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TOPIC HIGHLIGHT

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Role of epithelial-mesenchymal transition in gastric cancer initiation and progression

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Abstract

Gastric cancer is one of the most common malignant tumors worldwide. Due to its intricate initiation and progression mechanisms, early detection and effective treatment of gastric cancer are difficult to achieve. The epithelial-mesenchymal transition (EMT) is characterized as a fundamental process that is critical for embryonic development, wound healing and fibrotic disease. Recent evidence has established that aberrant EMT activation in the human stomach is closely associated with gastric carcinogenesis and tumor progression. EMT activation endows gastric epithelial cells with increased characteristics of mesenchymal cells and reduces their epithelial features. Moreover, mesenchymal cells tend to dedifferentiate and acquire stem cell or tumorigenic phenotypes such as invasion, metastasis and apoptosis resistance as well as drug resistance during EMT progression. There are a number of molecules that indicate the stage of EMT (*e.g.*, E-cadherin, an epithelial cell biomarker); therefore, certain transcriptional proteins, especially E-cadherin transcriptional repressors, may participate in the regulation of EMT. In addition, EMT regulation may be associated with certain epigenetic mechanisms. The aforementioned molecules can be used as early diagnostic markers for gastric cancer, and EMT regulation can provide potential targets for gastric cancer therapy. Here, we review the role of these aspects of EMT in gastric cancer initiation and development.

Key words: Epithelial-mesenchymal transition; Gastric cancer; Tumorigenesis; Tumor progression; Cancer stem cells

Core tip: Gastric cancer is responsible for numerous deaths worldwide; therefore, investigations into its initiation and development are of great importance. Recent evidence has shown that epithelial-mesenchymal transition (EMT) plays an important role in tumorigenesis and progression. In this review, we investigate the role of EMT in gastric cancer. We discuss the role of EMT in both carcinogenesis and progression. We also summarize the regulators and signal pathways involved in EMT. A systemic understanding of the role of EMT could be helpful for the early detection and effective treatment of gastric cancer.

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INTRODUCTION

Gastric carcinoma (GC) is the fourth most common malignant tumor and is the second leading cause of cancer mortality worldwide[1]. In China, the incidence of GC ranks third among all malignant tumors, with an estimated 380000 new cases annually[2]. The mortality rate for GC in China is approximately 26.3 per 100000, the highest in the world according to a study from 2005[3]. Although the mortality of GC has declined in recent years primarily due to improvements in endoscopic detection[4], the early diagnosis and effective treatment of GC remain challenging. At present, GC diagnosis primarily relies on endoscopy; however, most cases are confirmed at advanced stages due to a lack of early stage symptoms. In addition, gastrectomy and chemotherapy are the only therapeutic options for these advanced-stage patients. Thus, the outcome of GC remains poor, with a 5-year survival rate of 20%. The prognosis of GC patients usually depends on the early detection and treatment of malignant tumor characteristics such as invasion and metastasis, which are the primary causes of treatment failure. Therefore, the exploration of GC initiation and progression mechanisms may improve early diagnosis and treatment efficacy.

The epithelial-mesenchymal transition (EMT) is characterized as a fundamental process that is critical for embryonic development, wound healing and fibrotic disease[5,6]. However, recent evidence has proven that the aberrant activation of EMT also plays a crucial role in the genesis, invasion and metastasis of various tumors[7,8], including gastric cancer[9]. As a consequence, a systematic exploration of the role of EMT in GC could deepen our understanding of GC tumorigenesis and progression, which may assist in early diagnosis and effective treatment. EMT is a process through which epithelial cells are converted into mesenchymal cells, and it involves profound phenotypic changes such as the loss of cell-cell adhesion, the loss of cell polarity and the acquisition of migratory and invasive properties. EMT occurrence and regulation both involve a series of signal transduction pathways and complex molecular mechanisms, which may be linked with transcription regulation, epigenetic modification and cancer stem cells; moreover, a number of growth factors, transcription factors and microRNA molecules may also participate in this progress. Here, we briefly review the role of EMT in GC. We separately discuss its role in both tumorigenesis and cancer progression and summarize the involved regulators and possible regulating signal pathways.

GENERAL CHARACTERISTICS OF EMT

During cell development, the cells of epithelial and mesenchymal origins convert between the two phenotypes in what has been described as the EMT and the mesenchymal-epithelial transition (MET). The common characteristics exhibited during EMT are the loss of epithelial cell contacts, the reorganization of cytoskeletal components to promote a motile phenotype and the remodeling of the surrounding extracellular matrix to allow for invasion[10]. EMT can be approximately divided into three types according to the phenotype of the output cells[11]. In type 1 EMT, epithelial cells convert into mesenchymal cells that form the diaspora of the basic body plan, and it is well known that type 1 EMT is the fundamental process in the embryonic development of multicellular organisms. For example, EMT has been shown to be activated during gastrulation as well as during the development of the neural crest, heart and musculoskeletal system[12,13]. The transition from epithelial cells to inflammation-induced fibroblasts can be observed in type 2 EMT, which is associated with wound healing, tissue repair and organ fibrosis[11]. Type 2 EMT can contribute to inflammatory responses and tissue repair under normal conditions but can also cause organ fibrosis. Type 3 EMT is a tumor progression process in which epithelial tumor cells transform into metastatic tumor mesenchymal cells that can leave their primary tumor site and migrate to a new tissue to form secondary tumor nodules. Type 3 EMT endows cancer cells with the ability to invade and metastasize, promoting carcinoma progression and treatment failure[10,14].

Because EMT involves significant phenotypic changes, there are a variety of molecules that can be used to act as EMT biomarkers. E-cadherin encoded by the CDH1 gene is a transmembrane glycoprotein expressed in epithelial cells that plays an important role in the maintenance of cell adherence and the structural integrity of epithelial sheets[12,15]. The loss or down-regulation of E-cadherin is considered an important EMT marker[16]. During the EMT, cadherin switches from E-cadherin to N-cadherin, which is expressed in mesenchymal cells. Thus, the down-regulated expression of E-cadherin and up-regulated expression of N-cadherin are observed during EMT, and both can be identified as EMT biomarkers. Other cell surface proteins, ECM proteins and cytoskeletal markers such as FSP1, β-catenin and α-SMA can also be used to characterize EMT[11]. In addition, certain transcription factors and microRNA molecules that participate in the regulation of the EMT can be identified as biomarkers or potential targets for intervention.

ROLE OF EMT IN GASTRIC TUMORIGENESIS

During the EMT process, epithelial cells dedifferentiate and acquire mesenchymal as well as stem cell phenotypes. In these stem cell phenotypes, the EMT-induced cancer stem cell (CSC) phenotypes may contribute the most to tumorigenesis in the stomach.

Previously, each cell was believed to be potentially cancerous; however, only a subset of these cells can actually initiate cancer[17], *i.e.*, CSCs. CSCs are a small subset of cancer cells that possess extensive proliferative and self-renewal potential and can differentiate into heterogeneous tumorigenic cancer cells. Reya *et al*[18] proposed the

"Cancer Stem Cells Theory" in 2001 and asserted that there were striking parallels between stem cells and CSCs. The authors proposed that tumors may often originate from CSCs and that there are similar signaling pathways in regulating the self-renewal of stem cells and cancer cells. Thus, cancer cells may include "Cancer Stem Cells", which are rare cells with the indefinite potential for self-renewal that can drive tumorigenesis.

The existence of gastric CSCs in the stomach has also been demonstrated. Takaishi *et al*[19] performed experiments and concluded that CD44-positive gastric cancer cells have CSC properties including the ability to initiate tumors, and these cells provide a cell reservoir that can cause tumor recurrence after therapy. Further evidence demonstrated that the gastric CSC marker CD44 was significantly associated with the expression of EMT-activating transcription factors, indicating that gastric CSCs may be associated with EMT[20]. Ryu *et al*[20] performed immunohistochemistry for EMT-related proteins including Snail-1, ZEB-1, E-cadherin, vimentin and β-catenin as well as the CSC marker CD44 in 276 consecutive primary gastric cancers and 54 matched lymph node metastases. Their results demonstrated that CD44 expression was significantly associated with the expression of Snail-1, ZEB-1 and E-cadherin. Moreover, in the gastric epithelium, the stem cells at the base of the pyloric gastric glands are reliant on an active and dynamically regulated Wnt pathway[21,22]. This dependency is reflected in the exclusive expression of Lgr5, which functions to amplify the Wnt signal in these stem cells[23,24], while the Wnt signal is also an important pathway that is activated during EMT. These items suggest that EMT is associated with CSCs and is sufficient to induce stemness and tumorigenicity.

Regarding the mechanisms involved in EMT-induced stemness and tumorigenicity, recent studies have demonstrated that the EGFR/Ras pathway required for sustaining gastric stem cells *in vivo* and *in vitro* is involved in the genesis and promotion of EMT-induced tumor-initiating cells[25]. Researchers have found that in the Runx3(-/-) p53(-/-) gastric epithelial cell line GIF-14, the TGF-β and EGFR pathways cooperate together to induce stemness[25]. Another study revealed that cancer-associated fibroblasts trigger WNT5A, which regulates EMT induction and the maintenance of the CSC properties in human gastric adenocarcinoma cell line MKN-7, and that WNT5A may play an important role in constructing an advantageous tumor microenvironment for GC progression and development[26].

ROLE OF EMT IN GC PROGRESSION

In addition to tumorigenesis, EMT also participates in tumor progression. EMT endows cells with migratory and invasive properties, induces stem cell properties, prevents apoptosis and senescence and contributes to immunosuppression, thus promoting tumor progression.

Tumor invasion is a series of discrete biological processes in which tumor cells move from the primary neoplasm to the underlying stroma; this process involves the loss of cellular adherence to other cells, cell adhesion to the extracellular matrix (ECM), the proteolytic degradation of the surrounding stroma and the motility to physically propel a tumor cell through the stroma[27]. After invasion, tumor metastasis occurs. Tumor metastasis is a multistep process by which tumor cells disseminate from the primary site and form secondary tumors at a distant site. The metastatic process occurs through the following steps: local invasion; intravasation; transport; extravasation; and colonization[28]. Both tumor invasion and metastasis must precede the loss of adherence between the cells and the adherence to the ECM.

In the gastric mucosa, epithelial cells establish close contact with neighboring cells and an apical-basal axis of polarity through the sequential arrangement of adherens junctions, desmosomes and tight junctions[27]. During this process, the first step is the formation of an adherens junction; a tight junction is then formed at the apical side of the adherens junction. The formation of the adherens junction relies on cadherin. E-cadherin, which is encoded by the *CDH1* gene, is the major component of the adherens junction. When aberrant EMT is activated, the cadherin switches from E-cadherin to N-cadherin, which is normally expressed in mesenchymal cells and has a capacity to facilitate adhesion between cells and the stroma. Moreover, the apical-basal axis of the polarity of epithelial cells is lost, and the cell morphology changes to a spindle shape and exhibits a mesenchymal phenotype that endows cells with the ability to degenerate the stroma. Thus, increased cell motility and invasiveness are acquired through the EMT progress. Tumor metastasis is also accelerated through the stimulation of cell migration and invasion, cell substrate adhesion, intravasation and extravasation during EMT. Substantial evidence has shown that the initiation of GC and its biological malignant behaviors are related to E-cadherin mutations[29,30]. Furthermore, N-cadherin expression has also been associated with the invasive phenotype of GC and has even been thought to override the function of E-cadherin[31].

In addition, the stemness of the CSC phenotype induced by EMT endows cancer cells with the ability to self-renew, the overexpression of drug resistance related genes and the prevention of apoptosis, which results in another challenging obstacle called multiple drug resistance (MDR) in cancer therapy. It is well known that chemotherapy is an important treatment in GC, and the induction of apoptosis is the major purpose of chemotherapy. Although there is no direct evidence that EMT-induced stemness contributes to MDR in GC, some studies in other cancers have indicated that the MDR in chemotherapy is associated with EMT[32,33]. Izumiya *et al*[32] reported that chemoresistance is associated with CSC-like properties and EMT in pancreatic cancer cells, and Li *et al*[33] reported that the overexpression of Snail (a key regulator in EMT) could accelerate adriamycin-induced MDR in breast cancer cells.

MECHANISMS THAT REGULATE EMT IN GC

E-cadherin is the central composition of cellular adhesion junctions and is required in the development of the epithelium in embryos and maintenance of the epithelial phenotype. Thus, loss of E-cadherin expression is considered a hallmark of EMT and is also a crucial step in tumor progression. Many efforts have been devoted to explore how E-cadherin is regulated during EMT and cancer progression, and a series of transcriptional and epigenetic mechanism have been revealed.

Transcriptional regulatory mechanisms

In the process of transcriptional regulation, several key transcription factors (including Snail, Twist, and ZEB) that repress E-cadherin expression are expressed selectively in gastric cancer[34]. These proteins have been shown to target E-boxes in the E-cadherin promoter, thus repressing its expression[35].

Snail is a member of the zinc finger protein family, a DNA-binding factor that recognizes E-box motifs in target promoters (CDH-1) and regulates the following E-cadherin repression[36]. Promoting E-cadherin expression can influence EMT and tumor development. The Snail gene-encoded transcriptional repressor with the SNAG domain can mediate binding to Sin3A/HDAC1/HDAC2, Ajuba-PRMT5-PRC2, and LSD1-coREST complexes and certain zinc finger domains[37-41]; the combination of Snail and CDH-1 depends on these complexes, and the SNAG domain and zinc finger domain play a decisive role in this combination[38]. Regarding Snail regulation, GSK3β binding to and phosphorylating Snail at two consensus motifs play an important role. Phosphorylation of the first motif leads to ubiquitination, and phosphorylation of the second motif alters the protein subcellular localization. These two phosphorylation events can lead to the degradation of Snail. Thus, the inhibition of GSK3β activity can up-regulate the function of Snail, resulting in E-cadherin repression. The Snail family comprises three members: Snail1 (originally identified as Snail); Snail2 (Slug); and Snail3 (Smuc). Among these, Snail1 and Snail2 are selectively expressed in gastric tumors. In addition, Castro Alves *et al*[35] demonstrated that Snail2 and ZEB2 may act synergistically in intestinal GC, whereas Snail1 and Snail2 may complement each other in diffused carcinoma. In addition to E-cadherin, Snail1 can repress the expression of other epithelial-specific genes by interacting with Smad3/Smad4[42].

Among the transcriptional factors that are overexpressed in metastatic GC, Twist was the first chosen for study. Ru *et al*[43] used quantitative real-time PCR and immunohistochemistry to analyze the relationship between Twist expression and tumors in 436 GC cases, and their results showed that Twist expression levels in tumor tissues and metastatic lymph nodes were up-regulated compared with normal gastric mucosa. The authors concluded that Twist expression in GC is significantly associated with positive lymph nodes and distant metastases[43]. A series of other experiments illustrated that Twist is specifically involved in the intravasation step of tumor metastasis, while having no significant impact on extravasation or the growth rate of the malignant tumor cells[44]. The regulatory effect of Twist on gene expression depends on its binding to other transcriptional factors, post-translational modifications and the dimerization partner[45]. However, the post-translational regulation of Twist is complex because the specific expression pattern of members and their affinities for each other regulate their capacity to form functional dimers. Because Twist belongs to the basic/helix-loop-helix (bHLH) family of transcription factors, Twist1 and Twist2 share a bHLH domain that regulates their binding to DNA and homo/hetero-dimerization[45]. Twist proteins bind to DNA using a consensus E-box site as homo/hetero-dimers, and these complexes can repress gene transcription such as E-cadherin[45]. In addition, under conditions of hypoxia, the hypoxia-inducible factor-1α (HIF-1α) can also up-regulate Twist expression by directly binding to the hypoxia-response element (HRE) in the Twist promoter, resulting in EMT activation and the promotion of tumor invasion and migration[46]. Moreover, GC cells transfected with Twist1 have increased migration and invasion abilities than untreated cells; those transfected with Twist1 also form more cancer nodules in the abdominal cavity and liver of nude mice after inoculation with the transfected cells[47].

The ZEB family consists of two members, ZEB1 and ZEB2, which is also known as SIP1. These members are characterized by the presence of two zinc-finger clusters at each end and a central homeodomain. Similar to the Snail gene family members, ZEB family members (especially ZEB2) can also bind to the E-box in the E-cadherin gene promoter through their two zinc finger domains; they then repress E-cadherin expression and trigger EMT[48].

Epigenetic regulatory mechanisms

In addition to transcriptional regulation, epigenetic regulation also plays an important role in controlling EMT and cancer progression; epigenetic regulation includes three types of changes: DNA methylation; histone modifications; and microRNAs[49].

DNA methylation usually occurs at CpG dinucleotides through the action of DNA methyltransferase (DNMT)[50], and DNA methylation in epithelial cells can silence gene expression, thereby restricting the developmental plasticity of epithelial cells[51]. Similarly, hypermethylation of the E-cadherin gene promoter leading to a loss of E-cadherin expression has been shown to contribute to EMT and promote tumor progression[52]. Many studies have demonstrated the frequent promoter methylation of CDH1 (the E-cadherin gene) in GC[53] and have shown E-cadherin promoter hypermethylation to correlate with GC aggressiveness and metastasis[54]. Interestingly, Lee *et al*[55] also observed the frequent promoter

methylation of CDH1 in the non-neoplastic mucosa of patients with sporadic diffuse GC.

Histone modifications such as methylation, acetylation and ubiquitination are other important epigenetic regulatory mechanisms during EMT. The methylation of histone proteins at specific residues plays a major role in the maintenance of active and silent states of gene expression in developmental processes[56]. Fujii *et al*[57] found that the enhancer of zeste homolog 2 (EZH2) can down-regulate E-cadherin by mediating histone H3 methylation in GC cells. EZH2 is a transcriptional repressor that has a crucial function in maintaining the delicate homeostatic balance between gene expression and repression, the disruption of which may lead to oncogenesis[58]. Studies have shown that histone H3 lysine 27 trimethylation, which is mediated by EZH2 at gene promoters, silences gene expression[59]. Acetylation is another form of histone modification. Histone acetylation, particularly at H3 and H4, leads to a relaxed chromatin structure and therefore an enhanced transcription rate. Acetylation reactions are catalyzed by various families of co-activators with histone acetyltransferase (HAT) activity[60]. It has been reported that the transcription factor hepatocyte nuclear factor 3 (HNF 3) synergizes with p300 and AML-1 to enhance E-cadherin gene expression and thus repress the metastatic potential of breast cancer cells[61]; HNF 4 has also been shown to play a regulatory role in GC[62].

MicroRNA (miRNA) is a type of small endogenous non-coding RNA that is an evolutionary conserved molecule approximately 22 nucleotides in length[63]. MiRNAs can regulate gene expression through the posttranscriptional silencing of target genes[64]. MiRNAs play an important role in a variety of physiological and pathological processes including cell proliferation, cell differentiation and tumor formation. In recent years, many publications have indicated that miRNAs may act as oncogenes or tumor suppressors in cancer development and progression[65-67]. A substantial number of deregulated miRNAs have been revealed in GC, and the biological significance of these miRNA has been confirmed in multiple functional experiments; however, the mechanisms by which miRNAs regulate GC metastasis remain poorly understood. Members of the miR-200 family (miR-200a/b/c, miR-141 and miR-429) maintain an epithelial state and prevent EMT through the inhibition of ZEB1 and ZEB2; in turn, miR-200 members are transcriptionally repressed by ZEB factors as well as Snail1, thus forming a double-negative loop that maintains cells in either an epithelial or mesenchymal state[68]. Cong *et al*[69] found that miR-200a suppresses Wnt/β-catenin signaling by interacting with β-catenin, thereby inhibiting migration, invasion and proliferation. The effects of miR-200a on Wnt/β-catenin signaling may provide a therapeutic target against EMT. In addition, the deregulation of other miRNAs including miR-101, miR-107, miR-221 and miR-222 has also been observed in GC[70]. Conversely, certain miRNAs can result in invasion and metastasis. Zhang *et al*[71] verified that miR-27 expression is increased in GC tissues, and the authors also provided evidence that miR-27 promotes EMT and human GC cell metastasis by activating the Wnt pathway. Although miRNAs have been documented to be involved in tumor invasion and metastasis in many recent studies, the relevance of miRNA and EMT in GC has remained a matter of debate until very recently.

SIGNAL PATHWAYS ASSOCIATED WITH EMT IN GC

Many studies have found that a variety of signaling pathways are involved in the EMT process in tumor cells. Recently, the activation of the phosphatidylinositol 3 kinase (PI3K)/AKT axis has emerged as a central feature of EMT. Matsuoka *et al*[72] recently concluded that PI3K/AKT signaling may be required for the integrin-dependent attachment and spreading of scirrhous GC cells. PI3K can phosphorylate PIP2 to generate PIP3, while PTEN dephosphorylates PIP3 back to PIP2[73,74]. PIP3 binding to the PH domain of AKT leads to its translocation to the plasma membrane, where AKT is phosphorylated and activated. GSK3β activity can be down-regulated by the PI3K/AKT signaling pathway, and PI3K/AKT are positive regulators in this pathway (whereas PTEN is the negative regulator). Therefore, the activation of the PI3K/AKT signaling pathway in GC can lead to EMT through Snail-mediated CDH-1 repression.

In addition to the PI3K/AKT signaling pathway, the Wnt/β-catenin signaling pathway also plays an important role in EMT. The regulation of the Wnt/β-catenin signal depends on the phosphorylation and degradation of β-catenin in the cytoplasm. When there is a deactivation of the Wnt signal, β-catenin in the cytoplasm binds to E-cadherin and actin. GSK3β phosphorylates β-catenin to maintain low β-catenin level in the plasma; when the Wnt signal is activated, β-catenin is dephosphorylated, and there is an accumulation of β-catenin in the plasma[75]. The excess free β-catenin moves into the nuclei and increases the expression of Snail, Slug and Twist, leading to the repression of E-cadherin and EMT. In turn, Snail interacts with β-catenin in the N-terminal region and activates the Wnt signal, resulting in a positive feedback of the Wnt signal[76]. Thus, the activation of the Wnt/β-catenin signaling pathway can also lead to EMT. In addition, Huang *et al*[77] found that EphA2 can promote EMT through the Wnt/β-catenin pathway in GC cells.

Transforming growth factor β (TGF-β) is an indispensable inducing factor during the EMT process, and the TGF-β pathway is also an important signaling pathway in EMT. In the TGF-β pathway, TGF-β activates TGF-β receptor type Ⅱ (TβR-Ⅱ), which phosphorylates TGF-β receptor type Ⅰ (TβR-Ⅰ)[78-80]. Activated TβRI kinase phosphorylates Smad2/3, which associate with Smad4 and translocate to the nucleus (as transcription factors[78-80] such as Snail and Slug[81]) and promote EMT. According to a study by Ono *et al*[82], protein-bound poly-

saccharide can inactivate Smad2 signaling to directly inhibit the TGF-β pathway in GC. Thus, the inhibition of the TGF-β pathway is a potential treatment for GC.

The Notch pathway plays a key role in EMT-induced CSCs. Notch signaling has been reported to promote CSC self-renewal in several malignancies and participate in tumor-stroma and tumor-endothelium interactions in CSC niches in primary and metastatic tumors[83]. In mammals, there are four transmembrane Notch receptors (Notch1, Notch2, Notch3 and Notch4) and five canonical transmembrane ligands [Delta-like (DLL)1, DLL3, DLL4, Jagged-1 and Jagged-2][83]. The deregulated expression of Notch proteins, ligands and targets, including Notch overexpression and activation, has been described in a multitude of solid tumors including GC. With regard to CSCs, Notch signaling regulates CSC formation and endows a self-renewal ability and drug resistance to the CSCs[84]. There is crosstalk between Notch and the EMT transcription factors such as Snail, Slug and TGF-β, and Notch can promote EMT through the regulation of Snail[85]. Thus, targeting Notch signaling can reverse EMT and CSC stemness.

CONCLUSION

EMT plays an important role in the formation, invasion and metastasis of GC. The loss of E-cadherin is a key step in the EMT process, and E-cadherin transcriptional repressors such as Snail, ZEB and Twist play an important role in EMT. These transcription factors have been shown to be significantly increased in GC and may provide new insight into GC. Other factors participating in embryonic development and EMT regulation can also be considered important avenues of investigation for tumors and EMT. These factors can also provide novel clinical targets to treat GC. Furthermore, EMT may provide a new perspective for cancer stem cell theory as well as stem cell research in the relevant area of tumor formation. Although its mechanism remains incompletely understood, further research into EMT will further elucidate its role and importance.

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