastasis gene networks, and further to use these as therapeutic targets with potential broad impacts in targeting the entire metastasis gene network.

Adding an additional layer of complexity to transcriptional regulation of metastasis, a number of transcription factors are now known to regulate the expression of miRNAs, which can in turn regulate hundreds of downstream genes. Indeed, it is possible that genes containing more abundant transcription factor binding sites have a greater chance of being post-transcriptionally regulated by miRNAs, indicating a potential coordination between transcription factor and miRNA regulation [67]. Gene networks are further complicated by the regulation of epigenetic mediators that can similarly control the expression of dozens of downstream genes. The presence of these layers of regulation is exemplified in the positive regulation of the tumor suppressive miR-34a by p53 (Figure 2). MiR-34a is subsequently capable of negatively regulating the expression of multiple genes including transcription factors such as Myc, Snail1, and E2F3, as well as the histone deacetylase SIRT1 [68]. On the other hand, SIRT1 can inhibit p53 through the deacetylation of Lys382, which deactivates downstream p53 signaling. Thus, signaling from p53 through miR-34a is capable of activating a positive feedback loop by inhibiting SIRT1 expression. At the same time, miR-34a is capable of inhibiting EMT through the repression of Snail1, which has been shown to signal through a double-feedback loop to regulate miR-34a. Thus, p53 promotes an epithelial phenotype, while the presence of p53 inactivating mutants can drive EMT in multiple tumor types [69]. Conversely, SIRT1 cooperates with Zeb1 to inhibit CDH1 expression, thereby promoting EMT in the absence of p53 [62]. These layers of complexity illustrate the difficulty in understanding the molecular mechanisms behind metastasis. At the same time, the identification of these regulatory nodes will help facilitate the development of effect therapeutics against metastasis.

Therapeutic application

Transcription factors have traditionally proven difficult to target in a translational setting, although recent studies have revealed a number of potential avenues for therapeutic development. In addition, since TFs can play an important role in all stages of metastasis (Figure 1), it is important to understand the spatial and temporal regulation of these proteins during tumor progression. A major impairment in designing therapeutics to inhibit transcription factors lies in the common lack of a hydrophobic binding site for small molecule drugs [70]. Modern pharmacological techniques have allowed for progress in this field, including the development of DNA binding small molecules [71], stapled peptides

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[70] or artificial transcription factors [72]. Although these techniques and others are promising, additional research is needed to fully develop the therapeutic capabilities.

Several classes of anti-metastasis agents targeting metastasis transcriptional network are currently under active development (Table 3). Due to the pleiotropic effect of TGFβ signaling on metastasis, there is significant clinical interest in TGFβ-targeting therapeutics, despite possible complication from its role in suppressing normal epithelial cell growth and early tumorigenesis. Pre-clinical approaches utilizing small molecule inhibitors, inhibitory antibodies and antisense oligonucleotides have been effective in abrogating many of the functional roles of TGFβ and reducing metastatic burden [73], while clinical trials are underway for multiple metastatic cancers [74]. Although the EMT program is clearly associated with increased migration, invasiveness, and metastasis, and is therefore a prime candidate for therapeutic targeting, the transient nature of the transition is a confounding variable. Anti-EMT therapeutic strategies employed in the early stages of tumor growth have the potential to inhibit tumor invasion, thereby limiting metastasis. Conversely, after cells have successfully entered circulation a reversion to an epithelial phenotype might inadvertently aid in colonization to distant sites [75]. These issues will surely confound future therapeutic efforts, but open the door for therapeutics, such as salinomycin, that specifically target the mesenchymal phenotype [76].

Interestingly, many of the TFs associated with metastatic progression have been shown to mediate chemoresistance and resistance to apoptosis. NF-κB transcriptionally activates numerous downstream genes associated with chemoresistance, including *cyclin D1, COX-2, bcl-xl* and the *bcl-2* gene family, and inhibition of NF-κB has been shown to sensitize tumors to chemotherapeutic agents [77]. Similarly, Snail and Slug can inhibit apoptosis through the direct repression of pro-apoptotic genes including PTEN, PUMA/BBC3, and ATM [78]. It is therefore possible that targeted therapeutics against certain metastasis-related TFs might also confer an additional advantage in the reversal of chemoprotection.

Epigenetic modifications are attractive targets for therapeutic intervention, due largely to the reversible nature of such alterations. Promoter silencing can be alleviated through the use of methyltransferase inhibiting drugs, including 5-azacytidine and decitabine which have been approved for use in treating myelodysplastic syndrome (Table3) [52]. Although experimental and clinical studies have shown promise for a number of HDAC inhibitors in angiogenesis and metastasis [79, 80] these drugs currently feature broad effects on transcription, and significant side effects have been reported. Ongoing clinical trials aim to examine the combined efficacy of HDAC inhibitors and targeted chemotherapy, which has already shown additive effects without significantly increasing toxicity [80]. In addition, a number of histone methyltransferase and demethylase inhibitors are reported to show efficacy in inhibiting metastasis in pre-clinical studies and may yet prove useful as targeted therapeutics (Table 3) [81, 82]). Despite the promise of these findings, there is currently only a small number of drugs targeting histone methylation status, and the usefulness in patients must still be evaluated.

Concluding remarks

As we have described above, there is tremendous potential for the use of therapies targeting transcriptional regulation during metastasis. Systems level analyses have led to the discovery of multigenic gene expression programs related to general or organ-tropic metastasis. While targeting individual downstream effective metastasis proteins is likely to achieve a certain degree of success in controlling the metastatic spread of cancer, such treatment strategies are unlikely to provide an effective cure for metastatic cancer. In contrast, combination treatments using multiple classes of metastasis inhibitors targeting

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different aspects of tumor-intrinsic properties or tumor-stromal interactions, are likely to be more effective. In particular, therapeutics that effectively disrupt the transcriptional control network of metastasis have the potential to reduce the function of multiple metastasis effector genes simultaneously, thereby maximizing the therapeutic efficacy.

Acknowledgments

We apologize to researchers whose studies we were unable to cite due to the space limitation of this review. Research in our laboratory is supported by grants from the National Institutes of Health (R01CA134519 and R01CA141062), Department of Defense (BC123187), Komen for the Cure, the Brewster Foundation and the Champalimaud Foundation.

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HIGHLIGHTS

- Transcription factors (TFs) are key players and therapeutic targets in metastasis
- Oncogenic and tumor suppressive TFs can also affect metastasis
- Cell fate-regulating TFs have significant influence on invasion and metastasis
- Metastasis-promoting TFs are often induced by signals from tumor microenvironment
- Epigenetic alterations change the transcriptional landscape to regulate metastasis

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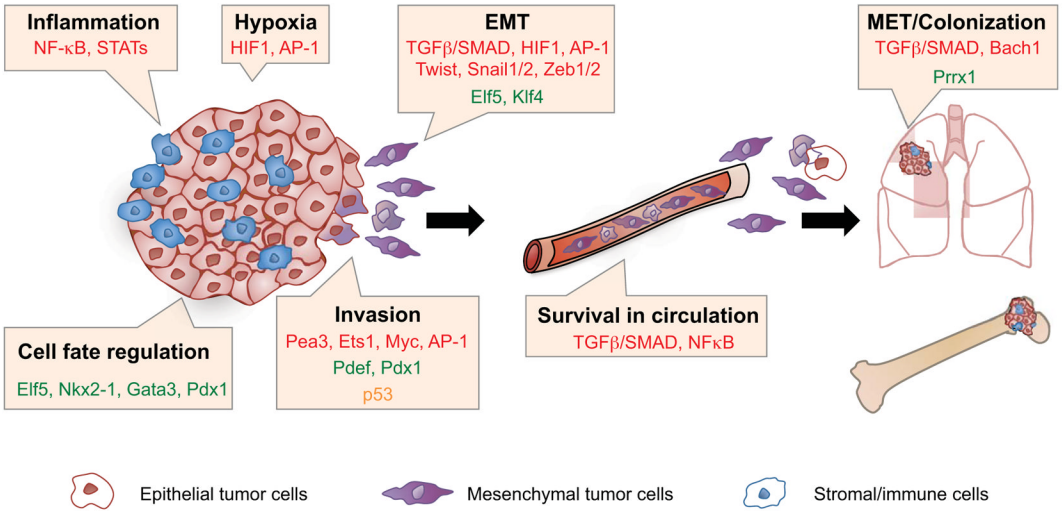

Figure 1.

Transcription factors contribute to every stage of metastasis. The upregulation (Red), downregulation (Green), or gain of function mutations (Orange) in individual transcription factors represent important events during metastatic progression. Altered TF expression mediates early events in metastatic progression, including cell fate (mis)regulation, inflammation, and the response to hypoxic conditions. Additional TFs can regulate EMT, invasion through surrounding tissues, and intravasation, as well as survival in circulation and the eventual colonization at distant sites. It is possible for individual transcription factors to regulate multiple steps during the metastatic cascade, such as TGF-β, which regulates EMT, inflammation, survival in circulation, and colonization at distant organs.

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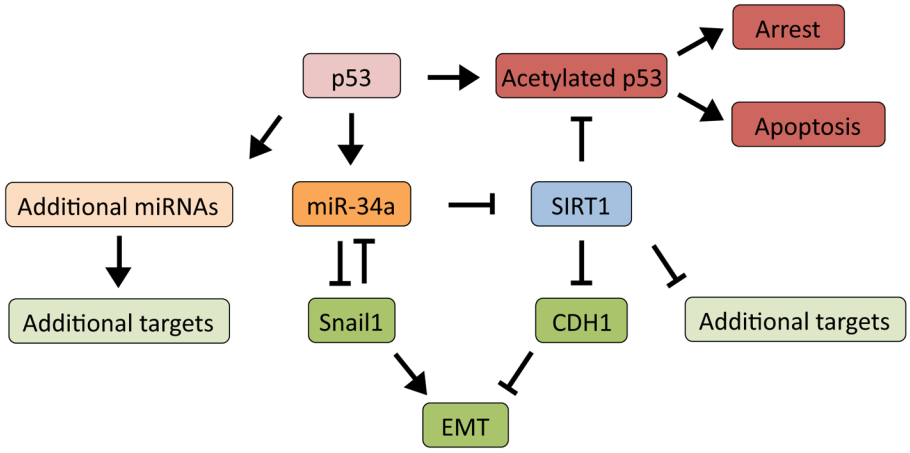

Figure 2.

Transcriptional regulatory pathways surrounding the p53-miR-34a-SIRT1 axis. p53 can activate multiple downstream components, including miRNAs such as miR-34a, leading to cellular arrest or apoptosis. Activation of miR-34a inhibits EMT by antagonizing Snail1 expression, while simultaneously inhibiting SIRT1. SIRT1 is capable of enhancing EMT through the repression of CDH1, but is also able to inhibit acetylated and activated p53. Thus, the p53–mediated repression of miR-34a leads to a positive feedback loop via the repression of SIRT1.

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Table 1

Representative transcription factors that regulate EMT

TF	EMT Function	References
Snail1 (Snail)	Directly suppresses *CDH1* transcription, inhibits miR-34, promotes stemness, stabilizes Twist protein	[28, 30, 90]
Snail2 (Slug)	Directly suppresses *CDH1* and *Claudin-1* transcription, induces *Zeb1*	[28, 91]
Zeb1	Directly suppresses *CDH1* transcription, inhibits miR-200s, induces *uPA* transcription, decreases mRNA stability of *PAI-1*	[28, 92–94]
Zeb2	Directly suppresses *CDH1*, *P-cadherin*, *Claudin 4*, and *Connexin 26* transcription	[28, 95]
Twist	Induces Zeb1, N-cadherin, Snail2, PDGFRα, and CCL2, induces invadopodia	[96–99]
Goosecoid	Induces FOXC2, enhances TGFβ-dependent EMT	[28, 100]
LEF-1	Suppresses *CDH1*, increases *Vimentin* and *Fibronectin* expression, induces TGFβ3	[101]
Ets-1	Increases *Zeb2* expression	[102]
FOXC2	Internalizes CDH1, increases *PDGFR-β* expression	[103, 104]
ELF-5	Directly suppresses *Snail2* transcription	[13]
SIM2s	Directly suppresses *Snail2*	[105]
KLF17	Inhibits *ID1* expression	[106]

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Table 2

Downstream effectors of TGFβ and HIF-1 signaling in metastasis

TGFβ targets	**Function**
TIMP	Angiogenesis
Fas Ligand	Immune regulation
Granzyme A/B	Immune regulation
Perforin	Immune regulation
Interferon γ	Immune regulation
VEGF	Angiogenesis
CTGF	Angiogenesis
PDGF	Angiogenesis/Invasion
MMP2/MMP9	Angiogenesis/Invasion
SOX4	Self renewal
Snail1/2	EMT
Twist	EMT
ANGPTL4	Extravasation
Jagged 1	Bone remodeling (osteoblast activation)
PTHrP	Bone remodeling (osteoblast activation)
IL-11	Bone remodeling (osteoclast activation)
HIF-1 targets	Function
c-MET	Motility
TGF-α	Motility
VEGF	Angiogenesis
LRP1	Angiogenesis
FGF3	Angiogenesis
MMP2	ECM organization
uPAR	ECM organization
CTSD	ECM organization
LOX	Collagen crosslinking/ECM organization
PLOD2	Collagen crosslinking/ECM organization
Snail1	EMT
Twist1	EMT
ZEB1/2	EMT

Note: Genes in red are up-regulated while genes in green are down-regulated.

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Table 3

Representative examples of therapeutic approaches to target transcriptional control of metastasis

Target	Agent	Source	Targeting mechanism
p53	PhiKan083	In silico small molecule screen	Reactivate wild-type function in mutant
	PRIMA-1	Screening of small molecules	Reactivate wild-type function in mutant
	CP-31398	Screening of small molecules to restore mutant p53 function	Reactivate wild-type function in mutant
	Tenovin	Screening of small molecules to activate p53	Activate p53
	Gene therapy	Introgen Therapeutics, Inc. (Advexin), Shenzhen SiBiono GeneTech (Gendicine)	Reintroduce wt p53
	MI-219	Structure-based screen	Inhibits p53-MDM2 interaction
Sp1	Terameprocol	Erimos	Inhibits Sp1 binding to DNA
TGFβ	AP12009	Antisense Pharma (Trabedersen)	Antisense Oligonucleotide
	Belagenpu matucel-L	NovaRx Corporation (Lucanix)	Antisense oligonucleotide, tumor virus
	Neutralizing Antibodies	Genzyme (Fresolimumab, metelimumab), Eli Lilly and Co. (LY2382770)	Monoclonal antibodies
	LY2157299	Eli Lilly and Co.	Small molecule inhibitor
HIF1α	2ME2	EntreMed, Inc. (Panzem)	Small molecule, depolymerizes microtubules and inhibits HIF-1a
	Topotecan	GlaxoSmithKline (Hycamtin)	Topoisomerase I inhibitor, Inhibits HIF1a
HDACs	Vorinostat	Merck (Zolinza)	Zinc-dependent HDAC inhibitor
	Romidepsin	Celgene (Istodax)	Class I HDAC inhibitor
	PXD101	TopoTarget (Belinostat)	Class I and II HDAC inhibitor
	Entinostat	Syndax	Class I HDAC inhibitor
DNA Methyltransferase	Azacitidine	Celgene (Vidaza)	Cytidine analog, hypomethylating agent
	Decitabine	Eisai (Dacogen)	Cytidine analog, hypomethylating agent
HMT	Chaetocin		Specific inhibitor of SU(VAR)3–9
	EPZ004777	Epizyme	Specific inhibitor of DOT1L