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NARRATIVE REVIEW

Endothelial-to-Mesenchymal Transition: Molecular Mechanisms of Induction and Regulation

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ABSTRACT

Endothelial-to-mesenchymal transition (EndoMT) is a form of cellular transdifferentiation essential for cardiovascular development but now recognized as a driver of vascular dysfunction in numerous adult diseases. It is also increasingly appreciated as a mechanistic link between endothelial injury, fibrosis, and immune dysregulation observed in many of these pathologies. However, the exact events leading up to the induction and maintenance of EndoMT remain the subject of continued research. In this review, we discuss the numerous triggers of EndoMT identified to date as well as the pathways contributing to a persistent mesenchymal phenotype. Potential future directions are highlighted with an eye toward pharmacologic reversal of EndoMT and restoration of endothelial function.

Introduction

Endothelial-to-mesenchymal transition (EndoMT) is a form of cellular transdifferentiation that plays a critical role in embryonic cardiovascular development. However, a growing body of evidence suggests that this process can become reactivated under certain pathological conditions[1]. Accordingly, EndoMT has been found to contribute to the pathogenesis and pathophysiology of numerous fibrotic, connective tissue, and malignant diseases[2].

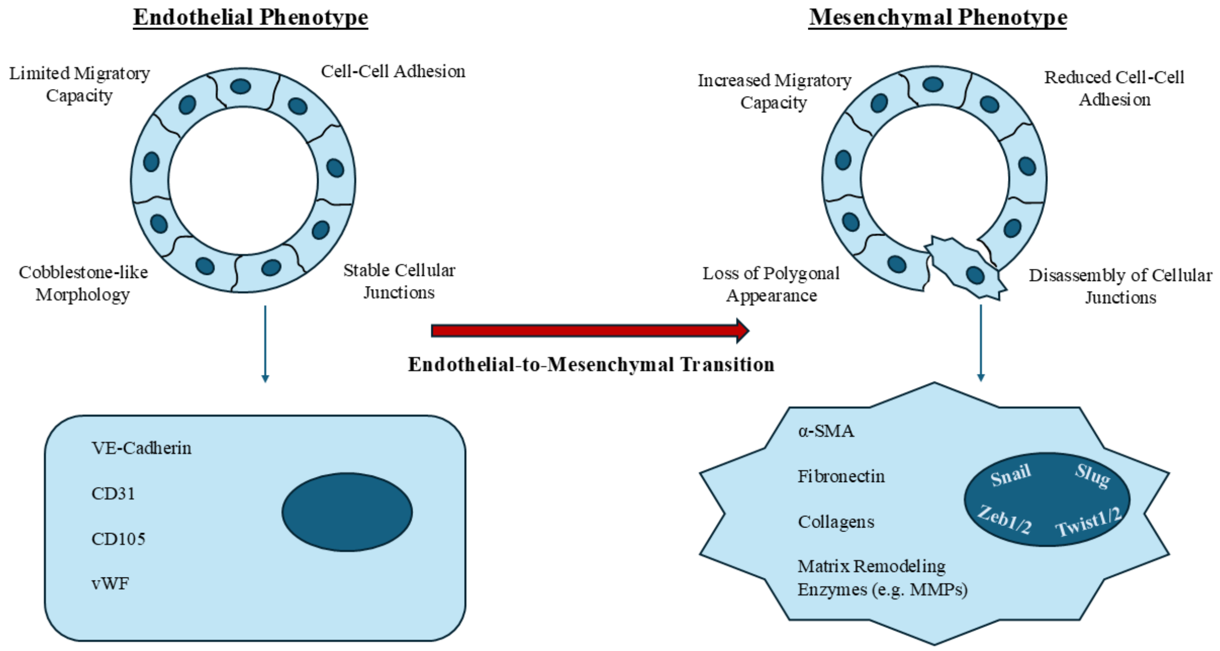

Figure 1: Overview of Endothelial-to-Mesenchymal Transition (EndoMT). EndoMT is characterized by progressive loss of endothelial morphology and markers concurrent with acquisition of mesenchymal characteristics. These phenotypic changes are driven by complex molecular mechanisms and transcriptional reprogramming involving SNAI, ZEB, and TWIST family transcription factors.

EndoMT involves a dramatic transition of endothelial cell phenotype to a mesenchymal, fibroblast-like form as summarized in *Figure 1.* During this process, endothelial cells undergo a multitude of molecular and morphological changes. Under normal biological conditions, endothelial cells form a uniform, cobblestone-like layer covering the inner lining of blood vessels. However, the process of EndoMT involves the conversion of endothelial cells to an elongated fibroblast-like morphology[2]. This process is accompanied by reduced cell-to-cell adhesion, increased migratory and invasive capacity, disassembly of intercellular junctions, and multiple other adverse morphological and functional changes that contribute to vascular dysfunction. A loss of endothelial markers including VE-cadherin, CD31, von Willebrand factor (vWF), and CD105 alongside increased expression of mesenchymal-linked molecules such as α-smooth muscle actin (α-SMA), fibronectin, fibrillary collagens, and matrix-remodeling enzymes are some of the most well-documented molecular features of EndoMT[3]. These changes are accompanied by induction of EndoMT-associated transcription factors such as SNAI1 (Snail), SNAI2 (Slug), TWIST1/2, and ZEB1/2[4]. Taken together, these events lead to functional consequences such as loss of endothelial barrier function, increased contractility, and enhanced matrix deposition that contribute to severe vascular and fibrotic pathologies.

As such, the exact biological events comprising EndoMT have been the subject of extensive investigation[1,2]. This review explores the molecular mechanisms involved in the induction and maintenance of EndoMT, with an emphasis on how signaling pathways, metabolic reprogramming, and epigenetic regulation interact to sustain mesenchymal endothelial phenotypes.

Induction of EndoMT

Despite extensive investigation, the factors responsible for the induction of EndoMT are complex and not fully defined. EndoMT appears to result from the convergence of multiple biochemical, mechanical, metabolic, and environmental stimuli, but outcomes appear highly dependent on cellular context and disease state. The following section summarizes the major stimuli identified to date that promote EndoMT induction.

OXIDATIVE STRESS

Oxidative stress and reactive oxygen species (ROS) have been increasingly recognized as inducers of EndoMT. One of the earliest such studies found that H_2O_2 induced EndoMT in HUVECs in a dose-dependent manner. This effect led to modulation in TGF- β production and involved Smad, p38, and NF-κB activation[5]. More recently, it was found that exosomes derived from adipose tissue alleviated H_2O_2-induced EndoMT in HUVECs via inhibition of the mir-486-3p/Sirt6/Smad pathway[6]. Multiple studies have also implicated ROS production from the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system (NOX). The isoforms NOX2 and NOX4 are the most widely present in the vasculature[7]. A recent study found that serum from patients with idiopathic pulmonary fibrosis (IPF) stimulated an increase in ROS production with a simultaneous transition to EndoMT in human pulmonary endothelial cells.[8] Pharmacological inhibition of NOX attenuated ROS generation in EndoMT. A similar effect was observed after inhibition of protein kinase C. Immunofluorescence analyses confirmed that the morphological alterations associated with EndoMT were reversed by NOX inhibition[8]. Another investigation found that trimetazidine, a fatty acid oxidation inhibitor, reduced EndoMT in isoproterenol-treated mice (a murine model of cardiac fibrosis) concomitant with reduced NOX activity. This effect was reproduced in TGF-β-treated HUVECs. Both *in vitro* and *in vivo* experiments showed an increase in the expression of NOX2, nuclear factor (NF)-κB, and Snail. This was reversed with trimetazidine treatment. Overexpression of NOX2, however, abolished these protective effects[9]. Unlike other NOX family members, NOX4 is constitutively active. Also unlike NOX2, its role in EndoMT has not been directly examined. Yet, the contribution of NOX4 to EndoMT may be implied by its activation in TGF-β signaling[10]. Other sources of oxidative stress continue to be identified. Sestrin-1 (SESN1), a redox-regulatory protein with anti-inflammatory functions was shown to be downregulated following stimulation of HUVECs with oxidized low-density lipoprotein (Ox-LDL). It was found that SESN1 overexpression was capable of reducing Ox-LDL-induced EndoMT in HUVECs[11].

FATTY ACID OXIDATION

The role of metabolic alterations in EndoMT has been increasingly examined in recent years. One such observation has been that TGF-β signaling-induced EndoMT occurs concurrently with an inhibition of fatty acid oxidation and a decrease in intracellular levels of acetyl-CoA, the primary product of fatty acid oxidation. Moreover, post-translational acetylation increases the stability of Smad7, a negative regulator of TGF-β, potentially implying a causal link between fatty acid oxidation and TGF-β signaling. Accordingly, it has been found that endogenous Smad7 expression is increased and decreased with higher and lower levels of acetate, respectively in murine endothelial cells. The effect of this observation on the EndoMT process was verified *in vivo*: disruption of fatty acid oxidation via knockdown of carnitine palmitoyltransferase II augmented EndoMT in mice[12].

LACTATE AND GLYCOLYSIS

In addition to the aforementioned metabolic observations regarding fatty acid oxidation, alterations to glycolysis may also be responsible for the induction of EndoMT. An analysis of systemic sclerosis (SSc) dermal fibroblasts found that glycolytic dysregulation may contribute to the induction of EndoMT. Fibroblasts were derived from the dermal skin of patients with SSc. It was found that these fibroblasts showed a boosted glycolytic metabolism with increased lactate levels compared to normal fibroblasts, acidifying the extracellular environment. Acidified endothelial cells acquired a mesenchymal-like morphology and exhibited molecular signs of EndoMT[13]. Other EndoMT initiators such as shear stress and environmental particulate exposure have also been shown to modulate glycolysis or genes associated with glycolysis and induce EndoMT[14,15]. Moreover, imbalances to lactate homeostasis may provide an additional mechanistic link via the novel epigenetic modification of histone lactylation.[16] Consistent with this possibility, histone lactylation was recently identified in an *in vitro* model of EndoMT in diabetic nephropathy and in a study of microplastic-induced EndoMT[15,17].

HYPOXIA

A large body of evidence implicates hypoxia as a potent inducer of EndoMT[18-20]. This effect is largely mediated by HIF-1α and likely involves induction of Snail[20]. The ability of hypoxia to induce EndoMT first reported *in vitro* has also been replicated in multiple murine models of induced hypoxia[21,22]. HIF2α has also emerged as a potential an additional mediator of hypoxia-induced EndoMT. Elevation of HIF2α was first identified in lung endothelial cells isolated from patients with pulmonary arterial hypertension cultured under normoxic conditions. HIF2α induced increased expression of Snail and Slug, leading to a mesenchymal phenotype[23]. A more recent investigation again found HIF2α to be an important mediator of hypoxia-induced EndoMT in a model of pulmonary hypertension. Cultured rat pulmonary microvascular endothelial cells were treated with hypoxia, leading to significant upregulation of HIF2α and SETDB1, which codes for a histone lysine methyltransferase. Upregulation of SETDB1 was found to occur in an HIF2α-dependent manner, and knockout of SETDB1 significantly inhibited hypoxia-induced EndoMT[24].

The precise mechanisms involved in hypoxia-induced EndoMT remain a subject of continued investigation. One study of cultured human cardiac microvascular endothelial cells demonstrated involvement of TGF-β and Notch. These pathways were mediated by the transcription factor RUNX3[25]. A separate investigation found that exposure of rat microvascular endothelial cells to hypoxia enhanced TGF-β/SMAD, shown by increased phosphorylation of SMAD1/5 and SMAD2. Inhibitors of TGF-β receptors ALK1 or ALK5 blocked this effect. Moreover, exposing ventricular cardiomyocytes to culture medium from hypoxic microvascular endothelial cells also enhanced SMAD2 phosphorylation and provoked apoptosis, indicating the participation of paracrine signaling. This effect was also blocked by ALK5 inhibition[26]. BMP-7 has also been implicated in the molecular processes underpinning hypoxia-induced EndoMT. One investigation found that hypoxic conditions decrease the expression of BMP-7 both *in vivo* and *in vitro*. BMP-7 deficiency induced EndoMT under normoxic conditions, and hypoxia-induced EndoMT was attenuated by pretreatment with rh-BMP-7. It was found that BMP-7 likely attenuates hypoxia-induced EndoMT by suppressing the m-TORC1 pathway[27]. Recent evidence also suggests that epigenetic alterations may play a role in the mechanism of hypoxia-induced EndoMT. For example, hypoxia upregulates histone 3 lysine 9 methyltransferase via HIF2α, potentially implicating histone modification[24]. A previous investigation also found that hypoxia upregulates the accumulation of the trimethylated histone H3K4me3 via HIF-1α[28].

HYPERGLYCEMIA

Owing to the serious consequences associated with microvascular complications of diabetic nephropathy, a growing body of research has attempted to characterize the role of EndoMT in hyperglycemic conditions. Numerous studies have found hyperglycemia capable of inducing EndoMT across a variety of endothelial cells and pathological models[29-32]. Early research found that this effect is mediated by angiotensin II both in human aortic endothelial cells and in rats and that administration of the angiotensin II receptor I inhibitor Irbesartan abrogated hyperglycemia-induced EndoMT[29,30]. A study in cultured retinal endothelial cells demonstrated a key role for TGF-β in this process alongside regulation by miR-200b[31]. Multiple mechanistic studies involving HUVECs have also implicated ROS-dependent activation of the MAPK/ERK pathway. In particular, hyperglycemia-induced EndoMT appears to be mediated by this pathway with downstream engagement of TGF-β signaling and cytoskeletal regulators such as ROCK1[32-34].

Recent work has demonstrated the involvement of multiple other pathways and molecules. An analysis of diabetic nephropathy patients found that expression of S1PR2, a GPCR involved in cell migration and barrier permeability, was significantly increased in glomerular endothelial cells. Treatment of diabetic nephropathy model mice and HUVECs with glucolipids also upregulated S1PR2, and inhibition of this receptor decreased expression of Wnt3a, RhoA, ROCK1, and β-catenin while reversing EndoMT in glomerular endothelial cells. This corroborates early findings suggesting involvement of ROCK1 with the additional suggestion of β-catenin-dependent Wnt signaling[35]. Subsequent work found that Apelin, an adipokine, inhibited hyperglycemia-induced EndoMT via increased expression of large conductance calcium-activated potassium channels and suppression of the Wnt/β-Catenin pathway[36]. AKT signaling has also been implicated. One study found that hyperglycemia increased AKT3 expression and induced EndoMT in diabetic rat aorta and in HUVECs. Inhibition of AKT3 reversed hyperglycemia-induced EndoMT in HUVECs. Expression of the transcription factor

BACH1 augmented AKT3 promoter activity, and the effect of BACH1 overexpression was similar to that of hyperglycemia in HUVECs[37]. The transcription factor STAT5A has also been found to be elevated in hyperglycemic human glomerular endothelial cells and in diabetic nephropathy rats. STAT5A was found to modulate EndoMT via enhancement of the GPCR ELTDF1. EndoMT was reversed by STAT5A silencing and inhibited by ELTD1 silencing *in vitro*[38].

Epigenetic alterations have also recently been implicated in the mechanisms of hyperglycemia-induced EndoMT. Multiple recent studies have identified SIRT7, which has histone deacetylase activity, as a key epigenetic regulator in hyperglycemia-induced EndoMT. One investigation found SIRT7 to be underexpressed in the glomerular endothelial cells of diabetic kidney disease patients and diabetes-induced renal injury rats. EndoMT was not reversed by normalization of glucose levels. Overexpression of Sirt7 reversed EndoMT in human glomerular endothelial cells[39]. A separate study corroborated the finding that Sirt7 levels are decreased in hyperglycemic human glomerular endothelial cells (HGECs) and in the kidneys of diabetic nephropathy mice. It was additionally found that an increase of Sirt7 decreases the expression of fascin, an actin-bundling protein whose inhibition was found to prevent EndoMT in HGECs in this study. This also inhibited EndoMT[40]. In addition to histone deacetylation, evidence of histone methylation has also been identified. A recent study identified the histone methyltransferase SETD8 as a protective epigenetic regulator in the kidney tissues of diabetic nephropathy patients and rats. Hyperglycemia was found to promote EndoMT via increased expression of Snail, an effect mediated by BACH1 upregulation. The transcription factor ELK1 was also found to directly activate BACH1 and physically associate with SETD8 at the BACH1 promoter[41]. Moreover, the recently discovered epigenetic mechanism of histone lactylation may also contribute to hyperglycemia-induced EndoMT. One study found that knockout of insulin-like growth factor-binding protein 5 (IGFBP5) inhibited high-glucose EndoMT in glomerular endothelial cells accompanied by simultaneous decreases in glycolytic activity and histone lactylation. These findings were replicated in a murine model of diabetic nephropathy[17]. Epigenetic regulations should continue to be studied in high glucose EndoMT and may provide a mechanistic explanation for the persistence of EndoMT even after restoration of normal glucose levels.

SHEAR STRESS FORCES

The endothelial lining is constantly subject to mechanical stress. These forces are primarily comprised of shear stress generated from intraluminal laminar flow and cyclic strain from repetitive pressure changes generated by the cardiac cycle. The vascular endothelium is highly sensitive to these hemodynamic forces and can induce changes in gene expression that appropriately alter vessel function in response[42]. Gene expression alterations are enacted by a variety of mechanosensitive signaling pathways in endothelial cells[43]. Owing to the ability of such forces to induce dramatic changes in endothelial phenotype, a significant amount of work has been dedicated to characterizing their role in EndoMT.

Generally, it is agreed that shear stress within normal physiological ranges—on the order of roughly 5-20 dyn/cm^2 in large arteries and under 1 dym/cm^2 in large veins—is protective to the endothelial phenotype[44,45]. However, a variety of pathologies, particularly those that negatively impact cardiac output, can cause low shear stress. Multiple studies have associated low laminar shear stress with EndoMT. Early *in vitro* work using a shear stress bioreactor demonstrated that porcine aortic valve endothelial cells underwent EndoMT following low shear stress (2 dyn/ cm^2)[46]. This process was found to involve regulation via SNAIL in murine aorta or carotid arteries modified with flow-altering cuffs[47]. A recent study corroborated the finding that low shear stress (2 dyn/cm^2 *in vitro* or local carotid artery ligation *in vivo*) is capable of inducing EndoMT both *in vivo* and *in vitro*. This process coincided with expression of the gene MEST. Overexpression of MEST significantly promoted EndoMT, and MEST knockdown inhibited EndoMT. Hydrogen sulfide, a protective mediator, inhibited the expression of MEST and the EndoMT process *in vitro* under low shear stress conditions[48]. Furthermore, a study of cultured HUVECs found that low shear stress (4 or 15 dyn/cm^2) downregulated the expression of TET2, a DNA demethylation enzyme, while promoting EndoMT. Loss of TET2 promoted EndoMT via activation of the Wnt/β-catenin pathway, and overexpression of TET2 attenuated this transition. TET2 overexpression attenuated EndoMT in mice subjected to carotid artery ligation[49]. Conversely, some work has shown high shear stress to be protective. One investigation found that endothelial cells treated with TGF-β2 and inflammatory cytokines (IL-1β and TNF-α) were protected from EndoMT by high shear stress (25 dyn/cm^2) compared to cells that were not subjected to fluid shear stress. Furthermore, it was revealed that high fluid shear stress blocked the Smad2/3 pathway. In an *in vivo* analysis of mice injected with TGF-β2 and the inflammatory cytokines, it was found that the regions of the aorta that underwent the highest laminar shear stress experienced a smaller degree of Smad2/3 nuclear translocation[50]. However, pathological levels of high sheer stress may actually stimulate EndoMT. A recent investigation found that abnormally high shear stress (100 dyn/cm^2) can stimulate EndoMT via downregulation of the transcription factor ERG in pulmonary artery endothelial cells. This effect was replicated in model mice, and ERG delivery reduced EndoMT *in vivo*[51].

In addition to the magnitude of shear stress, the disruption of laminar flow has also been shown to induce EndoMT. Oscillatory or otherwise nonuniform shear stress, henceforth referred to as disturbed shear stress, severely interrupts endothelial homeostasis. One early study in human and porcine myo-endothelial cells demonstrated that laminar shear stress can inhibit EndoMT while cells exposed to disturbed shear stress underwent EndoMT in the absence of other stimuli[52]. More recent work has attempted to further elucidate the mechanisms of this condition. One study of human varicose veins found EndoMT and upregulation of the BMP4/SMAD5 pathway in patient samples. An *in vitro* flow assay of HUVECs found that even small disturbances in shear stress can induce a change in phenotype via BMP4/SMAD5. Administration of the BMP4 inhibitor LDN193189 reduced SNAIL and SLUG expression in HUVECs exposed to disturbed flow, implying a mechanism of BMP4/SMAD5/SNAIL/SLUG signaling[53]. Another study corroborated the finding that abnormal flow can induce EndoMT in a rodent model and found that losartan reduced the observed endocardial fibroelastosis. An *in vitro* analysis of human endocardial endothelial cells showed that laminar flow suppressed mesenchymal gene expression[54]. Interleukin-1 receptor type-1 was also recently established as a mechanosensitive link between disturbed shear stress and IL-1 signaling. It was found that exposure of endothelial cells to oscillatory shear stress resulted in a loss of endothelial markers and increased IL-1R1 expression *in vitro.* Genetic silencing of IL-1R1 reduced the severity of EndoMT and nuclear localization of Snail after exposure of endothelial cells to oscillatory shear stress, and IL-1R1 upregulation was also recorded in areas of high disturbed shear stress *in vivo*[55]. Disturbed shear stress has also been observed to induce pathways including Notch and Piezo1-KLF2, a mechanotransduction axis[56,57].

ENVIRONMENTAL PARTICULATES

Air pollution has been identified as a major environmental health risk for many years now, and health complications associated with airborne particulate matter (PM) have been identified as a leading contributor to global disease burden[58]. Among these complications is increased prevalence and severity of pulmonary fibrosis[59,60]. As such, multiple investigations have sought to identify a link between environmental particulates and EndoMT.

One of the earliest such studies exposed mice to air containing PM2.5 (particulate matter with an aerodynamic radius under 2.5 μm) for five hours a day over the course of 16 weeks. Analysis of the pulmonary vessels revealed that PM2.5 was capable of inducing EndoMT. This was repeated in an *in vitro* assay of mouse pulmonary vascular endothelial cells. It was also demonstrated that PM2.5 induced EndoMT via regulation of the TGF-β1/Smad3/p-Smad3 pathway and that the long noncoding RNA lncRNA Gm15410 plays a role in mediating this process[61]. Another analysis found a unique mechanism by which iron-containing PM2.5 particles initiate EndoMT in cardiac endothelial cells. It was demonstrated that this matter initiates EndoMT by binding to the ferritinophagy receptor NCOA4, promoting binding of the transcription factor Kruppel-like factor 5 to the TGF- β1 promoter[62]. PM-induced EndoMT has also been implicated in cerebrovascular pathology. Exposure of human brain endothelial cells to PM induced EndoMT in a manner dependent on β-site amyloid precursor protein cleaving enzyme (BACE1). Transcriptomic analyses identified growth differentiation factor 15, a stress-related molecule and member of the TGF-β superfamily, as a mediator in this process. Increased BACE1 and GDF15 together with EndoMT phenotypes were observed in postmortem brain tissue from individuals with CNS vasculopathy, which included varying degrees of atherosclerosis and lacunar infarct, potentially suggesting a link between PM, EndoMT, and cerebrovascular dysfunction. It was also found that BACE1 is upregulated in the endothelial cells of diabetic patients, and treatment with PM significantly increased BACE1 and EndoMT gene expression in these cultured cells[63]. Finally, microplastics have also been identified as a potential initiator of EndoMT. An RNA sequencing analysis of human pulmonary artery endothelial cells exposed to microplastics demonstrated that microplastics induce EndoMT, and that this process occurs via histone lactylation. Glycolysis was also upregulated in the HPAECs alongside upregulation of glycolytic genes such as HK2. HK2 was found the mediate this process, and knockdown of HK2 attenuated microplastic-induced EndoMT[15].

Canonical and Non-canonical TGF-β Signaling

TGF-B

Transforming Growth Factor-β (TGF-β) is a pleiotropic cytokine that exists as one of three isoforms (TGF-β1, TGF-β2, and TGF-β3) and regulates tissue repair, fibrosis, embryonal development, and various other functions[64]. It is also one of the most well-studied and important pathways by which propagation of EndoMT occurs[65]. All three TGF-β isoforms are capable of inducing EndoMT, with one investigation finding TGF-β2 to be the most potent inducer and regulator in cultured human microvascular endothelial cells (HMVECs)[66]. However, the exact phenotypic changes induced by TGF-β are highly context-dependent[67]. TGF-β signaling occurs via one of two major signaling arms: canonical (SMAD-dependent) and non-canonical (SMAD-independent). Canonical TGF-β plays a key mechanistic role in EndoMT, and knockdown of the receptor-regulated Smads 2 and 3 has been shown to alleviate effects of EndoMT *in vitro*[65,68]. A variety of transcription factors linked to expression of a mesenchymal phenotype are downstream of this pathway including Snail, Slug. and the Zeb and Twist families[68-70]. Evidence also suggests that Smad-dependent signaling can promote EndoMT via convergence with Smad-independent signaling[70].

Participation of numerous noncanonical pathways has been identified in EndoMT. TGF-β is capable of activating all three branches of the mitogen-associated protein kinase (MAPK) pathways: ERKs, JNKs, and p38. Dephosphorylation of specific MAPKs has been shown to ameliorate EndoMT[71]. Moreover, a study of human cutaneous microvascular endothelial cells found that pretreatment inhibition of the p38 MAPK and ERK prevented changes in cell morphology after exposure to TGF-β2. These findings were additionally repeated for PI3K/AKT signaling[70]. TGF-β has also been found to engage the Rho-family GTPases and Rho-associated kinases (ROCK) to drive phenotype changes associated with EndoMT[72]. ROCK inhibitors have ameliorated TGF-β-induced EndoMT *in vitro*[73]. One investigation found that the nonreceptor tyrosine kinases c-Abl and PKC-δ are important mediators and that both are required for TGF-β induction of EndoMT[74]. It has also been found that inactivation of glycogen synthase kinase-3β (GSK-3β) via phosphorylation by AKT contributes to EndoMT induction in TGF-β signaling. Normally, GSK-3β targets Snail for degradation. As expected, experimental evidence has shown that GSK-3β inhibition allows Snail overexpression and subsequent mesenchymal transition[70]. Crosstalk between TGF-β signaling and the inflammatory NF-κB and Janus kinase (JAK)/STAT pathways has also been documented[72]. Overall, it should be noted that this evidence generally suggests convergence with the Smad cascade rather than mutually exclusive mechanisms[70]. Significant research therefore demonstrates that both canonical and noncanonical signals act concomitantly to regulate EndoMT.

Non-TGF-β Signaling Pathways

Wnt

Wnt signal transduction consists of a highly conserved multigene family of proteins involved in a variety of morphogenic functions. Wnt proteins are growth stimulatory factors that lead to cell proliferation via regulation of various steps of the cell cycle. Dysfunctions in this pathway are related to a variety of pathologies, and numerous studies have demonstrated Wnt signaling involvement in EndoMT[75]. The earliest evidence of Wnt in EndoMT came from a murine model of myocardial infarction, where canonical (β-catenin-dependent) Wnt activation was found to induce EndoMT in cardiac endothelial cells[76]. Multiple subsequent investigations in numerous other *in vivo* and *in vitro* disease models have corroborated a role of β-catenin-dependent Wnt signaling in EndoMT[77-79]. Moreover, a recent study of lung tissue from thirteen IPF patients demonstrated the involvement of Smad-dependent TGF-β signaling and canonical Wnt signaling in driving EndoMT and pulmonary arterial remodeling, indicating simultaneous regulation of EndoMT from both pathways for the first time[78]. Inhibitors of β-catenin have also been demonstrated to alleviate the effects of EndoMT while inducers of β-catenin have promoted it, further supporting a regulatory role of the canonical pathway[80-82]. The role of noncanonical Wnt signaling is less certain, and limited evidence exists of its direct contribution to EndoMT. One investigation found that tumor cell-derived Wnt5B induced EndoMT and increased Snail and Slug transcription factors in cultured lymphatic endothelial cells. The expression of Snail and Slug was abolished by IWR-1-endo and Rac1 inhibitors, which are involved in WNT/β-catenin and planar cell polarity pathways, respectively, suggesting involvement of both canonical and non-canonical Wnt signaling pathways in lymphatic EndoMT[83]. However, additional work is needed to further characterize the role of noncanonical Wnt signaling.

A variety of molecules have been demonstrated to promote EndoMT via Wnt signaling. One investigation of cardiac fibrosis found that CD146, an adhesion molecule highly expressed in endothelial cells, was upregulated in the cardiac endothelial cells of mice treated with Angiotensin II. A subsequent *in vitro* analysis of HUVECs showed that CD146 knockdown upregulated Wnt pathway-related genes, increased β-catenin translocation, and facilitated EndoMT. CD146 overexpression attenuated these effects[84]. Dickkopf-3 (DKK3), a ligand of the canonical Wnt pathway, was found to be a potent inducer of myofibroblast activation and enhanced EndoMT in cultured renal microvascular endothelial cells. It also antagonized the effects of DKK1, an inhibitor of the Wnt pathway. Sulindac sulfide, an inhibitor of the Wnt pathway, suppressed DKK3 signals and renal fibrosis[85]. Multiple molecules have also been shown to inhibit EndoMT via suppression of Wnt/β-Catenin signaling in multiple disease models. These include inhibitors of Wnt receptors Frizzled and LRP6, regulators of the β-catenin promoter, chemokines, and others[36,80,81,86-89]. Crosstalk between Wnt signaling and the AKT and ERK pathways has also been observed in inhibition of EndoMT via the chemokine/receptor interaction of SDF-1/CXCR7[80]. DKK1, an inhibitor of canonical Wnt/β-catenin signaling, has paradoxically been shown to contribute to EndoMT[90]. A study of aortic endothelial cells corroborated the pro-EndoMT activity of DKK1, and it was found that DKK1 likely exacted this effect via ALK/Smad pathways[91].

CAV-1

Caveolin-1 (CAV-1) is the primary protein component of caveolae, which are invaginations of the plasma membrane with multiple functions including an important role in endocytosis and signal regulation. Among other functions, it diverts TGF-β receptors toward degradation primarily via ubiquination and has also been shown to regulate canonical and non-canonical TGF-β signaling[92,93]. CAV-1 has been implicated in various fibrotic diseases[94,95]. As such, its role in EndoMT is a subject of continued interest, and loss of CAV-1 has been shown to promote EndoMT in multiple studies including a CAV-1 knockout murine model and cultured HUVECs[96,97]. A recent *in vitro* study investigating inflammation and DKK1 signaling in cultured lung microvascular and human coronary artery endothelial cells found a potential link between CAV-1 silencing and AKT activation. CAV-1 knockout via siRNA led to an increase in DKK1—a known promoter of EndoMT—secretion and subsequent AKT (S473) and STAT (STAT1 and STAT2) phosphorylation indirectly via this cytokine. Similar results were observed in NR2F2 and BPMR2 loss[90].

ET-1

Endothelin-1 (ET-1) is a pleiotropic vasoactive peptide secreted by endothelial cells, especially in response to stress[98]. It also contributes to the pathogenesis of multiple diseases. Multiple studies have demonstrated a likely role of ET-1 in EndoMT.

ET-1's role in EndoMT was first examined in dermal endothelial cells derived from patients with systemic sclerosis. It was found that ET-1 production is significantly increased in untreated systemic sclerosis endothelial cells relative to healthy controls and remains significantly higher even after both healthy and systemic sclerosis endothelial cells were treated with TGF-β. Further, it was demonstrated that treatment with ET-1 was sufficient to induce EndoMT in both healthy control and systemic sclerosis endothelial cells and led to an increase in SMAD signaling. Treatment with Macitentan, a dual ET-1 receptor antagonist, inhibited the effects of both TGF-β and ET-1 treatment[99]. A subsequent study in cultured human microvascular endothelial cells (HMVECs) corroborated the finding that ET-1 is capable of inducing EndoMT in healthy endothelial cells *in vitro*, and that Macitentan was capable of partially restoring cell function. It was also found that ET-1 inhibited endothelial cell damage repair functionality. However, cells treated with TGF-β were unaffected by Macitentan treatment[100]. The interactions of ET-1 and TGF-β were further characterized in murine lung MVECs. ET-1 was found to induce expression of TGF-β receptors 1 and 2 as well as of TGF-β1 and TGF-β2. Although ET-1 was found to not be capable of inducing EndoMT independently, it appeared to be capable of enhancing the effects of TGF-β-induced EndoMT. These results were also validated in mice *in vivo*[101]. Recent work further supports the mechanistic interaction between TGF-β and ET-1. It was demonstrated that stimulation of human pulmonary arterial endothelial cells (HPAECs) with TGF-β1 leads to a significant increase in ET-1 expression. This effect was prevented by coincubation with an ALK5 inhibitor and, to a lesser extent, an ALK1 inhibitor, supporting the role of SMAD signaling in the TGF-β ET-1 axis[102].

Interactions with other molecules have also been demonstrated. MMP19, a matrix metalloproteinase, was analyzed in the context of pulmonary fibrosis among idiopathic pulmonary fibrosis (IPF) patients and bleomycin-treated mice. MMP19 was found to promote EndoMT both *in vitro* in human pulmonary microvascular endothelial cells (HPMECs) and *in vivo* in a murine model of IPF. Moreover, ET-1 expression was positively correlated with MMP19 both in a genetic dataset and in bleomycin-treated mice. It was also physically associated with MMP19 in HPMECs and was colocalized with MMP19 in IPF patient pulmonary endothelial cells. Bosentan, an ET-1 receptor antagonist, alleviated the effects of MMP19-induced EndoMT[103]. ET-1 was also found to interact with TNF-α, a pro-inflammatory cytokine, in cultured HUVECs. TNF-α promoted EndoMT and strongly increased ET-1 expression in cultured. ET-1 also enhanced TNF-α expression via phosphorylation of SMAD2, and inhibition of ET-1 greatly reduced the effect of TNF-α in EndoMT[104].

NOTCH

The Notch signaling pathway is a highly conserved intercellular communication pathway that regulates key processes including apoptosis, proliferation, homeostasis, and differentiation[105]. Its effects are highly context dependent[106]. Endothelial cells express multiple Notch receptors and ligands, enabling the regulation of the endothelial cell phenotype via Notch signaling[107]. Multiple studies have demonstrated a role of Notch signaling in the EndoMT process.

Several recent studies have indicated Notch signaling to be protective to the endothelial phenotype. One study found that Serelaxin, a recombinant form of the hormone Relaxin-2, inhibited TGF-β1-induced EndoMT via preservation of Notch-Jagged signaling in human coronary artery endothelial cells and murine cardiac endothelial cells. Similar results were observed in a murine model of cardiac fibrosis. Furthermore, supplementation with DAPT, a Notch inhibitor, mitigated the EndoMT-inhibitory effect of Serelaxin, implying that Serelaxin ameliorates TGF-β1-induced EndoMT via activation of Notch. Serelaxin also inhibited EndoMT in mouse cardiac endothelial cells in a murine model of hypertension-induced cardiac fibrosis[108]. Transcription factors associated with Notch signaling have also been shown to modulate EndoMT. Murine knockout of Rbpj, the main transcription factor of Notch signaling, increased expression of EndoMT markers. Similar results were observed following Notch signaling inhibition in human endothelial colony forming cells. Conversely, murine knockout of Sox9, a transcription factor that can oppose the actions of Rbpj, enhanced Notch signaling and reduced EndoMT in skin tissue. It was also observed that endothelial cells transitioning to a mesenchymal phenotype expressed increased Sox9 and reduced Rbpj. Topical administration of siRNA against Sox9 on skin blocked EndoMT[109].

However, some studies have associated Notch upregulation with promotion of EndoMT. Hepatocyte Growth Factor was found to attenuate the development of TGF-β1-induced EndoMT via downregulation of Notch signaling in HUVECs[110]. Another recent study investigated the effects of Morin, an MMP9 inhibitor, on TGF-β1-induced EndoMT in HUVECs. Morin inhibited EndoMT while suppressing upregulation of Notch signaling. Moreover, overexpression of MMP9 activated Notch-1 signaling and reversed morin's inhibition of EndoMT[111]. Moreover, one investigation found that Notch activation may be able to modulate EndoMT via intercellular interactions. Cardiac mesenchymal cells (CMCs) and HUVECs were treated with NICD, the active form of Notch1, or BMP2, a member of the TGF-β superfamily. Notch activation led to active transcription of Snail and Slug in both cell types and increased EndoMT markers. BMP2 only led to Snail activation in CMCs. Double transduction by BMP2 and NICD did not increase the expression level of EndoMT marker genes. The cells were then co-cultured. Treatment with NICD alone again increased mesenchymal markers in both cell types. However, co-culturing of HUVECs and CMC led to significant differences in these treatments. Double transduction of the CMC/HUVEC co-culture with BMP2 and NICD resulted in a suppression of the expression of EndoMT markers. It was also observed that the expression of Snail was suppressed in response to Notch induction and double transduction in the co-culture[112]. Together, these studies highlight the context-dependence of Notch signaling and its impact on EndoMT.

CYTOKINES AND CYTOKINE-MEDIATED PATHWAYS

A variety of inflammatory mediators have been implicated in the induction of EndoMT. The inflammatory cytokine IL-1β was one of the first identified and among the most potent initiators[113,114]. Numerous *in vitro* studies have demonstrated IL-1β to be a potent inducer of EndoMT, often acting synergistically with TGF-β[115,116]. Recent evidence suggests that IL-1β induces EndoMT in part via the BMP signaling cascade. An *in vitro* study of HUVECs found that IL-1β treatment induced EndoMT markers and increased levels of dipeptidyl peptidase IV (DPP-4), a peptidase implicated in ECM remodeling. This was found to be initiated by BMP/Smad and non-Smad BMP signaling. Treatment with the DPP-4 inhibitor gemigliptin reversed morphological and molecular EndoMT alterations[117]. The IL-1 receptor also may serve as a mechanosensitive link. An *in vivo* model of atherosclerosis found that atheroprone flow led to an increase in IL-1R1 and Snail expression relative to regions experiencing laminar flow. Analysis of human aortic endothelial cells similarly found that oscillatory shear stress increased IL-1R1 protein and mRNA levels and resulted in induction of EndoMT markers. Silencing of IL-1R1 mitigated these effects[55]. Another well-established inducer is tumor necrosis factor α (TNF-α), a pleiotropic inflammatory cytokine that drives endothelial activation[118,119]. A recent study again found TNF-α to be a potent inducer of EndoMT in HMVECs and that this conversion is reversible following TNF-α removal. It was also found that TNF-α downregulates the expression of TIE1, an endothelial receptor tyrosine kinase, and that TIE1 overexpression partially prevents TNF-α-induced EndoMT[120].

Various other cytokines may play a role. Multiple *in vitro* analyses have demonstrated IL-6 capable of inducing EndoMT. These effects involved the Akt/NFκβ pathway and may involve canonical TGF-β pathway activation[121]. It has also been shown that chronic endothelial stress can instigate an IL-6 dependent autocrine loop leading to EndoMT. A recent study showed that inhibition of autophagy, the system involved in clearing cellular waste, led to induction of EndoMT and a simultaneous increase in IL-6 levels in HMVECs. Neutralization of IL-6 via antibody, however, inhibited the induction of EndoMT[122]. One study documented IL-13 induced EndoMT in human pulmonary artery endothelial cells, possibly involving the mTOR pathway[123]. CXCL8 (IL-8) was found to enhance TGF-β1-induced EndoMT of HUVECs while promoting nuclear localization of NF-κB p65[124]. Conversely, IL-35, an anti-inflammatory cytokine, was found to attenuate lipopolysaccharide-induced EndoMT in HUVECs and mice[125]. Multiple studies have also implicated interferon-γ (IFN-γ) in EndoMT with potential regulation via JAK/STAT1 signaling[126,127].

Despite the diversity of cytokines involved in EndoMT, many including IL-6, IL-8, IL-35, and IL-1β have been shown to intersect with or modulate the NF-κB pathway[115,121,124,125]. This pathway regulates crucial functions such as immunity, inflammation, cell survival, and stress responses. Early work demonstrated that stimulation of HUVECs with IL-1β and TGF-β2 induced EndoMT and that this transition was mediated by this pathway[115]. A recent study further validated the central role of the NF-κB. Transcriptomic analysis of EndoMT-induced endothelial cells revealed downregulation of TNFAIP3, a negative regulator of NF-κB. An *in vitro* analysis of human coronary artery endothelial cells demonstrated that knockdown of TNFAIP3 significantly enhances EndoMT. This was again demonstrated in a murine knockout model. Both *in vitro* and *in vivo* experiments revealed an increase in phosphorylation of p65 and VCAM-1 alongside upregulation of Snail and mesenchymal markers, implicating the NF-κB/Snail signaling pathway in this process. Finally, it was demonstrated that METTL3-mediated m6a RNA modification of TNFAIP3 leads to TNFAIP3 mRNA degradation and subsequent hyperactive NF-κB signaling[128]. As such, NF-κB may serve as a central inflammatory axis that integrates diverse cytokine inputs and potentiates mesenchymal reprogramming during EndoMT.

Multiple immune cells, especially certain granulocytes and macrophages, have been shown to play a role in EndoMT. A recent analysis study performed a co-culture of mouse bone marrow-derived M1 macrophages and aortic endothelial cells and found that M1 macrophages significantly promoted EndoMT. TNF involvement was suggested as TNF-α levels in the supernatant were significantly increased[129]. It was also recently found that anti-inflammatory M2 (CD163+) macrophages may induce EndoMT in a model of atheroma. Human aortic endothelial cells cultured with supernatants from hemoglobin/haptoglobin-exposed macrophages exhibited molecular markers of EndoMT. NF-κB activation by pro-inflammatory cytokines released from CD163+ macrophages directly regulated the expression of Snail. Increased expression of the TGF-β receptor TGF-βR was also found in cells exposed to the supernatant[130]. On the other hand, neutrophils have been found to induce EndoMT through the release of neutrophil extracellular traps (NETs), which are fibrous protein-DNA networks designed to trap and destroy pathogens[131]. A recent report found that pharmacological blocking of NETs via Cl-amidine reduced lesion burden, coagulation, and EndoMT in a murine model of cerebral cavernous malformation[132].

Future Therapeutic Directions

True reversal of EndoMT remains elusive outside of experimental contexts. Nevertheless, multiple molecules featured in this review demonstrated early potential and are deserving of further study. Some are already used in other disease contexts. Gemigliptin, a DPP-4 inhibitor used for the treatment of type-2 diabetes in some countries, was capable of reversing IL-1β-induced EndoMT *in vitro*[117]. Trimetazidine, which is approved to treat angina in several countries, also reversed EndoMT in TGF-β-induced HUVECs and in the fibrotic heart tissue of mice treated with isoproterenol[9]. Neither drug is approved in the US and trimetazidine in particular carries serious side effects, but further testing is likely warranted in more diverse models of EndoMT.

Although central to EndoMT, systemic inhibition of the canonical TGF-β pathway is highly difficult due to its context-dependence and pleiotropic roles in normal physiology. Pan-TGF-β inhibitors often elicit disproportionately high rates of adverse events. Isoform-selective approaches may improve tolerability, evidenced by one recent study in healthy volunteers that found an anti-TGFβ3 antibody to be well tolerated[133]. Downstream products or noncanonical pathways may also be a viable alternative. It has been shown *in vitro* that PI3K/AKT, p38 MAPK, and ERK signaling are necessary for induction of EndoMT after TGF-β2 treatment[70]. AKT signaling seems to be a promising target—inhibition of AKT3 was recently shown to reverse EndoMT in hyperglycemia-treated HUVECs[37]. Global AKT inhibitors such as Ipatasertib, Uprosertib, and others exist but carry risks of systemic toxicity in long-term use. Development of isoform-specific AKT inhibitors may be possible and deserves continued research[134]. Other downstream targets including JAK/STAT, RhoA-ROCK, and tyrosine kinases show promise but yield inconsistent results with respect to EndoMT reversal in preclinical work.

Numerous studies have reported that the limited reversibility of the mesenchymal phenotype remains a critical barrier to reversal of EndoMT. Restoration of normal conditions after exposure to molecular or environmental inducers of EndoMT often fails to fully restore endothelial characteristics. One explanation for this may be found in the growing body of work demonstrating epigenetic modifications to the endothelial cell genome during EndoMT. Once epigenetically stabilized, EndoMT appears markedly more difficult to reverse. Accordingly, restoration of SIRT7, an NAD^+-dependent histone deacetylase, was recently demonstrated to reverse EndoMT in a HUVEC model of hyperglycemia[40]. However, an approach as targeted as this would likely require gene therapy and global epigenetic regulators carry systemic toxicity in long-term use[135]. A viable alternative that additionally serves as a link between the widespread metabolic dysfunction present in EndoMT and epigenetic regulation through the novel modification of histone lactylation is the glycolysis byproduct lactate. Although difficult to inhibit directly due to the central role of anaerobic glycolysis, viable indirect alternatives exist. For example, targeting HCAR1, a lactate receptor, could ameliorate paracrine signaling effects.[136] Inhibition of monocarboxylate transporters (MCTs), which transport lactate, could reduce cellular lactate uptake and intracellular lactylation substrate availability. Pharmacologic inhibition of MCTs has already been tested in multiple studies and disease models[137].

Conclusion

Despite an ever-increasing degree of research interest, EndoMT remains a highly complex process involving the convergence of numerous molecular pathways. Future work should be directed to further characterize the interaction of these pathways. Moreover, understanding the persistence of mesenchymal characteristics, with a particular focus on the role of epigenetic regulation, likely remains crucial to the development of a therapeutic capable of reverting EndoMT.

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