Eomesodermin in renal cell carcinoma: Epigenetic and immune crosstalk driving tumor progression (Review)

ZHIFEI CHE[1*], DONGWEN HUANG[1*], JIAMING LIN[1*], XINCEN WANG[1*], RONGJIN FENG[1], XIANPING CHE[2] and YUBIN WANG[1]

[1]Key Laboratory of Reproductive Health Diseases Research and Translation of Ministry of Education, Department of Urology, The First Affiliated Hospital, Hainan Medical University, Haikou, Hainan 570102, P.R. China; [2]Department of Urology, The Second Affiliated Hospital of Hainan Medical University, Haikou, Hainan 570100, P.R. China

Received November 25, 2025; Accepted August 21, 2026

DOI: 10.3892/ijo.2026.5941

Abstract. Renal cell carcinoma (RCC) is the main pathological type of kidney cancer, which accounts for approximately 85-95% of all cases of kidney cancer. Despite the emergence of targeted therapies and immunotherapies, however, the development of resistance remains common. Eomesodermin (Eomes) is a member of the T-box transcription factor family that links both developmental biology and immune regulation with tumor-associated programs. In RCC, its function appears to be context-dependent. In tumor-infiltrating leukocytes, Eomes has been shown to support mature natural killer cell and memory $CD8^+$ T-cell function, whereas persistent or dysregulated Eomes is associated with exhausted $CD8^+$ T cells and Eomes-positive type 1 regulatory T-like immunosuppressive cells. In both intrinsic RCC tumor cells and stromal/endothelial compartments, current knowledge remains relatively limited, and what evidence there is has often been derived from indirect RCC pathway research, other tumor types or developmental models. The present review summarizes Eomes-associated mechanisms in RCC through distinguishing among infiltrating leukocytes, tumor cells and stromal/endothelial compartments, and also through separating direct RCC evidence from indirectly derived mechanistic inferences. Epigenetic regulation, PI3K/Akt/mTOR signaling, Wnt/β-catenin signaling, angiogenesis and therapeutic resistance are also discussed according to the strength of the available evidence. Current data support that Eomes stands as an exploratory biomarker and hypothesis-generating therapeutic node, rather than as an established clinical target. Further research should be performed, however, to validate the cell-type-specific functions of Eomes in RCC tissues, single-cell and spatial datasets, in addition to experimental RCC models.

Correspondence to: Dr Yubin Wang, Key Laboratory of Reproductive Health Diseases Research and Translation of Ministry of Education, Department of Urology, The First Affiliated Hospital, Hainan Medical University, 31 Longhua Road, Longhua, Haikou, Hainan 570102, P.R. China
E-mail: wangyb1980@163.com

Dr Xianping Che, Department of Urology, The Second Affiliated Hospital of Hainan Medical University, 368 Yehai Road, Longhua, Haikou, Hainan 570100, P.R. China
E-mail: chexianping2008@163.com

*Contributed equally

Key words: renal cell carcinoma, eomesodermin, tumor microenvironment, therapeutic target

Contents

1. Introduction
2. Literature retrieval strategy
3. Structure and biological function of Eomes
4. Role of Eomes in the immune microenvironment of RCC
5. Regulation of RCC progression by Eomes
6. Role of Eomes in stromal/endothelial regulation and RCC angiogenesis
7. Regulation of Eomes-associated epigenetic regulation mechanisms and signaling pathways
8. Potential of Eomes as an exploratory biomarker, and cell-type-specific therapeutic targets for RCC
9. Conclusions

1. Introduction

Renal cell carcinoma (RCC) ranks among one of the most common urinary system malignancies, with a steadily rising global incidence, especially in the male population (1,2). RCC comprises 85-95% of all cases of kidney cancer, with clear cell RCC (ccRCC) having been identified as the primary subtype (3). Targeted therapies and immunotherapies, including VEGF inhibitors, mTOR inhibitors and immune checkpoint inhibitors (ICIs), are extensively utilized in RCC treatment; however, patients frequently exhibit poor immunotherapy responses, secondary resistance or disease progression, despite treatment (4). Identifying novel targets to improve the efficacy of RCC immunotherapy therefore remains a key focus in oncology research.

Eomesodermin (Eomes) is a highly conserved T-box transcription factor that was first identified as having participatory roles in early embryogenesis, mesoderm formation and neural development (5). Eomes has been shown to have a crucial role in the normal functioning of immunity in organisms, especially in $CD8^+$ T cells, natural killer (NK) cells and innate lymphoid cells (ILCs) (6-8). Eomes maintains effector immune cell cytotoxicity through upregulation of various factors, including perforin (PRF1), granzyme B (GZMB) and IFN-γ (9). Furthermore, it has been shown to actively contribute to $CD8^+$ T cell lineage commitment, whilst orchestrating NK cell maturation and tissue migration (10). However, studies by Weulersse *et al* (11) and Gao *et al* (12) have shown that associated chronic inflammatory and immunosuppressive signals frequently trigger the misexpression of Eomes, causing immune cell dysfunction or the conversion of immune cells into suppressive phenotypes, thereby forming hard-to-reverse immune tolerance in immunotherapy.

In addition, Eomes has been associated with tumor immune escape and tumor progression mechanisms. Previous studies have demonstrated that Eomes orchestrates T-cell exhaustion, where its high expression was associated with $CD8^+$ T-cell terminal exhaustion. Eomes subsequently sustains this exhaustion process through upregulation of immune checkpoints (13,14). By contrast, Eomes deficiency in NK cells has been shown to impair their effector functions, especially in the tumor microenvironment (TME). Its downregulation drives a shift in NK cell phenotype toward an 'ILC1-like' state, which was found to be accompanied by the loss of cytotoxic factors and an increase in immune-suppressive factor release, ultimately weakening innate immunity control over oncogenesis (15,16). Furthermore, Eomes modulates immune cell functions, and may also exert a direct influence on various malignant phenotypes, including the maintenance of cancer stemness, the induction of epithelial-mesenchymal transition (EMT), the promotion of angiogenesis, and the conferral of apoptosis resistance, especially in RCC (17-20). The regulation of Eomes is governed by intricate epigenetic and signaling networks, comprising multi-level control, including histone modifications (such as acetylation, methylation and ubiquitination) and non-coding RNA-mediated interference (18,21-23). Notably, these mechanisms are present in both immune and tumor cells, and provide theoretical support for the development of targeted therapies against Eomes; however, the therapeutic potential of Eomes is complicated by its divergent and context-specific biological effects across distinct cell populations, acting as a functional 'double-edged sword' (for example, promoting T-cell exhaustion in certain contexts, while maintaining effector function in others) (6,16). This aspect creates challenges in terms of designing therapeutic strategies that require precise, cell-specific regulation.

To summarize, based on current knowledge, Eomes may play a role in linking tumor immunity, stemness, epigenetic regulation and signaling pathway crosstalk in RCC. However, the direction of its effects depends on both the cellular compartment and the evidence source. In the present review, the role of Eomes is therefore interpreted separately in infiltrating leukocytes, intrinsic RCC tumor cells and stromal/endothelial compartments, and direct RCC evidence is distinguished from the indirect evidence derived from other cancer types, chronic infection models and developmental biology. This framework is intended to both reduce overinterpretation, and to clarify why the global activation or inhibition of Eomes is unlikely to be appropriate without cell type-specific validation.

2. Literature retrieval strategy

The present article is a narrative review, rather than a systematic review or meta-analysis. Publications were retrieved from PubMed, Web of Science, Google Scholar, The Cancer Genome Atlas (TCGA)/Clinical Proteomic Tumor Analysis Consortium (CPTAC)-associated online resources and the Human Protein Atlas up to June 2026. Search terms included 'EOMES', 'eomesodermin', 'renal cell carcinoma', 'clear cell renal cell carcinoma', 'ccRCC', 'tumor microenvironment', '$CD8^+$ T cell', 'natural killer cell', 'ILC1', 'Tr1-like cell', 'epigenetic regulation', 'PI3K/Akt/mTOR', 'Wnt/β-catenin', 'angiogenesis' and 'immunotherapy'. Original research articles, clinical cohort studies, single-cell studies and authoritative reviews were considered when they addressed Eomes biology, RCC immunobiology, epigenetic regulation, tumor progression or therapeutic resistance. Studies were excluded if they did not contain mechanistic or translational information relevant to Eomes, RCC or the cell compartments discussed in this review. Since direct RCC evidence remains incomplete for several of the proposed mechanisms, studies from other tumor types, chronic infection models and developmental biology were used only as hypothesis-generating evidence, and these are identified as such in the text.

3. Structure and biological function of Eomes

Eomes was first identified in embryonic development, where it governs cell fate, embryo implantation and neural development (24,25). Eomes shares high homology with T-bet, the master regulator of T helper type 1 (Th1) cells, which also regulates immune cell differentiation and function (15) (Fig. 1). The human Eomes gene resides on chromosome 3p24.1, spanning ~6,761 bp (NCBI Gene ID: 8320; GRCh38.p14 assembly). The Eomes gene encompasses a highly conserved DNA-binding domain (T-box domain), its most important functional module, which is located between the N-terminus and mid-region (specifically, amino acids 278-457). This domain specifically recognizes T-site DNA elements enriched with the 'AGGTGTGA' sequence (26,27). By means of this domain, Eomes directly interacts with the T-box consensus sequence located in the promoter region of target genes, thereby regulating their transcription downstream (28). Belinson *et al* (29) demonstrated that, in the embryonic brain, β-catenin and Eomes are able to co-bind proliferation-associated enhancers in the cortex. These findings suggested a possible Eome-β-catenin interaction, although its relevance to RCC requires direct validation.

Eomes has also been shown to mediate dual ontogenetic roles. It is able to coordinate morphogenetic processes during embryonic development. By contrast, it can also simultaneously regulate immune cell dynamics through the modulation of differentiation trajectories, functional sustainability and memory programming in NK cells, $CD8^+$ T cells and ILCs (6,7,30). In immune cells, both the expression patterns

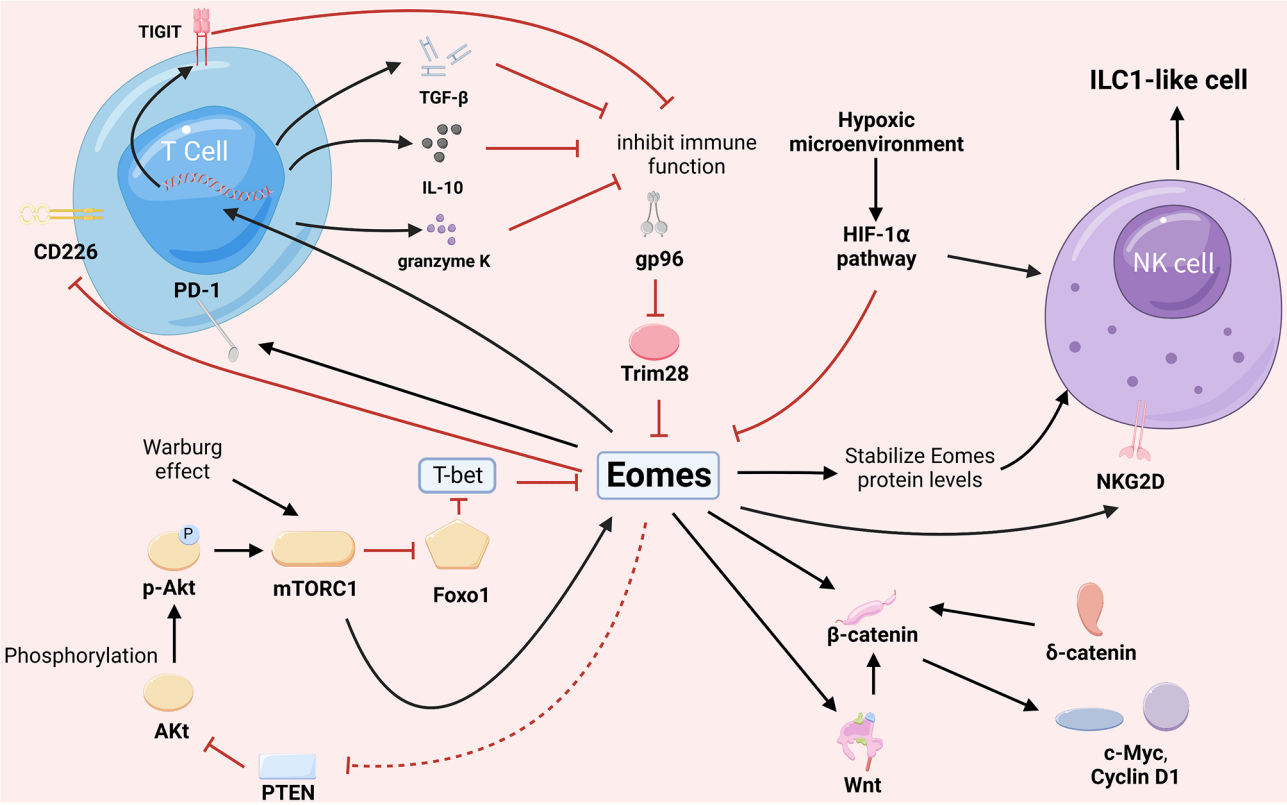

Figure 1. Compartment-specific framework of Eomes in RCC. The figure separates Eomes-associated mechanisms into three TME compartments: Infiltrating leukocytes, intrinsic RCC tumor cells and stromal/endothelial components. In infiltrating leukocytes, Eomes may support mature NK-cell cytotoxicity through gp96/TRIM28-dependent protein stability and effector programs, whereas persistent Eomes activity in exhausted $CD8^+$ T cells or Tr1-like cells may support PD-1/TIGIT expression, IL-10/TGF-β secretion and immune suppression. In tumor cells, possible Eomes links with the Wnt/β-catenin and PI3K/Akt/mTOR axes, cell stemness and apoptosis resistance are shown as hypothesis-generating mechanisms. In stromal/endothelial compartments, Eomes-associated angiogenic effects are shown mainly as indirect immune-cytokine-mediated effects. Solid black arrows represent activating regulatory relationships that are supported by available research evidence. Solid red lines denote inhibitory or degradative negative regulation with supporting experimental evidence. The dashed red line indicates an indirect, putative negative regulatory relationship. Eomes, eomesodermin; RCC, renal cell carcinoma; TME, tumor microenvironment; NK, natural killer; gp96, heat shock protein glycoprotein 96; TRIM28, tripartite motif-containing 28; TIGIT, T cell immunoglobulin and ITIM domain; HIF-1α, hypoxia-inducible factor-1α; NKG2D, natural killer group 2D.

and the functions of Eomes serve as cell markers. Together with T-bet, Eomes sustains NK cytotoxicity function. NK cells with high Eomes expression have been typically shown to exhibit stronger cytotoxicity and a stronger IFN-γ secretion capability, whereas NK cells with lower Eomes expression were shown to exhibit a tendency to differentiate into ILC1 cell types, which resulted in markedly reduced antitumor activity (31). In $CD8^+$ T cells, Eomes was shown to enhance interleukin (IL)-2 signaling via increasing the expression of CD25, thereby promoting the proliferation and survival of effector T cells, and contributing to the formation and maintenance of memory T cells (32). In addition, Eomes was shown to directly bind to the promoter regions of immune checkpoint molecules, such as T cell immunoglobulin and ITIM domain (TIGIT) and programmed cell death protein 1 (PD-1), thereby promoting their expression and inducing T-cell exhaustion (33,34).

Eomes expression and activity have been demonstrated to be subject to various modes of epigenetic control. In γ-δ T cells, PRF1 and GZMB production was found to be suppressed as a result of a reduction in Eomes expression induced by histone deacetylase (HDAC) inhibitors (35). Furthermore, the phosphorylated form of lysine-specific demethylase 1 (nLSD1p) was found to regulate the nuclear localization and transcriptional activity of Eomes through its interaction with Eomes, inducing $CD8^+$ T-cell exhaustion (18,36). Additionally, the process of ubiquitination has been shown to regulate the stability of Eomes. A study by Xu *et al* (21) revealed that the heat-shock protein glycoprotein 96 (gp96) inhibits tripartite motif-containing 28 (TRIM28)-mediated Eomes ubiquitination and degradation, thereby enhancing NK maturation and antitumor effects.

Cell-compartment-specific framework of Eomes in RCC. To integrate the operation of the mechanisms described below, Eomes should be interpreted in three major RCC TME compartments. First, with respect to infiltrating leukocytes, divergent functions have been identified for Eomes in $CD8^+$ T cells, NK cells, ILC1-like cells and type 1 Tregs (Tr1-like) cells. Secondly, in intrinsic RCC tumor cells, possible links with cell stemness, EMT, apoptosis resistance and proliferative signaling remain incompletely validated, and the links should therefore be interpreted with caution. Thirdly, in stromal and endothelial compartments, the majority of the Eomes-associated effects that have been proposed are probably indirect, mediated through immune cytokines, angiogenic signaling or tumor-stroma crosstalk. This compartment-based framework also explains the 'double-edged' character of

Table I. Evidence hierarchy for Eomes-related mechanisms in RCC.

Evidence source	Eomes-related mechanism	Main compartment	Interpretation in RCC	Evidence strength
Human RCC tissues and single-cell studies	Eomes-positive CD8+ T-cell exhaustion, PD-1/TIGIT expression and Eomes-positive Tr1-like immunosuppressive cells	Infiltrating leukocytes	Supports an association with immune dysfunction, tumor progression and response to immunotherapy; causality still requires functional validation.	Direct RCC clinical/single-cell evidence
RCC-associated NK-cell observations and immune-cell models	Eomes maintenance of NK-cell cytotoxicity, gp96/TRIM28-dependent Eomes stability and NK-to-ILC1-like plasticity	Infiltrating leukocytes	Supports a protective role of Eomes in mature NK cells, whereas TGF-β and HIF-1α may suppress Eomes in NK-cell contexts.	RCC-associated plus immune-model evidence
RCC pathway studies and non-RCC tumor models	PI3K/Akt/mTOR, PTEN, Wnt/β-catenin, apoptosis, EMT and stemness-related mechanisms	Tumor cells	Tumor-cell-intrinsic effects remain incompletely validated in RCC and should be interpreted as hypotheses requiring gain- and loss-of-function experiments.	Indirect or hypothesis-generating evidence
RCC angiogenesis studies and IFN-γ biology	IFN-γ, VEGF/bFGF, CXCL9/CXCL10 and PinX1/miR-125a-3p/VEGF signaling	Stroma/endothelium	Eomes may affect angiogenesis indirectly through immune-cell-derived IFN-γ; direct endothelial or stromal Eomes evidence in RCC is limited.	Indirect RCC-related evidence
Developmental biology, chronic infection, CAR-T and other cancer studies	BAF interaction, β-catenin coactivation, LSD1/G9a modulation and engineered T-cell approaches	Cross-model/translational hypotheses	These findings provide mechanistic leads but should not be presented as established RCC mechanisms or clinical strategies.	Cross-model evidence

Eomes, eomesodermin; RCC, renal cell carcinoma; RCC, renal cell carcinoma; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; Tr1, type 1 Tregs; NK, natural killer; gp96, glucose-regulated protein 96; TRIM28, tripartite motif-containing protein 28; ILC1, group 1 innate lymphoid cell; HIF-1α, hypoxia-inducible factor 1-alpha; EMT, epithelial-mesenchymal transition; bFGF, basic fibroblast growth factor; CXCL9, C-X-C motif chemokine ligand 9; CXCL10, C-X-C motif chemokine ligand 10; PinX1, PIN2/TRF1-interacting telomerase inhibitor 1; miR-125a-3p, microRNA-125a-3p; BAF, SWItch/sucrose non-fermentable; LSD1, lysine-specific demethylase 1; G9a, euchromatic histone-lysine N-methyltransferase 2; CAR-T, chimeric antigen receptor T-cell.

Eomes: Restoring Eomes may support NK-cell cytotoxicity, whereas persistent Eomes in exhausted or regulatory lymphocyte populations may reinforce immune suppression. This evidence hierarchy, spanning direct RCC clinical/single-cell data, RCC-associated model evidence, and indirect or cross-model inferences, is summarized in Table I.

4. Role of Eomes in the immune microenvironment of RCC

Role of Eomes in infiltrating CD8+ T cells. The TME of RCC harbors a diverse array of dysfunctional immune cells. Among them, CD8+ T-cell exhaustion is central to immune evasion (36,37). Eomes has been shown to modulate the efficacy of antitumor immune responses through alterations in CD8+ T-cell differentiation and functional status (6,38). In addition, previous studies have shown that, in advanced or metastatic RCC, tumor-infiltrating CD8+ T cells exhibit heterogeneous Eomes expression patterns. In particular, the population of CD8+ T cells of the Eomes+ T-bet^{low} subtype has been observed to be increased, which represents the dysfunctional phenotype with diminished secretion of key cytokines (including IFN-γ and TNF-α) and decreased cytotoxicity (namely, reduced expression of PRF1 and GZMB) (14,36,39). In terms of the underlying mechanism, Eomes engages the promoter locus of TIGIT, thereby promoting its expression. TIGIT is a key immune checkpoint receptor that mediates its function via binding to CD155, thereby inhibiting T-cell activity; this forms an Eomes-TIGIT regulatory axis that may exacerbate T-cell exhaustion (33).

The balance between the nuclear and cytoplasmic localization of Eomes is critical for CD8+ T-cell function (28). In chronic viral infection models, exhausted CD8+ T cells have been shown to exhibit high nuclear Eomes/T-bet ratios, leading to the transcriptional activation of inhibitory receptors,

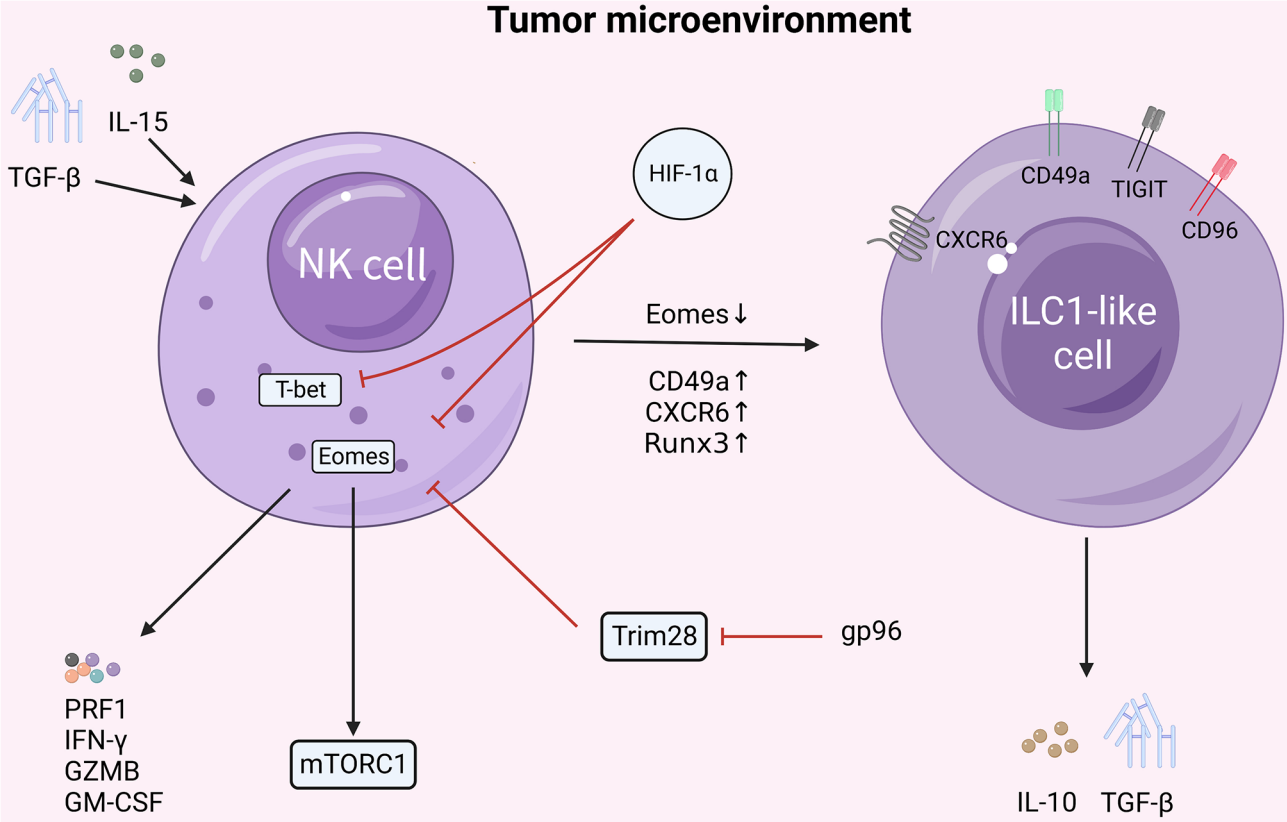

Figure 2. Proposed mechanism via which Eomes regulates NK cells and their antitumor functions in the hypoxic TME of RCC. NK cells with high expression exhibit cytotoxic activity, and secrete effector molecules, including PRF1, IFN-γ, GZMB and GM-CSF. gp96 may maintain Eomes stability by limiting TRIM28-mediated degradation. IL-15 and TGF-β can promote the transformation of NK cells into ILC1-like cells by activating transcription factors associated with ILC1 differentiation, such as RUNX3. Sustained HIF-1α activation may inhibit Eomes in NK-cell contexts, promoting ILC1-like markers such as CD49a and CXCR6, and reducing cytotoxic capacity. These mechanisms are shown as RCC-associated or immune-model-supported pathways, rather than as fully validated RCC-specific causal chains. Solid black arrows represent stimulatory/activating regulation, cellular phenotypic transition, and the secretion of effector molecules; and solid red lines represent inhibitory or degradative regulatory effects. Eomes, eomesodermin; RCC, renal carcinoma; NK, natural killer; TME, tumor microenvironment; PRF1, perforin; GZMB, granzyme B; GM-CSF, granulocyte-macrophage colony-stimulating factor; gp96, heat shock protein glycoprotein 96; TRIM28, tripartite motif-containing 28; ILC1, innate lymphoid cell 1; RUNX3, runt-related transcription factor 3; HIF-1α, hypoxia-inducible factor-1α; CXCR6, CXC motif chemokine receptor 6; TIGIT, T cell immunoglobulin and ITIM domain.

such as PD-1 (28,40). In patients with RCC, nuclear Eomes in tumor-infiltrating $CD8^+$ T cells may competitively bind to T-box elements in the promoter of the *PDCD1* gene (which encodes PD-1), thereby both weakening the transcriptional repression mediated by T-bet and sustaining high expression levels of PD-1 (14,28). Eomes has also been shown to downregulate the co-stimulatory molecule CD226, which further limits the activation and proliferation of $CD8^+$ T cells. Bhat *et al* (35) demonstrated that CD226 expression is reduced in $Eomes^+$ $CD8^+$ T cells, where the loss of CD226 was found to be associated with resistance to anti-PD-1 therapy. However, since several of the mechanistic details have been determined from cases of chronic infection or non-RCC immune models, these findings should be interpreted as supportive evidence, rather than as definitive proof of RCC-specific causality.

Role of Eomes in NK cell and ILC1 differentiation. NK cells perform a vital role in immune surveillance of RCC (41,42). Eomes is a critical transcription factor for NK cell maturation and functional maintenance. Its expression has been shown to be closely correlated with NK cell cytotoxicity and cytokine production (43) (Fig. 2). Although NK cells and ILC1 cells share a similar lineage and phenotypic markers, they differ significantly in terms of their function. High expression levels of Eomes support the maturation of NK cells with cytotoxicity and immune surveillance, whereas the loss or downregulation of Eomes induces a shift toward an 'ILC1-like' phenotype (43-45). Within the RCC TME, both activation of the TGF-β signaling pathway and other inhibitory signals may suppress Eomes expression, thereby contributing to NK cell dysfunction (12,46,47). Under physiological conditions, Eomes maintains NK cell cytotoxicity by transcriptionally activating effectors, such as PRF1, GZMB, IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF), and also by supporting activating receptors and chemokine receptors that are involved in tumor recognition and tissue homing (44,48-51). Hypoxia-inducible factor-1α (HIF-1α) in the hypoxic TME may inhibit Eomes expression in the NK-cell context, thereby promoting ILC1-like markers such as CD49a and C-X-C motif chemokine receptor 6 (CXCR6) (52-55). Therefore, selectively modulating the HIF-1α-Eomes axis in NK cells should be viewed as an experimental strategy, rather than as an established RCC therapy. In addition, decreased expression levels of gp96 in RCC have been documented to relieve its suppression of the ubiquitin ligase Trim28, thereby promoting Eomes ubiquitination and

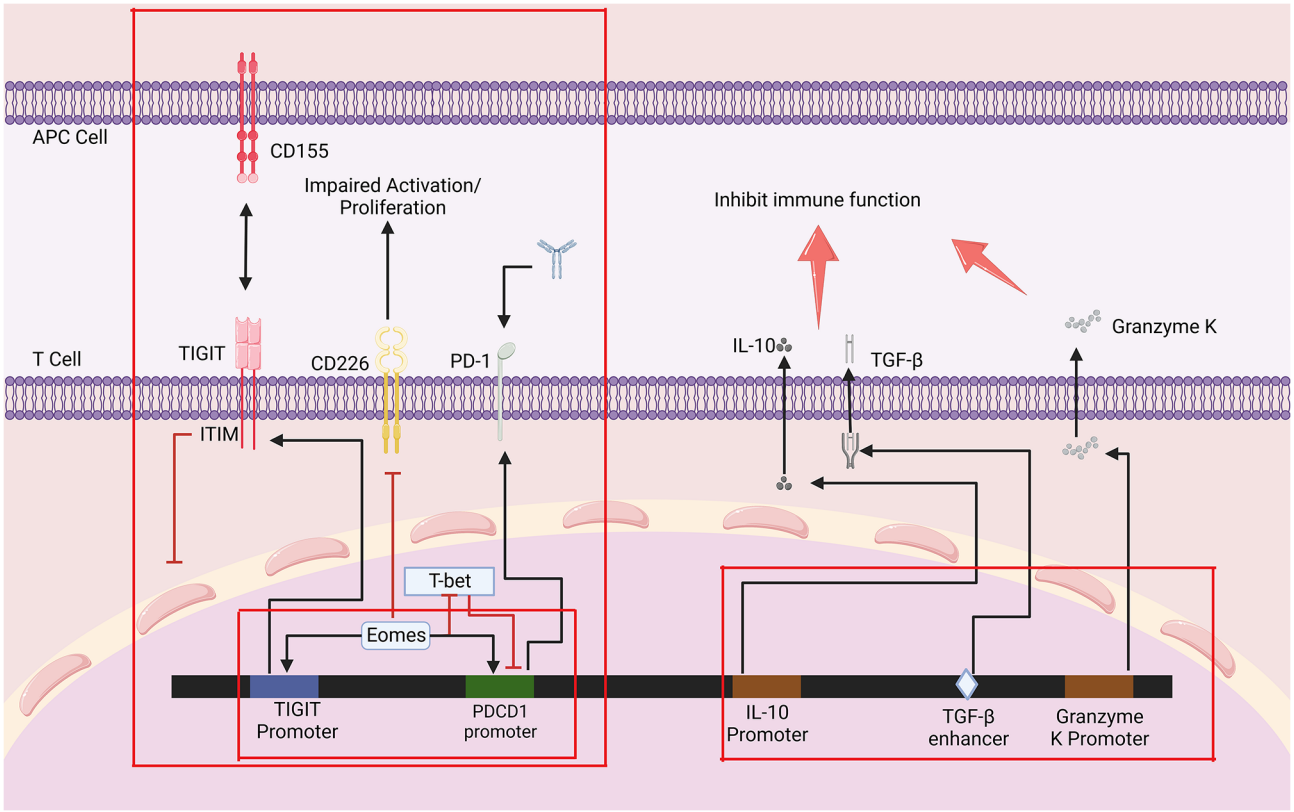

Figure 3. Eomes-associated transcriptional programs in exhausted or regulatory lymphocyte states. Eomes can regulate or correlate with immune checkpoints and regulatory molecules, including TIGIT, CD226, PD-1, IL-10, TGF-β and granzyme K, depending on cell state. By inhibiting T-bet, an inhibitor of PD-1 expression, Eomes may support TIGIT and PD-1 expression and reduce co-stimulatory signaling, whereas in Tr1-like cells it may contribute to IL-10/TGF-β-associated immunosuppression. Mechanistic links validated outside RCC are shown as indirect evidence, and these require RCC-specific confirmation. Solid black arrows represent stimulatory/activating regulation, cellular phenotypic transition, and the secretion of effector molecules; solid red lines represent inhibitory or degradative regulatory effects. Red arrows represent IL-10, TGF-β and granzyme K, which all play a role in inhibiting immune function. Red boxes demarcate two independent functional regulatory modules: The left box outlines the transcriptional regulatory module of immune checkpoint receptors on T cells, and the right box outlines the transcriptional regulatory module of immunosuppressive effector molecules. Eomes, eomesodermin; TIGIT, T cell immunoglobulin and ITIM domain; PD-1, programmed cell death protein 1; RCC, renal cell carcinoma.

degradation, as well as contributing to NK cell dysfunction (21). Dysregulated cytokines, such as TGF-β and IL-15, have been shown to activate ILC1 differentiation-associated transcription factors, including homolog of Blimp-1 in T cells (Hobit) and runt-related transcription factor 3 (Runx3), thereby reprogramming Eomes-deficient NK cells into an ILC1-like state (7,56,57). This remodeling is characterized by the downregulation of cytotoxic factors and an increased expression both of inhibitory receptors, such as TIGIT and CD96, and of immune-regulating factors, such as IL-10 and TGF-β (58,59).

Accumulating evidence suggests that Eomes^{low} or Eomes-ILC1-like cells can be enriched in the RCC TME, where their heightened presence has been associated with tumor progression and resistance to immunotherapy (15,60).

In conclusion, Eomes has been demonstrated to act as a core controller of NK cell function, although the therapeutic implications are cell-type-specific. Restoring or stabilizing Eomes may be useful for mature NK cells when its loss drives the conversion of NK cells into the ILC1-like state, and cytotoxic failure. This does not imply that a global activation of Eomes would be beneficial, however, since other Eomes-positive lymphocyte states may contribute to exhaustion or immunosuppression.

Eomes modulates regulatory T cells (Tregs) and the immunosuppressive microenvironment. Eomes reshapes the immune microenvironment of RCC. It can promote immune escape during tumor progression by modulating the recruitment, expansion and functional polarization of immunosuppressive populations (Fig. 3). These immunosuppressive cells include Tregs and Tr1-like cells (61,62). A single-cell transcriptomic study previously conducted by Bonnal *et al* (62) identified a subset of Eomes^{+} Tr1-like cells within the TME. These cells underwent clonal expansion, expressed high levels of IL-10 and granzyme K, and exhibited potent immunosuppressive functions. Unlike conventional Forkhead box (FOX)P3^{+} Tregs, however, Tr1-like cells primarily inhibited effector T-cell responses through cytokine secretion, instead of via direct cell-cell contact. In particular, their abundance was shown to be positively correlated with cancer progression (62). A study by Jian *et al* (63) revealed that tumor cells with high Eomes expression promoted the secretion of C-C motif chemokine ligand 20 (CCL20), also recruiting C-C chemokine receptor type 6 (CCR6)$^{+}$ Tregs into the TME, thereby enhancing immunosuppression. Collectively, these studies suggested that Eomes may function as a vital regulator in remodeling the immune microenvironment of RCC by enhancing the function of Tregs and other immunosuppressive cells.

The accumulation of Eomes$^+$ Tr1-like cells has also been associated with resistance to immunotherapy in RCC. An increase in their numbers was negatively correlated with progression-free survival in patients receiving anti-PD-1 therapy. This may be due to Eomes$^+$ Tr1-like cells producing high levels of IL-10 and TGF-β, which has the effect of inhibiting both the infiltration and activation of effector T cells (62,64). In particular, Eomes$^+$ Tr1-like cells do not produce the same specific effector cytokines as are produced by Th1 or Th2 cells, such as IFN-γ or IL-4 respectively (65-67). Furthermore, Eomes may sculpt the immune microenvironment through regulation of macrophage polarization. For example, in hepatocellular carcinoma, macrophage-derived itaconic acid was shown to upregulate the expression of Eomes via an epigenetic mechanism (namely, H3K4me3 modification) to promote CD8$^+$ T-cell exhaustion (68). Given the abundance of M2 macrophages in the RCC microenvironment, a similar mechanism is plausible, although the evidence remains indirect and requires RCC-specific validation.

5. Regulation of RCC progression by Eomes

Role of Eomes in cancer stemness. Cancer stem cells (CSCs) perform a key role in progression, distant metastasis and treatment resistance in RCC. CSCs are characterized by self-renewal and multipotent differentiation potential (69-71). In solid tumors, including RCC, the presence of CSCs is closely associated with poor clinical outcomes. Previous studies have suggested that the concurrent expression of stemness markers (such as Oct4 and Nanog) in RCC tissues is associated with poor patient prognosis (72,73). In the embryonic hematopoietic system, Eomes operates upstream of runt-related transcription factor 1 (Runx1) in the hemogenic endothelium lineage, serving to regulate lineage differentiation and the self-renewal of hematopoietic stem cells (74). On the basis of this developmental role, Eomes may regulate genetic networks that are involved in CSC-like properties in RCC; however, this tumor-cell-intrinsic mechanism requires further experimental validation in RCC models.

The long non-coding RNA (lncRNA) HOX transcript antisense RNA has been shown to promote RCC stemness and angiogenesis both through formation of a feedback loop with the androgen receptor, and by synergistically activating the transcription of glioma-associated oncogene family zinc finger 2 (GLI2) (75). Similar regulatory mechanisms governing RCC stemness may also be observed in the Wnt/β-catenin cascade. In RCC, δ-catenin has been documented to induce the transcription and expression of downstream target genes, including those encoding c-Myc, cyclin D1, membrane type 1 matrix metalloproteinase (MT1-MMP) and Bcl-2, by enhancing the nuclear translocation of β-catenin and driving signaling pathways that are associated with stemness maintenance (76). Eomes may act as a transcriptional co-activator of β-catenin, although the direct contribution of this proposed Eomes-β-catenin mechanism to RCC CSC biology has yet to be validated (76).

Role of Eomes on cell proliferation, apoptosis and metastasis of RCC. Although Eomes is conventionally recognized for immune regulation, abnormal expression in tumor cells may influence malignant biological behavior. Research on human protein expression patterns has suggested that Eomes exhibits high expression levels in renal cancer tissues (77). A regulatory link between aberrant PI3K/Akt/mTOR signaling and Eomes expression in RCC is plausible, but direct tumor-cell causality remains incompletely established. Phosphorylation of Akt by mechanistic target of rapamycin complex 1 (mTORC1) inhibits FOXO1, and suppressed FOXO1 activity upregulates T-bet and inhibits Eomes expression. By contrast, activated FOXO1 can promote Eomes transcription, suggesting a potential Akt/FOXO1/T-bet/Eomes feedback axis. In parallel, Wong *et al* (15) found that deletion of Eomes impaired IL-15 receptor signaling and downstream PI3K/Akt activation in immune cells. Collectively, these findings suggested that Eomes may influence RCC progression directly in tumor cells, or indirectly through antitumor immune cells, although these two contexts should not be conflated. In another tumor model, Eomes promoted G_2/M phase cell cycle progression by promoting CCL20 and CCR6 expression; its relevance to RCC proliferation remains hypothesis-generating (63) (Fig. 4).

In terms of apoptosis regulation, Eomes may affect cell survival through pathways involving Bax, caspase-3 and Bcl-2 (16,78,79). In a study by Wagner *et al* (16), inducible knockout of Eomes led to rapid NK cell loss, accompanied by increased caspase-3 expression and upregulation of the Bax pathway. These findings support a survival role for Eomes in NK cells. Whether a similar mechanism operates in RCC cells remains uncertain. Concomitantly, Junction adhesion molecule 3 (JAM3) has been demonstrated to facilitate RCC cell migration, whilst inhibiting apoptosis by upregulating N-cadherin and MMP2. Considering that Eomes is a T-box transcription factor, Eomes may contribute to JAM3-associated RCC migration by transcriptional regulation, although direct promoter binding requires validation (80). In addition, Eomes has been linked to EMT-associated transcriptional programs in other contexts. Therefore, its proposed role in regulating E-cadherin, N-cadherin, vimentin and Twist in RCC should be regarded as an experimental hypothesis (61,81).

6. Role of Eomes in stromal/endothelial regulation and RCC angiogenesis

Through indirect pathways, Eomes profoundly affects the function and phenotype of stromal cells, thereby reshaping the structure and function of the entire TME at the macro level. The clearest indirect regulation occurs in angiogenesis. Angiogenesis is a hallmark of RCC progression that is primarily driven by the dysregulated activation of the VEGF/VEGFR pathway (75). Eomes was found to both enhance IFN-γ production and bind to the *Ifng* promoter and *cis*-regulatory non-coding sequences in BW5147 cells (a murine T-cell lymphoma cell line), with the caveat that this cell line should not be interpreted as an RCC TME component (82). IFN-γ is a classical anti-angiogenic cytokine that blocks neovascularization by inducing CXC-motif ligand (CXCL)9/10, thereby inhibiting endothelial cell proliferation and downregulating VEGF and fibroblast growth factor (FGF) signalling (83,84) (Fig. 5). In RCC cell lines, exogenously added IFN-γ has been shown to reduce the mRNA transcript levels of VEGF and basic (b)FGF. Therefore, the most cautious interpretation

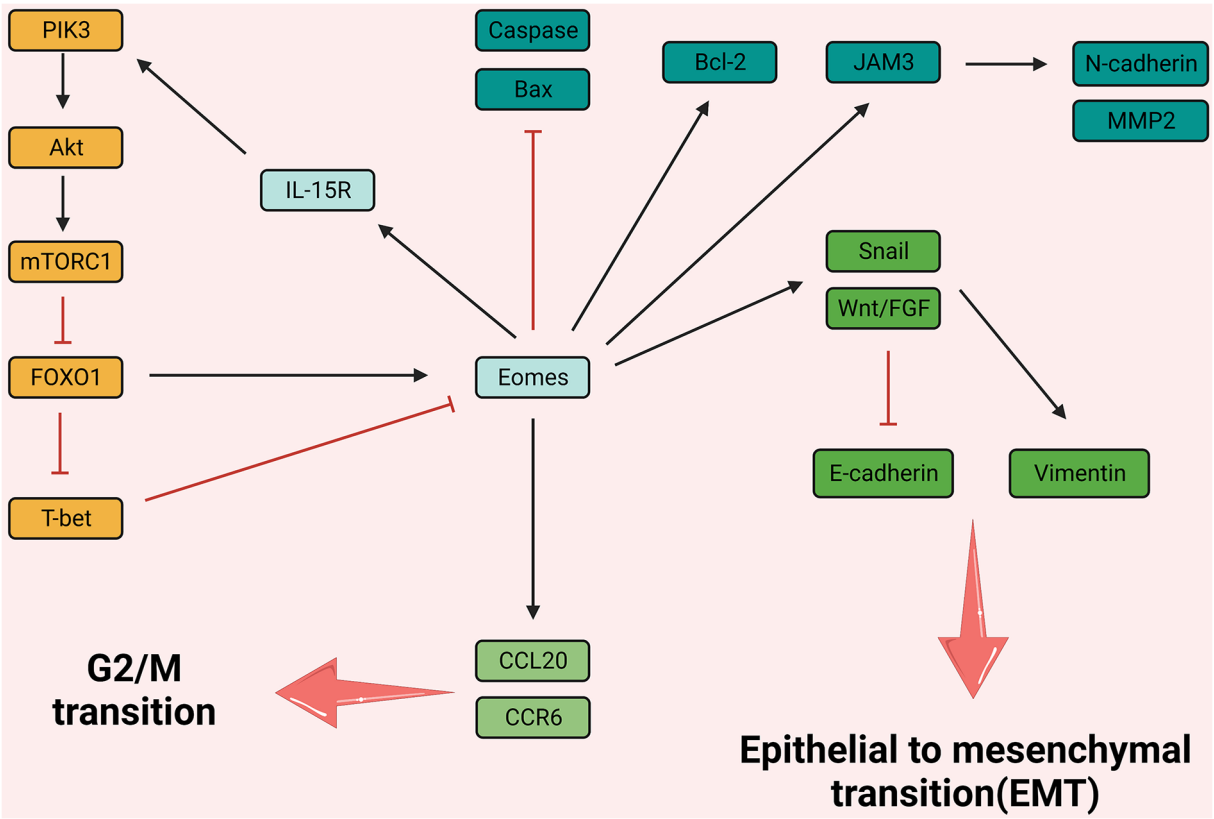

Figure 4. Proposed mechanisms linking Eomes with RCC proliferation, apoptosis and EMT. PI3K/Akt/mTOR, FOXO1, CCL20/CCR6, JAM3, Bax/caspase-3, Bcl-2 and Wnt/FGF-related EMT markers are shown as candidate pathways. Solid black arrows represent stimulatory/activating regulatory relationships. Solid red lines denote inhibitory or suppressive regulatory effects. Red arrows indicate the overall functional outcomes of the corresponding pathways. Eomes, eomesodermin; RCC, renal cell carcinoma; FOXO, Forkhead box; CCL20, C-C motif chemokine ligand 20; CCR6, C-C chemokine receptor type 6; JAM3, junctional adhesion molecule 3; FGF, fibroblast growth factor; EMT, epithelial-mesenchymal transition.

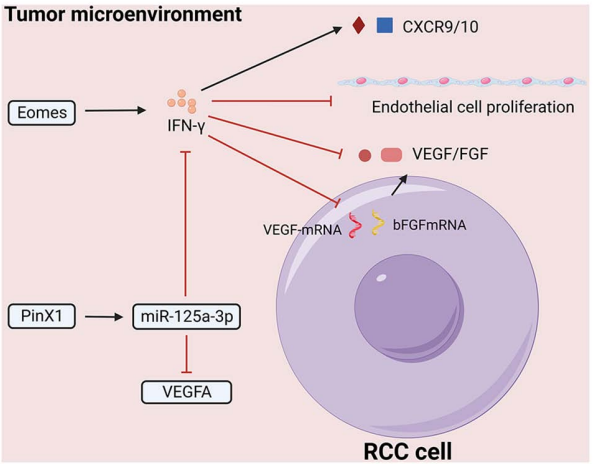

Figure 5. Proposed association between Eomes-associated immune signaling and RCC angiogenesis. RCC tumor cells and stromal/endothelial cells regulate angiogenesis through VEGF, bFGF and VEGFR signaling. IFN-γ may indirectly inhibit endothelial proliferation and angiogenic signaling by inducing CXCL9/CXCL10, and reducing VEGF/bFGF, expression. The PinX1/miR-125a3p/VEGF axis represents an RCC-associated angiogenesis pathway that may interact with immune cytokine signaling. Solid black arrows represent stimulatory/activating regulatory effects. Solid red lines denote inhibitory regulatory effects. The red triangle represents CXCR9, and the blue square represents CXCR10. The red circle represents VEGF, while the pink rectangle represents FGF. Eomes, eomesodermin; RCC, renal cell carcinoma; bFGF, basic fibroblast growth factor; CXCL, C-X-C motif chemokine ligand; PinX1, PIN2/TERF1-interacting telomerase inhibitor 1; miR, microRNA.

one may offer is that Eomes influences endothelial behavior indirectly through immune-cell-derived IFN-γ, rather than through a proven endothelial-cell-intrinsic Eomes pathway.

PIN2/TERF1-interacting telomerase inhibitor 1 (PinX1) is a tumor suppressor in RCC that is able to transcriptionally activate microRNA (miR or miRNA)-125a-3p in a specificity protein 1 (Sp1)-dependent manner. This miRNA binds directly to the 3'-untranslated region (3'-UTR) of VEGFA, thereby suppressing its translation (85,86). However, high miR-125a-3p expression in Tr1-like T cells was shown to negatively regulate IFN-γ, suggesting that a dynamic balance exists between the PinX1/miR-125a-3p/VEGF and the Eomes/IFN-γ signaling axes (87); in spite of this, this association should be regarded as a mechanistic model, rather than as a validated therapeutic basis for combined Eomes-directed and anti-VEGF treatment.

7. Regulation of Eomes-associated epigenetic regulation mechanisms and signaling pathways

Epigenetic regulation of Eomes expression. Eomes expression is tightly controlled by various epigenetic mechanisms. HDAC inhibitors, such as trichostatin A, have been reported to reduce Eomes expression and to suppress the production of PRF1 and GZMB in γ-δ T cells (35,88,89). This suggests that HDAC activity can affect Eomes-associated cytotoxic programs in immune cells. Additionally, nLSD1p has been shown to interact with Eomes, regulating its nuclear localization and

transcriptional activity and thereby influencing $CD8^+$ T-cell function (18). In patients with immune-resistant melanoma, nLSD1p was found to be overexpressed in PD-1^+CD8^+ T cells, and it co-localized with Eomes in the nucleus. Collectively, these findings have provided a useful immune-oncology model, although direct validation in RCC remains necessary (18,90).

DNA methylation is a key epigenetic regulatory mechanism. In RCC, the tumor suppressor gene serine protease inhibitor Kazal-type 5 (SPINK5) is silenced by H3K9me2 methylation at its promoter. Euchromatic histone-lysine N-methyltransferase 2 (EHMT2; also commonly known as G9a) is the main enzyme that catalyzes H3K9me2 methylation, and its high expression has been associated with RCC progression (91,92). If H3K9me2 modifications occur at the Eomes promoter, G9a may inhibit EOMES transcription by increasing chromatin compaction, although this specific axis has not yet been fully established in RCC. Additionally, Eomes expression is regulated by lncRNAs and miRNAs. In $CD4^+$ T cell-based competing endogenous RNA (ceRNA) networks, Eomes has been shown to be modulated by the small, non-coding miRNA has-miR-23b-3p, which is, in turn, modulated by the lncRNA AC104820.2. By contrast, in the $CD8^+$ T-cell ceRNA network, Eomes is regulated by the small, non-coding miRNA has-miR-23a-3p, which is itself regulated by the lncRNA AC000476.1. At the present time, these axes should be regarded as candidate regulatory mechanisms, pending RCC-specific functional verification (93,94).

Eomes and the PI3K/Akt/mTOR signaling pathway. Aberrant activation of the PI3K/Akt/mTOR signaling pathway is a hallmark of RCC, which causes enhanced tumor cell proliferation and survival, and metabolic reprogramming (95). In RCC, the Ras-related protein RAP2a has been shown to promote metastasis by upregulating phosphorylated Akt (96). A bidirectional regulatory association between Eomes and this signaling pathway is plausible; however, the direction may differ between immune cells and tumor cells. In immune cells, Eomes may be associated with IL-15 receptor signaling and Akt activation, whereas in tumor cells, Eomes may either be downstream of, or interact with, PI3K/Akt/mTOR-associated transcriptional programs. However, the direct binding of Eomes to PI3K/Akt target gene promoters in RCC has yet to be firmly established, and additional evidence is required.

In NK cells, a positive feedback loop involving IL-15, phosphoinositide-dependent kinase 1 (PDK1), mTOR, nuclear factor IL-3-regulated protein, Eomes and CD122 serves a vital role in primary stages of NK cell development. Within this loop, Eomes enhances the responsiveness of NK cells to IL-15 by upregulating CD122, thereby promoting its own expression in a self-reinforcing circuit (96,97). Furthermore, Zeng *et al* (98) suggested that in RCC, the lncRNA distal-less homeo box 6-antisense 1 (DLX6-AS1) sequesters miR-26a (functioning as a ceRNA) to upregulate the tumor suppressor gene PTEN, a negative regulator of the PI3K/Akt pathway, thereby limiting tumor progression; this study did not examine Eomes. Whether Eomes intersects with this DLX6-AS1/miR-26a/PTEN axis in RCC has not been directly investigated and remains an open question for future study. Given that Eomes is a key regulator of Akt activation, and PTEN is a critical negative modulator of the PI3K/Akt pathway, Eomes may indirectly regulate PTEN expression and downstream Akt activation by interacting with DLX6-AS1 or miR-26a; for example, by transcriptionally regulating DLX6-AS1 expression or modulating miR-26a maturation (98,99).

The regulation of mTORC1 signaling has also been known to intersect with metabolic reprogramming. In NK cells, inhibiting mTORC1 activity may suppress ubiquitin-mediated Eomes degradation, thereby enhancing the antitumor function of NK cells (100). In RCC, the Warburg effect has been demonstrated to activate mTORC1 signaling, and may alter Eomes-associated transcriptional programs; however, supporting evidence for a direct mTORC1-Eomes oncogenic axis in RCC remains scarce (101,102). Therefore, targeting the mTORC1-Eomes axis should currently be viewed as a preclinical hypothesis, rather than as a validated treatment strategy.

Eomes and the Wnt/β-catenin pathway. The pathogenesis and progression of RCC are also impacted by the Wnt/β-catenin signaling pathway (Fig. 6). As discussed above, RCC-specific evidence supports a role for δ-catenin- and β-catenin-associated signaling in cell proliferation and apoptosis resistance (76). However, direct Eomes-β-catenin co-activation is supported mainly by developmental models, and requires further validation in RCC. Therefore, the Eomes-Wnt/β-catenin signaling axis is best interpreted as a hypothesis-generating bridge between developmental transcriptional programs and RCC stemness, rather than as a proven RCC driver (29,76,103). Beyond a direct protein-protein interaction with β-catenin, Eomes also cooperates with chromatin remodelers to amplify Wnt-dependent transcription, and the BAF complex (a large ATP-dependent protein group that moves and changes nucleosomes to control gene activity) represents a critical epigenetic cofactor in this process. During embryonic development, Eomes interacts with the BAF chromatin remodeling complex, which serves to maintain chromatin accessibility in the trophoblast ectoderm (TE) and to regulate TE-specific gene expression (104). Given that Eomes often functions as a transcriptional activator, and the BAF complex facilitates chromatin accessibility for target gene binding, it is plausible that the Eomes-BAF complex may target and activate c-Myc expression in RCC cells, a process that would further enhance RCC cell proliferation, given that c-Myc is a well-established driver of RCC cell proliferation. However, this regulatory axis (Eomes-BAF→c-Myc) requires further validation via chromatin immunoprecipitation sequencing, co-immunoprecipitation analysis and functional assays in RCC models.

8. Potential of Eomes as an exploratory biomarker, and cell-type-specific therapeutic targets for RCC

Role of Eomes in the prognosis evaluation of RCC. Single-cell transcriptomic data from a previous study showed that $CD8^+$ T cells within RCC tissues express Eomes at high levels, and the clonal expansion of $Eomes^+$ Tr1-like cells is associated with RCC disease progression (61,62). These findings suggest that either the expression level of Eomes or the proportion of Eomes-positive immune-cell subsets could be explored as prognostic biomarkers. However, Eomes should not currently be considered as a standalone diagnostic marker without

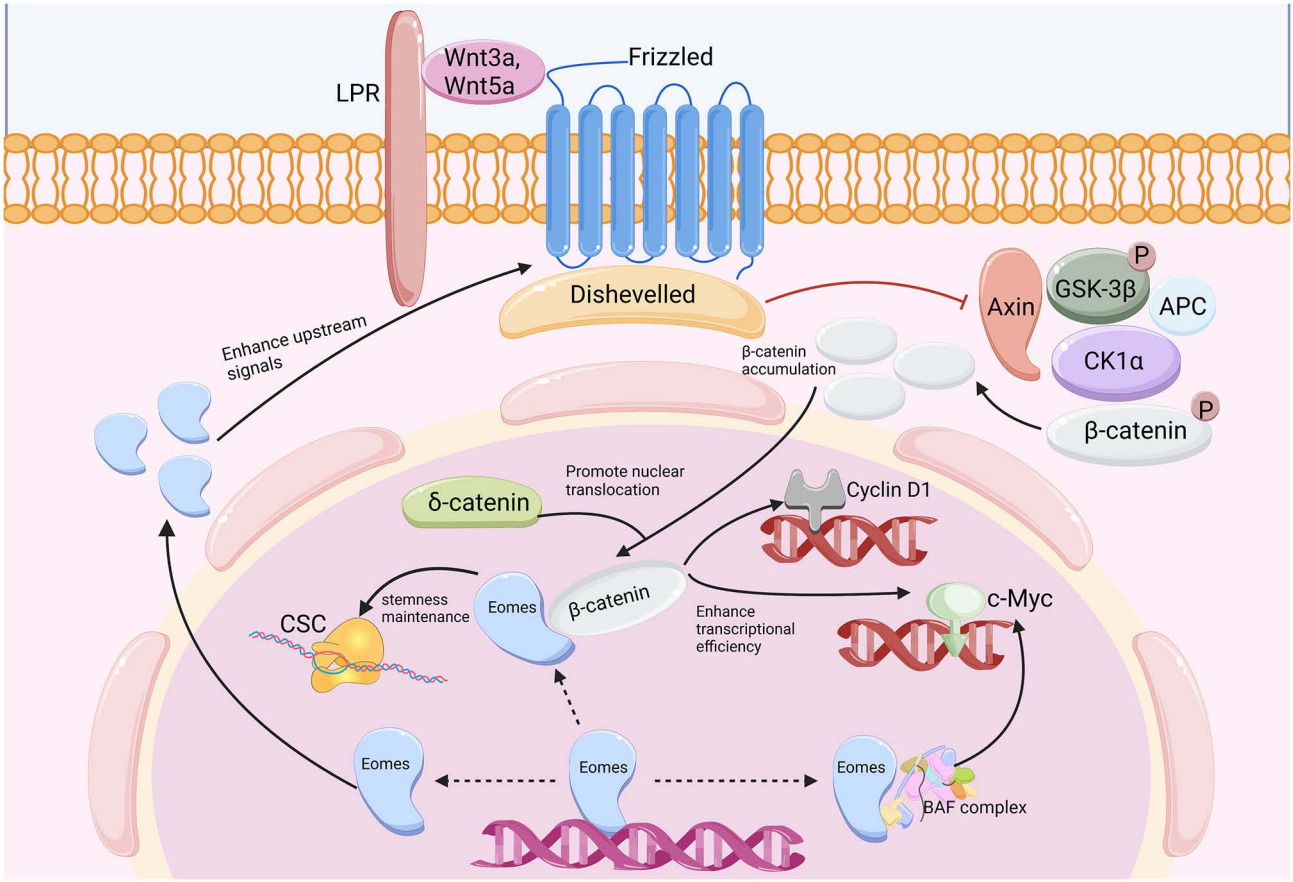

Figure 6. Eomes-Wnt/β-catenin signaling model. Wnt ligands (Wnt3a/Wnt5a) can bind to FZD receptors and promote β-catenin accumulation and nuclear translocation. In RCC, δ-catenin- and β-catenin-associated pathways have been associated with cell proliferation and apoptosis resistance. Eomes-β-catenin cooperation and BAF-dependent chromatin remodeling are mainly inferred from developmental models, although these require direct RCC validation. Solid black arrows represent stimulatory/activating regulatory relationships. Solid red lines denote inhibitory regulatory effects. Black dashed arrows indicate indirect, putative regulatory interactions and functional cooperativity that lack direct experimental validation in RCC. Eomes, eomesodermin; FZD, frizzled; RCC, renal cell carcinoma; CK1α, casein kinase 1; GSK-3β, glycogen synthase kinase 3β; CSCs, cancer stem cells; BAF, SWItch/sucrose non-fermentable.

independent validation in large RCC cohorts and in matched protein-level assays.

The expression levels of Eomes may vary among different RCC subtypes; however, the present evidence is insufficient to conclude that Eomes is able to reliably distinguish ccRCC from papillary RCC, or from other RCC subtypes. ccRCC is characterized by activation of the HIF pathway, whereas HIF-1α may suppress Eomes in the context of NK cells. This apparent tension can be reconciled by considering the cell types separately: In tumor-infiltrating NK cells, hypoxic HIF-1α signaling may suppress Eomes and promote NK dysfunction, whereas in intrinsic tumor cells, HIF-associated metabolic and epigenetic programs may be correlated with different Eomes expression patterns. Therefore, any subtype-differentiation claim requires direct analysis of TCGA, CPTAC, Human Protein Atlas and RCC single-cell datasets before any sort of clinical use can be proposed (12,54,55).

Application prospects of Eomes-targeted therapy in RCC

Eomes regulation and immunotherapy. ICIs represent a significant therapeutic approach for RCC, although their efficacy is influenced by immune-cell functional status in the TME. As a key regulator of immune cell function, Eomes may be explored as a target for improving ICI responses; however, any intervention would require cell-type-specific modulation experiments to be performed. Enhancing the activity of Eomes may be beneficial in mature NK cells or selected memory $CD8^+$ T-cell states, whereas reducing persistent Eomes activity may be considered in exhausted or Tr1-like immunosuppressive populations. HDAC inhibitors, PD-1 inhibitors and CD226-associated strategies should therefore be discussed as experimental combinations, rather than as established Eomes-directed RCC therapies (11,35).

Chimeric antigen receptor T-cell (CAR-T) therapy has shown promising results in hematological malignancies, although its efficacy in solid tumors is limited by T-cell exhaustion. Eomes expression has been shown to promote both the proliferation and survival of engineered T cells, and their IL-2 responsiveness, in certain contexts. However, Eomes-engineered CAR-T cells have not been validated as an RCC therapy, and the overexpression of Eomes may also carry exhaustion-associated risks, depending on the T-cell state. Therefore, Eomes modulation in CAR-T cells should be presented as a preclinical hypothesis that requires further RCC-specific testing (105,106).

Epigenetic regulation and Eomes-targeted drug development. As an alternative approach, targeting the epigenetic regulatory mechanisms of Eomes may provide experimental

strategies for RCC research. Through the disruption of the interaction between nLSD1p and Eomes, LSD1 inhibitors are capable of restoring the transcriptional activity of Eomes, and enhancing $CD8^+$ T-cell function in selected immune contexts (18,90). In RCC, G9a has been shown to suppress SPINK5 expression through H3K9me2 methylation, but whether G9a inhibitors modulate Eomes in RCC has yet to be fully determined. Similarly, non-coding RNA axes associated with Eomes should be regarded as candidate mechanisms only, until their direct role in RCC has been validated (93,94).

Eomes-targeted application of Eomes-associated signaling pathway inhibitors. The interaction between Eomes and the PI3K/Akt/mTOR and Wnt/β-catenin signaling pathways offers possible experimental combinations for RCC. mTOR inhibitors such as everolimus are clinically used in RCC, although their Eomes-dependent effects have yet to be established. At the present time, combining mTOR inhibitors, PD-1 inhibitors or β-catenin inhibitors with Eomes-directed modulation should be considered as a research hypothesis, not as a near-clinical strategy. At present, no Eomes-specific drug, validated predictive assay or completed RCC clinical trial supports routine Eomes-targeted treatment (100).

9. Conclusion

Although progress has been made in studying the role of Eomes in RCC, its clinical translation faces significant challenges. The dual role of Eomes in immune and tumor cells may result in off-target effects during targeted therapies. Upregulation of Eomes enhances effector T-cell function, but may concurrently promote tumor progression. Therefore, developing cell-type-specific Eomes modulation strategies (using immune cell-specific promoters to drive Eomes expression) is crucial (12,63). The functional overlap and compensatory mechanisms between Eomes and other transcription factors (such as T-bet) may compromise the efficacy of targeted therapies. Previous studies have shown that T-bet and Eomes can compete for binding to the *PDCD1* promoter in $CD8^+$ T cells; therefore, regulating the ratio of the two may be more effective, instead of targeting them individually (2,14,28).

Eomes may have exploratory clinical value; however, the assessment of its use as a biomarker or therapeutic target remains preliminary. A biomarker model incorporating Eomes should be validated with other markers, such as Oct4, Nanog and CD226, and should distinguish Eomes-positive cell types, rather than measuring bulk expression alone. Future research directions should prioritize the following: i) Characterizing the heterogeneity and functional subsets of $Eomes^+$ cells within the RCC microenvironment using single-cell sequencing technologies; ii) testing cell-type-specific Eomes modulation in RCC models before considering clinical trials; iii) exploring the combinatorial detection of Eomes with other biomarkers (such as Oct4, Nanog and CD226) to optimize the RCC prognosis assessment model; and iv) defining how Eomes interacts with T-bet, HIF signaling, and the PI3K/Akt/mTOR and Wnt/β-catenin signaling pathways in each cellular compartment.

Acknowledgements

Not applicable.

Funding

This study was supported by the National Natural Science Foundation of China (grant no. 82560531), the Academic Enhancement Support Program of Hainan Medical University (grant no. XSTS2025005), the College Students' Innovation and Entrepreneurship Training Program of the Education Department of Hainan province (grant no. S202511810006), the College Students' Research Innovation Training Program of Hainan Medical University (grant no. RZ2500002143), the Hainan Provincial Joint Project for Health Science and Technology Innovation (grant no.WSJK2026QNO82), the Natural Science Foundation of Shanxi Province (grant no. 202103021224375), the Fund Program for the Scientific Activities of Selected Returned Overseas Professionals in Shanxi Province (grant no. 2022047) and the Research Project Supported by Shanxi Scholarship Council of China (grant no. 2022-2024).

Availability of data and materials

Not applicable.

Authors' contributions

ZC and XW designed the scope and overall structure of this review. DH, JL and RF performed the structured literature searches, and critically synthesized and interpreted the included research findings. ZC, DH and JL contributed to the visual presentation of the synthesized evidence. DH and JL drafted the major sections of the manuscript, while ZC, YW and XC were responsible for critical revision and editing of the full manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bukavina L, Bensalah K, Bray F, Carlo M, Challacombe B, Karam JA, Kassouf W, Mitchell T, Montironi R, O'Brien T, *et al*: Epidemiology of renal cell carcinoma: 2022 update. Eur Urol 82: 529-542, 2022.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
3. Badoiu SC, Greabu M, Miricescu D, Stanescu-Spinu II, Ilinca R, Balan DG, Balcangiu-Stroescu AE, Mihai DA, Vacaroiu IA, Stefani C, *et al*: PI3K/AKT/mTOR dysregulation and reprogramming metabolic pathways in renal cancer: Crosstalk with the VHL/HIF axis. Int J Mol Sci 24: 8391, 2023.

4. Braun DA, Bakouny Z, Hirsch L, Flippot R, Allen EMV, Wu CJ and Choueiri TK: Beyond conventional immune-checkpoint inhibition-novel immunotherapies for renal cell carcinoma. Nat Rev Clin Oncol 18: 199-214, 2021.
5. Talbot CD, Walsh MD, Cutty SJ, Elsayed R, Vlachaki E, Bruce AEE, Wardle FC and Nelson AC: Eomes function is conserved between zebrafish and mouse and controls left-right organiser progenitor gene expression via interlocking feedforward loops. Front Cell Dev Biol 10: 982477, 2022.
6. Lin YH, Duong HG, Limary AE, Kim ES, Hsu P, Patel SA, Wong WH, Indralingam CS, Liu YC, Yao P, *et al*: Small intestine and colon tissue-resident memory CD8+ T cells exhibit molecular heterogeneity and differential dependence on Eomes. Immunity 56: 207-223.e8, 2023.
7. Liang Z, Anderson HD, Locher V, O'Leary C, Riesenfeld SJ, Jabri B, McDonald BD and Bendelac A: Eomes expression identifies the early bone marrow precursor to classical NK cells. Nat Immunol 25: 1172-1182, 2024.
8. Zhang J, Marotel M, Fauteux-Daniel S, Mathieu AL, Viel S, Marçais A and Walzer T: T-bet and Eomes govern differentiation and function of mouse and human NK cells and ILC1. Eur J Immunol 48: 738-750, 2018.
9. Pearce EL, Mullen AC, Martins GA, Krawczyk CM, Hutchins AS, Zediak VP, Banica M, DiCioccio CB, Gross DA, Mao CA, *et al*: Control of effector CD8+ T cell function by the transcription factor Eomesodermin. Science 302: 1041-1043, 2003.
10. He J, Chen D, Xiong W, Hou X, Quan Y, Yang M and Dong Z: Eomesodermin spatiotemporally orchestrates the early and late stages of NK cell development by targeting KLF2 and T-bet, respectively. Cell Mol Immunol 21: 662-673, 2024.
11. Weulersse M, Asrir A, Pichler AC, Lemaitre L, Braun M, Carrié N, Joubert MV, Le Moine M, Do Souto L, Gaud G, *et al*: Eomes-Dependent loss of the Co-activating Receptor CD226 Restrains CD8+ T Cell Anti-tumor functions and limits the efficacy of cancer immunotherapy. Immunity 53: 824-839.e10, 2020.
12. Gao Y, Souza-Fonseca-Guimaraes F, Bald T, Ng SS, Young A, Ngiow SF, Rautela J, Straube J, Waddell N, Blake SJ, *et al*: Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells. Nat Immunol 18: 1004-1015, 2017.
13. Long SA, Thorpe J, DeBerg HA, Gersuk V, Eddy J, Harris KM, Ehlers M, Herold KC, Nepom GT and Linsley PS: Partial exhaustion of CD8 T cells and clinical response to teplizumab in new-onset type 1 diabetes. Sci Immunol 1: eaai7793, 2016.
14. Li J, He Y, Hao J, Ni L and Dong C: High levels of eomes promote exhaustion of Anti-tumor CD8+ T cells. Front Immunol 9: 2981, 2018.
15. Wong P, Foltz JA, Chang L, Neal CC, Yao T, Cubitt CC, Tran J, Kersting-Schadek S, Palakurty S, Jaeger N, *et al*: T-BET and EOMES sustain mature human NK cell identity and antitumor function. J Clin Invest 133: e162530, 2023.
16. Wagner JA, Wong P, Schappe T, Berrien-Elliott MM, Cubitt C, Jaeger N, Lee M, Keppel CR, Marin ND, Foltz JA, *et al*: Stage-specific requirement for eomes in mature NK cell homeostasis and cytotoxicity. Cell Rep 31: 107720, 2020.
17. Arnold SJ, Hofmann UK, Bikoff EK and Robertson EJ: Pivotal roles for eomesodermin during axis formation, epithelium-to-mesenchyme transition and endoderm specification in the mouse. Development 135: 501-511, 2008.
18. Tu WJ, McCuaig RD, Tan AHY, Hardy K, Seddiki N, Ali S, Dahlstrom JE, Bean EG, Dunn J, Forwood J, *et al*: Targeting nuclear LSD1 to reprogram cancer cells and reinvigorate exhausted T cells via a novel LSD1-EOMES switch. Front Immunol 11: 1228, 2020.
19. Matinzadeh M, Ebrahimi E, Saffari M and Shirkoohi R: Type I EMT Inducer Eomesodermin has a significant expression in breast cancer. Basic Clin Cancer Res 8: 17-22, 2016.
20. Wang R, Kang Y, Löhr CV, Fischer KA, Bradford CS, Johnson G, Dashwood WM, Williams DE, Ho E and Dashwood RH: Reciprocal regulation of BMF and BIRC5 (Survivin) linked to Eomes overexpression in colorectal cancer. Cancer Lett 381: 341-348, 2016.
21. Xu Y, Li X, Cheng F, Zhao B, Fang M, Li Z and Meng S: Heat shock protein gp96 drives natural killer cell maturation and anti-tumor immunity by counteracting Trim28 to stabilize Eomes. Nat Commun 15: 1106, 2024.
22. Lyu Y, Jia W, Wu Y, Zhao X, Xia Y, Guo X and Kang J: Cpmer: A new conserved eEF1A2-binding partner that regulates Eomes translation and cardiomyocyte differentiation. Stem Cell Reports 17: 1154-1169, 2022.
23. Araki Y, Fann M, Wersto R and Weng NP: Histone acetylation facilitates rapid and robust memory CD8 T cell response through differential expression of effector molecules (eomesodermin and its targets: Perforin and granzyme B). J Immunol 180: 8102-8108, 2008.
24. Russ AP, Wattler S, Colledge WH, Aparicio SA, Carlton MB, Pearce JJ, Barton SC, Surani MA, Ryan K, Nehls MC, *et al*: Eomesodermin is required for mouse trophoblast development and mesoderm formation. Nature 404: 95-99, 2000.
25. Shimojo H, Masaki T and Kageyama R: The Neurog2-Tbr2 axis forms a continuous transition to the neurogenic gene expression state in neural stem cells. Dev Cell 59: 1913-1923.e6, 2024.
26. Müller CW and Herrmann BG: Crystallographic structure of the T domain-DNA complex of the Brachyury transcription factor. Nature 389: 884-888, 1997.
27. Naiche LA, Harrelson Z, Kelly RG and Papaioannou VE: T-box genes in vertebrate development. Annu Rev Genet 39: 219-239, 2005.
28. McLane LM, Ngiow SF, Chen Z, Attanasio J, Manne S, Ruthel G, Wu JE, Staupe RP, Xu W, Amaravadi RK, *et al*: Role of nuclear localization in the regulation and function of T-bet and Eomes in exhausted CD8 T cells. Cell Rep 35: 109120, 2021.
29. Belinson H, Nakatani J, Babineau BA, Birnbaum RY, Ellegood J, Bershteyn M, McEvilly RJ, Long JM, Willert K, Klein OD, *et al*: Prenatal β-catenin/Brn2/Tbr2 transcriptional cascade regulates adult social and stereotypic behaviors. Mol Psychiatry 21: 1417-1433, 2016.
30. Barbarin A, Cayssials E, Jacomet F, Nunez NG, Basbous S, Lefèvre L, Abdallah M, Piccirilli N, Morin B, Lavoue V, *et al*: Phenotype of NK-Like CD8(+) T cells with innate features in humans and their relevance in cancer diseases. Front Immunol 8: 316, 2017.
31. Verma R, Er JZ, Pu RW, Sheik Mohamed J, Soo RA, Muthiah HM, Tam JKC and Ding JL: Eomes expression defines group 1 innate lymphoid cells during metastasis in human and mouse. Front Immunol 11: 1190, 2020.
32. Furusawa A, Reiser J, Sadashivaiah K, Simpson H and Banerjee A: Eomesodermin Increases Survival and IL-2 Responsiveness of Tumor-specific CD8+ T cells in an adoptive transfer model of cancer immunotherapy. J Immunother 41: 53-63, 2018.
33. Jia B, Zhao C, Rakszawski KL, Claxton DF, Ehmann WC, Rybka WB, Mineishi S, Wang M, Shike H, Bayerl MG, *et al*: Eomes+T-betlow CD8+ T cells are functionally impaired and are associated with poor clinical outcome in patients with acute myeloid leukemia. Cancer Res 79: 1635-1645, 2019.
34. He H, Yi Y, Cai X, Wang J, Ni X, Fu Y and Qiu S: Down-regulation of EOMES drives T-cell exhaustion via abolishing EOMES-mediated repression of inhibitory receptors of T cells in liver cancer. J Cell Mol Med 25: 161-169, 2021.
35. Bhat SA, Vedpathak DM and Chiplunkar SV: Checkpoint blockade rescues the repressive effect of histone deacetylases inhibitors on γδ T cell function. Front Immunol 9: 1615, 2018.
36. Braun DA, Street K, Burke KP, Cookmeyer DL, Denize T, Pedersen CB, Gohil SH, Schindler N, Pomerance L, Hirsch L, *et al*: Progressive immune dysfunction with advancing disease stage in renal cell carcinoma. Cancer Cell 39: 632-648.e8, 2021.
37. Pichler R, Siska PJ, Tymoszuk P, Martowicz A, Untergasser G, Mayr R, Weber F, Seeber A, Kocher F, Barth DA, *et al*: A chemokine network of T cell exhaustion and metabolic reprogramming in renal cell carcinoma. Front Immunol 14: 1095195, 2023.
38. Ruan X, Wu L, Tang Z, Li Y, Wang J, Jiang H, Zhang L, Wang S, Chen Z, Yuan C, *et al*: Two chemotherapeutic agents expand stem-like CD62L+CD8+ T cells in antitumor immune responses. Front Immunol 16: 1533857, 2025.
39. Chevrier S, Levine JH, Zanotelli VRT, Silina K, Schulz D, Bacac M, Ries CH, Ailles L, Jewett MAS, Moch H, *et al*: An immune atlas of clear cell renal cell carcinoma. Cell 169: 736-749.e18, 2017.
40. Kao C, Oestreich KJ, Paley MA, Crawford A, Angelosanto JM, Ali MA, Intlekofer AM, Boss JM, Reiner SL, Weinmann AS and Wherry EJ: Transcription factor T-bet represses expression of the inhibitory receptor PD-1 and sustains virus-specific CD8+ T cell responses during chronic infection. Nat Immunol 12: 663-671, 2011.
41. Terrén I, Orrantia A, Mikelez-Alonso I, Vitallé J, Zenarruzabeitia O and Borrego F: NK Cell-Based immunotherapy in renal cell carcinoma. Cancers (Basel) 12: 316, 2020.

42. Ziblat A, Iraolagoitia XLR, Nuñez SY, Torres NI, Secchiari F, Sierra JM, Spallanzani RG, Rovegno A, Secin FP, Fuertes MB, *et al*: Circulating and Tumor-Infiltrating NK cells from clear cell renal cell carcinoma patients exhibit a predominantly inhibitory phenotype characterized by overexpression of CD85j, CD45, CD48 and PD-1. Front Immunol 12: 681615, 2021.
43. Zhang J, Le Gras S, Pouxvielh K, Faure F, Fallone L, Kern N, Moreews M, Mathieu AL, Schneider R, Marliac Q, *et al*: Sequential actions of EOMES and T-BET promote stepwise maturation of natural killer cells. Nat Commun 12: 5446, 2021.
44. Kiekens L, Van Loocke W, Taveirne S, Wahlen S, Persyn E, Van Ammel E, Van Ammel E, De Vos Z, Matthys P, Van Nieuwerburgh F, *et al*: T-BET and EOMES accelerate and enhance functional differentiation of human natural killer cells. Front Immunol 12: 732511, 2021.
45. Daussy C, Faure F, Mayol K, Viel S, Gasteiger G, Charrier E, Bienvenu J, Henry T, Debien E, Hasan UA, *et al*: T-bet and Eomes instruct the development of two distinct natural killer cell lineages in the liver and in the bone marrow. J Exp Med 211: 563-577, 2014.
46. Kajdaniuk D, Hudy D, Strzelczyk JK, Młynarek K, Słomian S, Potyka A, Szymonik E, Strzelczyk J, Foltyn W, Kos-Kudła B and Marek B: Transforming growth factors β and their signaling pathway in renal cell carcinoma and peritumoral space-transcriptome analysis. Clin Transl Oncol 26: 1229-1239, 2024.
47. Regis S, Dondero A, Caliendo F, Bottino C and Castriconi R: NK cell function regulation by TGF-β-Induced epigenetic mechanisms. Front Immunol 11: 311, 2020.
48. Ma S, Yan J, Barr T, Zhang J, Chen Z, Wang LS, Sun JC, Chen J, Caligiuri MA and Yu J: The RNA m6A reader YTHDF2 controls NK cell antitumor and antiviral immunity. J Exp Med 218: e20210279, 2021.
49. Thelen B, Schipperges V, Knörlein P, Hummel JF, Arnold F, Kupferschmid L, Klose CSN, Arnold SJ, Boerries M and Tanriver Y: Eomes is sufficient to regulate IL-10 expression and cytotoxic effector molecules in murine CD4+ T cells. Front Immunol 14: 1058267, 2023.
50. Gordon SM, Chaix J, Rupp LJ, Wu J, Madera S, Sun JC, Lindsten T and Reiner SL: The transcription factors T-bet and Eomes control key checkpoints of natural killer cell maturation. Immunity 36: 55-67, 2012.
51. Russo E, D'Aquino C, Di Censo C, Laffranchi M, Tomaipitinca L, Licursi V, Garofalo S, Promeuschel J, Peruzzi G, Sozio F, *et al*: Cxcr3 promotes protection from colorectal cancer liver metastasis by driving NK cell infiltration and plasticity. J Clin Invest 135: e184036, 2025.
52. Liikanen I, Lauhan C, Quon S, Omilusik K, Phan AT, Bartrolí LB, Ferry A, Goulding J, Chen J, Scott-Browne JP, *et al*: Hypoxia-inducible factor activity promotes antitumor effector function and tissue residency by CD8+ T cells. J Clin Invest 131: e143729, 2021.
53. Doedens AL, Phan AT, Stradner MH, Fujimoto JK, Nguyen JV, Yang E, Johnson RS and Goldrath AW: Hypoxia-inducible factors enhance the effector responses of CD8(+) T cells to persistent antigen. Nat Immunol 14: 1173-1182, 2013.
54. Sobecki M, Krzywinska E, Nagarajan S, Audigé A, Huỳnh K, Zacharjasz J, Debbache J, Kerdiles Y, Gotthardt D, Takeda N, *et al*: NK cells in hypoxic skin mediate a trade-off between wound healing and antibacterial defence. Nat Commun 12: 4700, 2021.
55. Ni J, Wang X, Stojanovic A, Zhang Q, Wincher M, Bühler L, Arnold A, Correia MP, Winkler M, Koch PS, *et al*: Single-Cell RNA Sequencing of Tumor-Infiltrating NK cells reveals that inhibition of transcription factor HIF-1α unleashes NK cell activity. Immunity 52: 1075-1087.e8, 2020.
56. Yomogida K, Bigley TM, Trsan T, Gilfillan S, Cella M, Yokoyama WM, Egawa T and Colonna M: Hobit confers tissue-dependent programs to type 1 innate lymphoid cells. Proc Natl Acad Sci USA 118: e2117965118, 2021.
57. Levanon D, Negreanu V, Lotem J, Bone KR, Brenner O, Leshkowitz D and Groner Y: Transcription factor Runx3 regulates interleukin-15-dependent natural killer cell activation. Mol Cell Biol 34: 1158-1169, 2014.
58. Sun H, Huang Q, Huang M, Wen H, Lin R, Zheng M, Qu K, Li K, Wei H, Xiao W, *et al*: Human CD96 correlates to natural killer cell exhaustion and predicts the prognosis of human hepatocellular carcinoma. Hepatology 70: 168-183, 2019.
59. Chen Y, Zhang W, Cheng M, Hao X, Wei H, Sun R and Tian Z: Galectin-3-ITGB1 signaling mediates interleukin 10 production of hepatic conventional natural killer cells in hepatitis B virus transgenic mice and correlates with hepatocellular carcinoma progression in patients. Viruses 16: 737, 2024.
60. Park E, Patel S, Wang Q, Andhey P, Zaitsev K, Porter S, Hershey M, Bern M, Plougastel-Douglas B, Collins P, *et al*: Toxoplasma gondii infection drives conversion of NK cells into ILC1-like cells. Elife 8: e47605, 2019.
61. Dielmann A, Letsch A, Nonnenmacher A, Miller K, Keilholz U and Busse A: Favorable prognostic influence of T-box transcription factor Eomesodermin in metastatic renal cell cancer patients. Cancer Immunol Immunother 65: 181-192, 2016.
62. Bonnal RJP, Rossetti G, Lugli E, De Simone M, Gruarin P, Brummelman J, Drufuca L, Passaro M, Bason R, Gervasoni F, *et al*: Clonally expanded EOMES+ Tr1-like cells in primary and metastatic tumors are associated with disease progression. Nat Immunol 22: 735-745, 2021.
63. Lian J, Liu S, Yue Y, Yang Q, Zhang Z, Yang S and Zhang Y: Eomes promotes esophageal carcinoma progression by recruiting Treg cells through the CCL20-CCR6 pathway. Cancer Sci 112: 144-154, 2021.
64. Roncarolo MG, Gregori S, Bacchetta R, Battaglia M and Gagliani N: The biology of T regulatory type 1 cells and their therapeutic application in Immune-mediated diseases. Immunity 49: 1004-1019, 2018.
65. Groux H, O'Garra A, Bigler M, Rouleau M, Antonenko S, de Vries JE and Roncarolo MG: A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature 389: 737-742, 1997.
66. Geginat J, Vasco C, Gruarin P, Bonnal R, Rossetti G, Silvestri Y, Carelli E, Pulvirenti N, Scantamburlo M, Moschetti G, *et al*: Eomesodermin-expressing type 1 regulatory (EOMES+ Tr1)-like T cells: Basic biology and role in immune-mediated diseases. Eur J Immunol 53: e2149775, 2023.
67. Bi K, He MX, Bakouny Z, Kanodia A, Napolitano S, Wu J, Grimaldi G, Braun DA, Cuoco MS, Mayorga A, *et al*: Tumor and immune reprogramming during immunotherapy in advanced renal cell carcinoma. Cancer Cell 39: 649-661.e5, 2021.
68. Gu X, Wei H, Suo C, Shen S, Zhu C, Chen L, Yan K, Li Z, Bian Z, Zhang P, *et al*: Itaconate promotes hepatocellular carcinoma progression by epigenetic induction of CD8+ T-cell exhaustion. Nat Commun 14: 8154, 2023.
69. Chu X, Tian W, Ning J, Xiao G, Zhou Y, Wang Z, Zhai Z, Tanzhu G, Yang J and Zhou R: Cancer stem cells: Advances in knowledge and implications for cancer therapy. Signal Transduct Target Ther 9: 170, 2024.
70. Murphy N, Shah P, Shih A, Khalili H, Liew A, Zhu X and Lee A: Single-cell sequencing in genitourinary malignancies. Adv Exp Med Biol 1255: 153-164, 2020.
71. Lasorsa F, Rutigliano M, Milella M, Ferro M, Pandolfo SD, Crocetto F, Autorino R, Battaglia M, Ditonno P and Lucarelli G: Cancer stem cells in renal cell carcinoma: Origins and biomarkers. Int J Mol Sci 24: 13179, 2023.
72. Rasti A, Mehrazma M, Madjd Z, Abolhasani M, Saeednejad Zanjani L and Asgari M: Co-expression of cancer stem cell markers OCT4 and NANOG predicts poor prognosis in renal cell carcinomas. Sci Rep 8: 11739, 2018.
73. Zhang Z and Zhang Y: Transcriptional regulation of cancer stem cell: Regulatory factors elucidation and cancer treatment strategies. J Exp Clin Cancer Res 43: 99, 2024.
74. Harland LTG, Simon CS, Senft AD, Costello I, Greder L, Imaz-Rosshandler I, Göttgens B, Marioni JC, Bikoff EK, Porcher C, *et al*: The T-box transcription factor Eomesodermin governs haemogenic competence of yolk sac mesodermal progenitors. Nat Cell Biol 23: 61-74, 2021.
75. Bai JY, Jin B, Ma JB, Liu TJ, Yang C, Chong Y, Wang X, He D and Guo P: HOTAIR and androgen receptor synergistically increase GLI2 transcription to promote tumor angiogenesis and cancer stemness in renal cell carcinoma. Cancer Lett 498: 70-79, 2021.
76. Ju L, Shan L, Yin B and Song Y: δ-Catenin regulates proliferation and apoptosis in renal cell carcinoma via promoting β-catenin nuclear localization and activating its downstream target genes. Cancer Med 9: 2201-2212, 2020.
77. Miricescu D, Balan DG, Tulin A, Stiru O, Vacaroiu IA, Mihai DA, Popa CC, Papacocea RI, Enyedi M, Sorin NA, *et al*: PI3K/AKT/mTOR signalling pathway involvement in renal cell carcinoma pathogenesis (Review). Exp Ther Med 21: 540, 2021.
78. Chaudhry MZ, Chen E, Man HO, Jones A, Denman R, Yu H, Huang Q, Ilich A, Schreuder J, Navarro S, *et al*: GFI1-driven transcriptional and epigenetic programs maintain CD8+ T cell stemness and persistence. Nat Immunol 26: 894-907, 2025.
79. Gobé G, Rubin M, Williams G, Sawczuk I and Buttyan R: Apoptosis and expression of Bcl-2, Bcl-XL, and Bax in renal cell carcinomas. Cancer Invest 20: 324-332, 2002.

80. Li X, Yin A, Zhang W, Zhao F, Lv J, Lv J and Sun J: Jam3 promotes migration and suppresses apoptosis of renal carcinoma cell lines. Int J Mol Med 42: 2923-2929, 2018.
81. Marconi GD, Fonticoli L, Rajan TS, Pierdomenico SD, Trubiani O, Pizzicannella J and Diomede F: Epithelial-mesenchymal transition (EMT): The Type-2 EMT in wound healing, tissue regeneration and organ fibrosis. Cells 10: 1587, 2021.
82. Fukuoka N, Harada M, Nishida A, Ito Y, Shiota H and Kataoka T: Eomesodermin promotes interferon-γ expression and binds to multiple conserved noncoding sequences across the Ifng locus in mouse thymoma cell lines. Genes Cells 21: 146-162, 2016.
83. Tokunaga R, Zhang W, Naseem M, Puccini A, Berger MD, Soni S, McSkane M, Baba H and Lenz HJ: CXCL9, CXCL10, CXCL11/CXCR3 axis for immune activation-A target for novel cancer therapy. Cancer Treat Rev 63: 40-47, 2018.
84. Sasamura H, Takahashi A, Miyao N, Yanase M, Masumori N, Kitamura H, Itoh N and Tsukamoto T: Inhibitory effect on expression of angiogenic factors by antiangiogenic agents in renal cell carcinoma. Br J Cancer 86: 768-773, 2002.
85. Hou P, Li H, Yong H, Chen F, Chu S, Zheng J and Bai J: PinX1 represses renal cancer angiogenesis via the mir-125a-3p/VEGF signaling pathway. Angiogenesis 22: 507-519, 2019.
86. You D, Tong K, Li Y, Zhang T, Wu Y, Wang L, Chen G and Zhang X: PinX1 plays multifaceted roles in human cancers: A review and perspectives. Mol Biol Rep 51: 1163, 2024.
87. De Simone M, Chirichella M, Emming S, Mazzara S, Ranzani V, Gruarin P, Moschetti G, Pulvirenti N, Maglie S, Vasco C, *et al*: Ex vivo microRNA and gene expression profiling of human Tr1-like cells suggests a role for miR-92a and -125a in the regulation of EOMES and IL-10R. Eur J Immunol 51: 3243-3246, 2021.
88. Cai S, Xue B, Li S, Wang X, Zeng X, Zhu Z, Fan X, Zou Y, Yu H, Qiao S and Zeng X: Methionine regulates maternal-fetal immune tolerance and endometrial receptivity by enhancing embryonic IL-5 secretion. Cell Rep 44: 115291, 2025.
89. Gil N, Perry RB, Mukamel Z, Tuck A, Bühler M and Ulitsky I: Complex regulation of Eomes levels mediated through distinct functional features of the Meteor long non-coding RNA locus. Cell Rep 42: 112569, 2023.
90. Splendiani E, Besharat ZM, Covre A, Maio M, Di Giacomo AM and Ferretti E: Immunotherapy in melanoma: Can we predict response to treatment with circulating biomarkers?. Pharmacol Ther 256: 108613, 2024.
91. Li RG, Deng H, Liu XH, Chen ZY, Wan SS and Wang L: Histone methyltransferase G9a promotes the development of renal cancer through epigenetic silencing of tumor suppressor gene SPINK5. Oxid Med Cell Longev 2021: 6650781, 2021.
92. Liao C, Wang Q, An J, Zhang M, Chen J, Li X, Xiao L, Wang J, Long Q, Liu J and Guan X: SPINKs in tumors: Potential therapeutic targets. Front Oncol 12: 833741, 2022.
93. Yan Z, Lijuan Y, Yinhang W, Yin J, Jiamin X, Wei W, Yuefen P and Shuwen H: Screening and analysis of RNAs associated with activated memory CD4 and CD8 T cells in liver cancer. World J Surg Oncol 20: 2, 2022.
94. Duan J, Pan Y, Yang X, Zhong L, Jin Y, Xu J, Zhuang J and Han S: Screening of T Cell-Related Long Noncoding RNA-MicroRNA-mRNA regulatory networks in Non-Small-cell lung cancer. Biomed Res Int 2020: 5816763, 2020.
95. Pantuck AJ, Seligson DB, Klatte T, Yu H, Leppert JT, Moore L, O'Toole T, Gibbons J, Belldegrun AS and Figlin RA: Prognostic relevance of the mTOR pathway in renal cell carcinoma: Implications for molecular patient selection for targeted therapy. Cancer 109: 2257-2267, 2007.
96. Wu JX, Du WQ, Wang XC, Wei LL, Huo FC, Pan YJ, Wu XJ and Pei DS: Rap2a serves as a potential prognostic indicator of renal cell carcinoma and promotes its migration and invasion through up-regulating p-Akt. Sci Rep 7: 6623, 2017.
97. Yang M, Chen S, Du J, He J, Wang Y, Li Z, Liu G, Peng W, Zeng X, Li D, *et al*: NK cell development requires Tsc1-dependent negative regulation of IL-15-triggered mTORC1 activation. Nat Commun 7: 12730, 2016.
98. Zeng X, Hu Z, Ke X, Tang H, Wu B, Wei X and Liu Z: Long noncoding RNA DLX6-AS1 promotes renal cell carcinoma progression via miR-26a/PTEN axis. Cell Cycle 16: 2212-2219, 2017.
99. Parsons R: Discovery of the PTEN tumor suppressor and its connection to the PI3K and AKT oncogenes. Cold Spring Harb Perspect Med 10: a036129, 2020.
100. He J, Chen D, Xiong W, Wang Y, Chen S, Yang M and Dong Z: A Single-cell analysis of the NK-cell landscape reveals that dietary restriction boosts NK-cell antitumor immunity via eomesodermin. Cancer Immunol Res 12: 1508-1524, 2024.
101. Lu J: The Warburg metabolism fuels tumor metastasis. Cancer Metastasis Rev 38: 157-164, 2019.
102. Kasprzak A: Insulin-like growth factor 1 (IGF-1) signaling in glucose metabolism in colorectal cancer. Int J Mol Sci 22: 6434, 2021.
103. Xu T, Su P, Wu L, Li D, Qin W, Li Q, Zhou J and Miao YL: OCT4 regulates WNT/β-catenin signaling and prevents mesoendoderm differentiation by repressing EOMES in porcine pluripotent stem cells. J Cell Physiol 238: 2855-2866, 2023.
104. Bisia AM, Xypolita ME, Bikoff EK, Robertson EJ and Costello I: Eomesodermin in conjunction with the BAF complex promotes expansion and invasion of the trophectoderm lineage. Nat Commun 16: 5079, 2025.
105. Zhang H, Yao J, Ajmal I, Farooq MA and Jiang W: shRNA-mediated gene silencing of HDAC11 empowers CAR-T cells against prostate cancer. Front Immunol 15: 1369406, 2024.
106. Albelda SM: CAR T cell therapy for patients with solid tumours: Key lessons to learn and unlearn. Nat Rev Clin Oncol 21: 47-66, 2024.