Multifaceted regulatory mechanisms of the EGR family in tumours and prospects for therapeutic applications (Review)

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Received February 19, 2025; Accepted May 14, 2025

DOI: 10.3892/ijmm.2025.5554

Abstract. The early growth response (EGR) family comprises four zinc finger transcription factors: EGR1, EGR2, EGR3 and EGR4. These transcription factors belong to the Cys_2-His_2-type zinc finger protein family and are essential in cell differentiation, proliferation, apoptosis and stress response. Initially, EGR1 was recognised for its essential regulatory role in tumourigenesis. Recent studies have identified similarities between other members of the EGR family and EGR1 in tumour regulation and the multifaceted regulatory mechanism employed by the EGR family to affect tumours. Therefore, the present review describes the dual roles of the EGR family in tumours and their regulatory mechanisms in immunity, metabolism and differentiation. Additionally, the present review offers a new perspective on relevant tumour therapeutic studies based on current EGR targeting.

Contents

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Key words: early growth response, tumour, proliferation, immunity, mechanisms, differentiation

1. Introduction

The early growth response (EGR) family comprises four closely related zinc finger transcription factors: EGR1, EGR2, EGR3 and EGR4. The activity of EGRs can be induced by different extracellular stimuli, including activation, growth and differentiation signals, tissue damage and apoptosis signals (1). Additionally, activity can be dynamically upregulated in response to various cellular stimuli, including growth factors and pro-differentiation factors (2). EGR1 and EGR2 were initially identified by screening complementary DNA libraries in mouse fibroblasts in response to growth factor or serum stimulation, respectively, and EGR2 exhibited functional properties similar to those of its human homologue (3,4). EGR3 was first described as a direct early growth-responsive gene induced in human fibroblasts by mitogenic stimulation, while EGR4 was initially identified through screening for neurally expressed genes and is closely associated with neuroplasticity and memory formation (3,4). The EGR genes are located in different chromosomal loci (5q31 for EGR1, 10q21 for EGR2, 8p21 for EGR3 and 2p13 for EGR4), and the EGR proteins possess highly conserved zinc finger structural domains that collectively recognise GCG(G/T)GGGCG sequences but differ in their binding affinities for specific nucleotides. Their isoform-specific flanking regions and cell type-specific expression determine their unique functions, positively and negatively regulating target gene expression (5).

Current studies on EGR family members have focused on EGR1, which is the most representative and extensively

studied family member. EGR1 often exhibits a dual function in various cancer types, mostly characterised by its ability to inhibit tumourigenesis; however, it may facilitate tumourigenesis and tumour progression under certain conditions. For instance, EGR1 is abnormally expressed in tumours of the urinary, digestive and nervous systems. In gastrointestinal tumours, EGR1 is closely associated with the pathological features of gastric cancer (GC), and its upregulation is closely associated with enhanced infiltration, tumour progression and poor prognosis (6); conversely, in prostate cancer, high EGR1 expression is positively correlated with the malignancy of the lesion, indicating its potential pro-carcinogenic role (7). Furthermore, in solid tumours, including glioma and melanoma, EGR1 induces apoptosis, partly through a mechanism potentially related to its regulation of cell cycle inhibitors, including p21[wild-type p53-activated fragment 1(Waf1)/CDK-interacting protein 1 (Cip1)], indicating its antitumour properties (8,9). The high sequence similarity among EGR1, EGR2 and EGR3 may account for their similar functional bidirectionality. EGR2 is an oncogenic factor in some cancer types, and its reduced expression is frequently associated with malignant progression. For instance, in hepatocellular, gastric and thyroid carcinoma, the downregulation of EGR2 expression is closely associated with enhanced cell proliferation and reduced apoptosis (10,11). Conversely, in other cancer types, including bladder and kidney cancer, EGR2 may be involved in promoting malignant behaviour, with its upregulation correlated with enhanced cell migration, invasion and metastatic potential (12,13). Among all EGR family members, EGR1 is regulated by a variety of upstream signalling pathways and exhibits a wider range of pro- or anticancer functions in a variety of tumour types (14,15). EGR2 is essential in cell differentiation and immune regulation, with its aberrations or mutations frequently associated with malignant behaviour [such as in chronic lymphocytic leukaemia (CLL)], and it uniquely regulates immune cell status (16,17). In prostate cancer and hepatocellular carcinoma (HCC), EGR3 typically acts as an anticancer agent by inhibiting epithelial-mesenchymal transition (EMT), promoting apoptosis and inhibiting cell proliferation (18,19); conversely, in breast cancer, EGR3 regulates the oestrogen signalling pathway and plays a pro-cancer role by upregulating anti-apoptotic genes including myeloid cell leukaemia 1 (MCL1), thereby enhancing drug resistance in cancer cells (20,21). Additionally, EGR3 is essential in regulating the expression of inflammatory factors within the tumour microenvironment (TME) and facilitating the differentiation of specific tumour cells (22,23). Although EGR4 has slightly lower sequence similarity to the other EGRs (EGR1, EGR2 and EGR3), EGR4 has anticancer activity in non-small cell lung cancer (NSCLC). ZNF205-AS1 is an antisense transcript of the zinc finger protein 205 (ZNF205) gene, classified as a non-coding RNA. EGR4 can upregulate ZNF205-AS1 expression, which reduces the negative regulation of its target mRNAs (p53 pathway components) by competing for binding to specific microRNAs (such as miR-150-5p), which subsequently increases tumour suppressor gene expression and promotes apoptosis. The promoting role of ZNF205 in NSCLC has not been widely demonstrated, and thus, the current research focuses more on the indirect regulation of other key tumour-associated pathways through the upregulation of ZNF205-AS1 (24). Unlike EGR1, which possesses a broader mechanistic pathway in tumours, the functions of EGR2 and EGR3 are likely more diverse, encompassing contributions to cellular differentiation, immune microenvironment and hormonal regulation. Furthermore, their mutation status is often indicative of a poor clinical prognosis (3,4,10,11). However, the functions of EGR2, EGR3 and EGR4 in tumours are comparatively underexplored and generally receive less attention than EGR1.

The immune system plays a critical role in tumour onset and progression; however, tumours tend to suppress the immune system through several immune evasion mechanisms, facilitating their growth and metastasis. Cytotoxic T lymphocytes [cluster of differentiation (CD)8^+ T cells], natural killer (NK) cells and dendritic cells (DCs) can exert an antitumour effect during the immune response (25,26); however, a number of immune cells exhibit a duality in their effects on tumours in the TME. For instance, antitumour immune cells such as $CD8^+$ T cells or M1-type macrophages can kill tumour cells directly or enhance the immune response by cytokine secretion (25). Conversely, pro-tumour immune cells [such as regulatory T cells (Tregs), M2-type tumour-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs)] can inhibit T-cell activity and promote tumour growth and immune escape (26). The EGR protein family contains a deterrent structural domain (R1) that interacts with the co-deterrent factor NGFI-A binding protein (NAB), and specific mutations in this region are associated with congenital hypomyelination neuropathy, with similar mutations playing a functional role in immune-related tumours (27).

The significance of the EGR gene family in tumour immunity is of increasing interest, especially during T-cell depletion. EGR2 and EGR3 regulate T cell apoptosis, maintain immune homeostasis by regulating Fas ligand (FasL) expression and play key roles in T cell energy metabolism and tolerance responses (28). EGR1 and EGR4 modulate T-cell function through synergistic regulation of calcium signalling pathways (29). The EGR family participates in the immune regulation of B cells and macrophages, with EGR1, EGR2 and EGR3 facilitating tumour immune escape by regulating cytokine production (30), while in macrophages, EGR2 is implicated in M2-type polarisation, including modulating shifts in the tumour immune response (31). In addition, the EGR family affects tumours by modulating metabolism and differentiation. Therefore, the present review provides an overview of the dual role of the EGR family in tumours and the mechanisms that regulate multiple aspects of immunity, metabolism and differentiation. Additionally, it describes current research on relevant tumour therapies targeting EGRs, offering new perspectives for therapies therein.

2. DNA binding properties and transcriptional regulation mechanism of EGR proteins

The DNA binding domain of each EGR protein has three homologous zinc finger structures that recognise DNA binding sites abundant in GC sequences (32). Notably, in EGR1, these zinc fingers have some similarity to the binding sites of the Sp1 transcription factor. The DNA sequence preferentially bound by the EGR protein is 5'-GCGGGGGGCG-3', a structural

feature that exhibits a clear rearrangement compared with the DNA binding site of Sp1 (5'-GGGGGGCGGGG-3'). Although Sp1, Sp3 and EGR1 do not engage with the same DNA binding sites in the regulation of certain target genes, they share competing binding sites in the promoter regions of some genes, including platelet-derived growth factor (PDGF) A and B chains and adenosine deaminase (32). This competition for these binding sites may affect the degree of transcriptional activation. Furthermore, the N-terminus of the EGR protein maps to various transcriptional activation domains that are essential for its function (32).

In EGR1, EGR2 and EGR3, a repressor domain has been identified alongside the DNA-binding and transcriptional activation domain. This repressor structural domain binds to the transcriptional repressors, NAB1 and NAB2, which inhibit the transcriptional activity of the EGR proteins by binding to them (33,34). Therefore, even when the transcriptional activation of EGR1 is neutralised, transcriptional induction of the EGR1 gene may have no biological effects. NAB1 and NAB2 interaction indicates that they regulate the function of EGR transcription factors through negative feedback in specific cells (33,34). Therefore, the function of EGR transcription factors is dependent on their direct DNA-binding ability and is regulated by interactions with NAB factors, offering a more complex perspective for understanding EGR function across different cellular and physiological conditions.

EGR1 facilitates several gene expression changes in response to different cellular stimuli, including cytokines, mitogens and oxidative stress (1-5). The activity of EGR1 is primarily regulated by the upregulation of its expression and post-translational modifications (2). The human EGR1 promoter has five serum-responsive elements (SREs) and one cAMP-responsive element (CRE) and can recruit different transcription factors to regulate its expression across diverse cell types (35). Moreover, EGR1 self-regulates by binding to its promoter or inducing the expression of the repressor NAB2, forming a negative feedback loop (33,34). ELK1 is an essential component in EGR1 regulation, activated by phosphorylation through the ERK, c-Jun N-terminal kinase (JNK) and p38 MAPK signalling pathways and associated with SREs (36,37). Furthermore, the PI3K/AKT pathway regulates EGR1 expression by interfering with the DNA-binding ability of forkhead box protein 01 through phosphorylation and deregulating its inhibition (38). EGR1 expression in presynaptic neurones is inhibited by the transcriptional repressor, C-terminal binding protein 1, and is activated upon removing this repression due to neuronal activity (39). During ultraviolet B-induced genotoxic stress, the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) initiates an apoptotic response by binding to the EGR1 promoter (40). During T-cell activation, EGR1 upregulates stromal interaction molecule 1 (STIM1), which increases cytoplasmic Ca^{2+} levels, which may further promote EGR1 expression. Previous studies have demonstrated that the Ca^{2+} chelator, BAPTA-AM, reduces EGR1 expression. BAPTA-AM blocks the phosphorylated activation of transcription factors (such as ELK1 and CREB) by Ca^{2+}-dependent kinases (including calcium/calmodulin-dependent protein kinase and calcineurin) by chelating intracellular Ca^{2+}, resulting in the inability of these factors to bind to EGR1 promoters on SREs and CREs, which in turn markedly reduces EGR1 transcript levels. This implies that SREs and CREs inside the EGR1 promoter are essential for transcriptional machinery recruitment (41,42). Additionally, in vascular smooth muscle cells, Ca^{2+} signalling modulates angiotensin II-induced EGR1 expression through calcium/calmodulin-dependent protein kinase II and CREB, highlighting the pivotal role of Ca^{2+} signalling in EGR1 regulation (43).

EGR1 function is regulated by various post-translational modifications, including phosphorylation, glycosylation and polymerisation. In resting cells, low phosphorylation levels reduce EGR1 stability (44); however, casein kinase II-mediated phosphorylation inhibits its DNA-binding ability (45), indicating that phosphorylation at different sites may confer different functional characteristics on EGR1. Additionally, AKT-mediated phosphorylation is a prerequisite for EGR1 to undergo small ubiquitin-like modifier modification, an important step in the ubiquitination and degradation of EGR1 (46). Additionally, *O*-linked glycosylation of the EGR1 transactivation structural domain is a key regulator of its activity (47).

3. EGR-mediated epigenetic modifications and DNA repair mechanisms

Recently, EGRs have been shown to be deeply involved in the epigenetic regulation of tumourigenesis and tumour progression. EGRs affect the expression of tumour-associated genes by regulating chromatin modification and DNA methylation, thereby controlling key behaviours, including cell proliferation, migration, differentiation and immune response while demonstrating dual regulatory effects of pro- and anticancer effects on tumours (48-67).

At the chromatin modification level, EGR1 recruits the histone acetyltransferase, CREB-binding protein (CBP)/E1A binding protein p300 (p300), which increases histone H3 lysine 27 acetylation (H3K27ac) levels in the promoter region of target genes and promotes chromatin opening and transcriptional activation. For instance, under hypoxic or inflammatory stimuli, EGR1 promotes the binding of CBP/p300 to target gene promoters by activating the signal transducer and activator of transcription 3 (STAT3)/NF-κB pathway (48). This recruitment relies on the DNA-binding activity of EGR1 and its interactions with the structural domains of the CBP/p300 protein. Under conditions of oxidative stress, EGR1-dependent CBP/p300 recruitment significantly increases H3K27ac levels in the promoters of target genes (such as Cathepsin L) and enhances chromatin accessibility, thus facilitating transcriptional activation (48,49). This mechanism is bidirectional in tumours; however, EGR1 promotes the proliferation of diffuse large B-cell lymphoma cells by upregulating the myelocytomatosis oncogene (MYC) and E2F transcription factor pathway-related genes through the CBP/p300-H3K27ac-BRD4 axis, while simultaneously inhibiting interferon (IFN) pathway genes by binding to the repressor NAB2, creating a balance between pro- and anticancer effects (50,51). In addition to regulating histone acetylation, EGR1 is regulated by histone methylation and enhancer of zeste homologue 2, the core histone methyltransferase of the polycomb repressive complex 2 complex, which silences the EGR1 promoter and inhibits its expression through histone H3 lysine 27 trimethylation (H3K27me3). This suppression diminishes the activation

of EGR1 oncogenes, including DNA damage-inducible 45 (GADD45) and DNA damage-inducible transcript 3 (DDIT3), and promotes breast cancer progression (52). In addition, the DNA binding ability of another member of the EGR family, EGR2, is correlated with the histone methylation status of their target sites as enrichment of H3K4me3 increases the efficiency of it binding to target genes (53,54).

EGRs are involved in the dynamic regulation of DNA methylation. The DNA binding ability of EGR1 is affected by the level of methylation at the target site; its gene activation relies on the hypomethylated state, while hypermethylation weakens its binding efficacy and leads to gene suppression (55,56). EGR2 interacts directly with ten-eleven translocation 2 (TET2) and facilitates 5-methylcytosine demethylation, promoting DNA demethylation in the promoter regions of specific genes. During monocyte differentiation, the EGR2-TET2 complex activates differentiation-associated genes (such as zinc finger protein 36 and suppressor of cytokine signalling 3) by dynamically regulating DNA methylation while inhibiting tumour-associated pathways (57,58). Accordingly, the importance of EGRs in maintaining the DNA methylation-demethylation dynamic balance is highlighted. The EGR family also affects the immunological milieu of the tumour, with expression levels closely associated with tumour-infiltrating T cells and macrophages, among others (59-67). Low expression of EGR1 results in increased methylation of IFN pathway-related genes, inhibits the antitumour immune response and facilitates immunological evasion in breast cancer (59). The stimulator of the IFN genes (STING) pathway is a central mechanism in antitumour immunity; its activation induces the secretion of type I IFNs, thus enhancing the maturation of DCs and T-cell infiltration (60,61). Low EGR1 expression may inhibit STING pathway-related genes (such as cyclic GMP-AMP synthase and IFN-β) through methylation, resulting in the inability of immune cells to effectively recognise tumour antigens (62,63). In immune NK T cells (iNKT), general control non-repressible 5 (GCN5) functions as a histone acetyltransferase, directly enhancing the transcriptional activity of EGR2 by catalysing its acetylation. Inhibition of GCN5 (whether through knockout or medications) markedly diminishes the acetylation level of EGR2, impairing its capacity to effectively activate downstream target genes, including promyelocytic leukaemia zinc finger (PLZF), runt-related transcription factor 1 (Runx1), interleukin-2 receptor β and T-box transcription factor (T-bet), which hinders the differentiation and development of iNKT cells (64,65). Additionally, GCN5 can directly modify EGR2 through histone acetylation and through non-histone mechanisms. For instance, GCN5 can directly acetylate specific sites on EGR2 rather than depending on histone deacetylases in the nucleosome remodelling and deacetylase complex (66), and this post-translational modification enhances the ability of EGR2 to bind to the promoters of its target genes. The acetylation status of EGR2 In iNKT cells affects its interaction with cofactors (such as TET2), which modulates DNA methylation dynamics and chromatin accessibility, which subsequently affects the expression of genes, including PLZF (67).

EGRs also have a potential role in regulating DNA repair and maintaining genomic stability. A study has demonstrated that EGR1 can directly bind to the promoters of several key DNA damage response (DDR) genes in $CD34^+$ umbilical cord blood haematopoietic stem/progenitor cells (HSPCs) and regulate their expression levels (50). These EGR1 target genes are extensively implicated in cell cycle regulation (G1/S checkpoint), DNA repair mechanisms (including the ataxia-telangiectasia mutated/ataxia-telangiectasia and rad3-related pathway, homologous recombination repair and non-homologous end joining) and oxidative stress defence, indicating that EGR1 may serve as a crucial transcriptional regulator connecting external stimuli to the DDR network (50). In a mouse model, EGR1 knockdown induced haematopoietic stem cell (HSC) depletion, indicating its essential role in preserving genomic integrity and that it may be involved in DNA repair in unstable chromosomal regions (such as 5q deletions) by modulating repair factors, including BRCA1/2 and radiation sensitivity 51 (61). EGR1 functionally overlaps with classical tumour suppressors, including p53 and phosphatase and tensin homologue (PTEN) (47,62). Under DNA damage induction, EGR1 can act in synergy with p53 to regulate repair gene expression, including GADD45, or participate in regulating the balance between repair and apoptosis by inhibiting PTEN and activating the AKT pathway (47). Moreover, oxidative stress significantly increases EGR1 expression, which may affect the DNA repair mechanism by regulating intracellular levels of reactive oxygen species (ROS). However, while EGR1 can increase the need for repair through ROS signalling, over-activation can cause aberrant expression of repair-associated genes, resulting in genomic instability and potentially facilitating tumourigenesis and tumour progression (63). Accordingly, EGR1 possesses a complex regulatory function in the DDR, and its dysregulated balance may serve as a potential oncogenic factor.

Aberrant expression of EGR family members is closely associated with defective DNA repair in various tumour types. For instance, EGR1/2/3 expression is significantly lower in several cancer types than in normal tissues (23,64,65); EGR1 downregulation increases resistance to chemotherapy in oesophageal cancer, while EGR1 deletion in breast cancer may be correlated with genomic instability induced by DNA replication stress (23,64). However, EGR4 is known for facilitating tumour proliferation in colorectal cancer by activating the inflammatory pathway [tumour necrosis factor (TNF)-α/TNF-κB] and may indirectly exacerbate oxidative DNA damage (65). EGR family expression levels were significantly and negatively correlated with tumour mutational burden, further supporting their key role in regulating DNA repair efficacy and affecting tumour mutation accumulation (66). Furthermore, the functions of EGR family members are regulated by epigenetic modifications, such as DNA methylation and histone acetylation, which affect their ability to bind to target gene promoters, thereby affecting the expression of DDR-related genes. Although studies have demonstrated a multi-level association between EGR families and DNA repair, most are still based on correlation analysis or indirect evidence. Additional experimental approaches, including chromatin immunoprecipitation-sequencing, gene editing and repair function assays, are required to classify their specific mechanisms in the DNA damage repair network.

Previous studies have demonstrated that the EGR family is essential in tumour progression by regulating multiple signalling pathways, including cell proliferation, apoptosis,

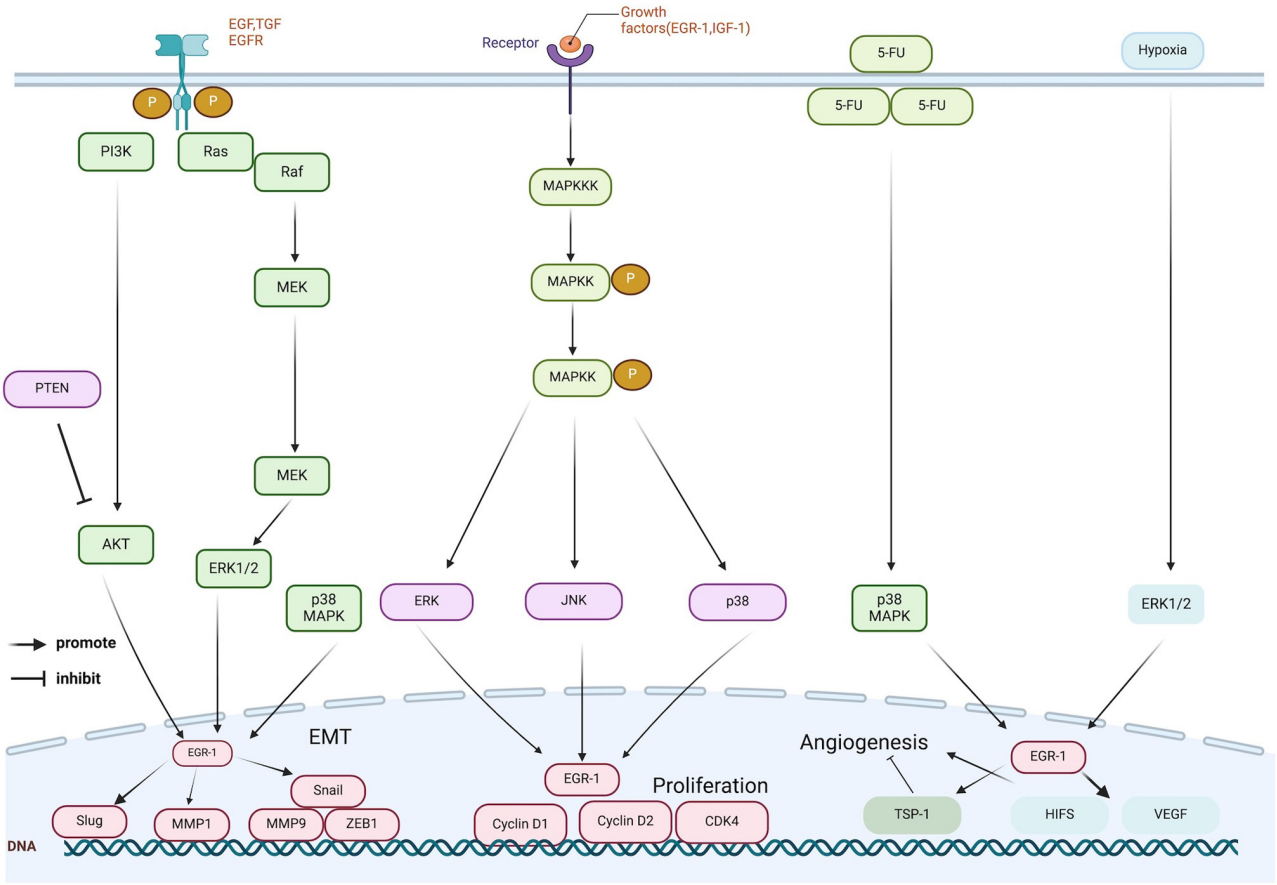

Figure 1. EGR1 signalling in EMT, proliferation and angiogenesis in cancer. EGR1, early growth response 1; EMT, epithelial-mesenchymal transition.

migration and immune response. However, ongoing studies are clarifying that the regulatory mechanism of the EGR family in tumours may involve deeper processes, including epigenetic regulation and DNA repair mechanisms. Similarly, the EGR family may further regulate the expression and function of tumour-associated genes by affecting chromatin conformation, DNA methylation status and DDR. This hypothesis remains unconfirmed, and more experimental data and comprehensive molecular mechanism studies are required to clarify the specific mechanisms.

4. Dual regulation of EGR in tumours

The functions of EGR family members vary across different cancer types, exhibiting notable heterogeneity that is dependent on the tumour type and influenced by the TME, including hypoxia, inflammation and hormone dependence (1-5,27). The variability in the 'on/off' mechanisms of EGRs (such as the activation or inhibition of specific signalling pathways) across cancer types may explain the diversity of these transcription factors in their pro- or oncogenic roles. Typically, the function of EGR in cancer is to influence tumour progression by regulating various cellular behaviours, including proliferation, migration, invasion and angiogenesis.

Carcinogenic regulation of EGR

Proliferation. Cell proliferation depends on several growth factors, and high expression of growth factors and their receptors is an essential feature of cancer cells. High expression of EGR1 may affect tumour cell proliferation by modulating the cell cycle. For instance, growth factor stimulation can enhance EGR1 through oestrogen receptor β activation of the RAF/MEK1/ERK/ELK1 pathway (15) (Fig. 1). Furthermore, inhibitors of the MAPK/ERK pathway significantly reduce EGR1 expression, indicating that EGR1 is a downstream gene within this pathway (14). Cyclin D1 is an important molecule in cell cycle regulation, and EGR1 enhances cell proliferation by directly binding to the cyclin D1 promoter, increasing cyclin D1 expression and facilitating the transition of cells from G1 to S phase (67) (Fig. 1). In addition, EGR1 upregulates other cell cycle-related proteins, including cyclin D2 and cyclin-dependent kinase 4, further promoting tumour cell proliferation (68). The JNK pathway within the MAPK family enhances EGR1 expression, creating a cyclic mechanism (69). Additionally, insulin-like growth factor-1 and its receptor activate the MAPK/ERK pathway, further reinforcing this cyclic process (67) (Fig. 1).

EGR1 is a transient transcription factor whose stability is regulated by the glycogen synthase kinase 3 β (GSK3β)/F-box and WD repeat domain containing 7 (FBXW7) axis, which affects cell proliferation in numerous cancer types (70). FBXW7 functions as an E3 ubiquitin ligase for EGR1 and facilitates its ubiquitination and degradation through GSK3β kinase activity. However, GSK3β inhibition or FBXW7 mutation prolongs the half-life and increases EGR1 levels. Under hypoxic conditions, FBXW7 enhances the ubiquitination of

EGR1, thereby diminishing its stability (70). The downregulation of EGR1 inhibits lung cancer cell growth; however, the downregulation of FBXW7 stimulates prostate cancer cell proliferation by stabilising EGR1 (70). In advanced CLL, mutations in the FBXW7 and EGR2 genes occur in similar patient populations (16% of patients with EGR2 mutations carry both NOTCH1/FBXW7 mutations, and FBXW7 mutations indirectly increase their signalling activity by inhibiting NOTCH1 degradation) and are both associated with a poorer prognosis (71). Consequently, it is possible that both genes are involved in the same pathogenic pathway or that their mutations collectively affect the malignant progression of tumours.

Metastasis and invasion. EMT is a process by which epithelial cells transform into mesenchymal cells, serving as a crucial mechanism for tumour cell invasion and metastasis. EGR1 facilitates EMT by inducing the expression of the epithelial cadherin (E-cadherin) transcriptional repressors, snail family transcriptional repressor 1 (SNAIL) and snail family transcriptional repressor 2 (SLUG), thereby promoting tumour invasion and metastasis (72) (Fig. 1). During tumour metastasis, mesenchymal-related genes including matrix metalloproteinases (MMPs; such as MMP1 and MMP9), histones and zinc finger E-box binding homeobox 1 (ZEB1) are crucial (73). EGR1 enhances the expression of the MMP1 promoter by binding directly to it, while SNAIL facilitates MMP9 and ZEB1 expression, thereby aiding tumour cell invasion and metastasis (74) (Fig. 1). Several MAPK pathways (including ERK, JNK and p38) upregulate EGR1 and contribute to TNF-α-induced MMP1 expression, further promoting invasion and metastasis (75). In hormone-independent prostate cancer, C-X-C motif chemokine ligand (CXCL)5 enhances EGR1 transcription and increases SNAIL expression through the RAF/MEK/ERK pathway, thereby facilitating tumour cell EMT and metastasis. Conversely, EGR1 inactivation reduces IL-6-associated metastasis, potentially through inhibition of the PI3K/PTEN/AKT pathway (68). EGR1 promotes tumour cell invasion in GC by regulating β-catenin expression (76). In ovarian cancer, EGF stimulates the EGR1-mediated upregulation of SLUG through activation of the p38 MAPK, ERK1/2 and PI3K/AKT pathways, resulting in E-cadherin inhibition and enhanced tumour metastasis (77). In pancreatic cancer, the EGR1-dependent p300/CBP cofactor binds to the SNAI2 promoter and activates its transcription, subsequently inhibiting E-cadherin expression and inducing EMT (78). In HCC, EGR1 upregulates SLUG expression through hepatocyte growth factor-induced binding to the SNAIL promoter or through the ERK/AKT/EGR1/SLUG pathway, thereby promoting EMT and metastasis (79). In breast cancer, S100 calcium-binding protein A4 enhances nuclear localisation of EGR1 by promoting its binding to input protein 7, which leads to the EGR1-mediated downregulation of β-catenin through the PTEN/AKT/GSK3β pathway, which in turn promotes tumour invasion and metastasis (80).

Studies on specific metastatic sites have demonstrated the critical role of EGR1. For instance, EGR1 has been implicated in the metastasis of prostate cancer to bone and the brain by regulating angiogenesis and osteoclastogenesis. EGR1 activates the NF-κB pathway by binding to TNFRSF12A (FN14) and enhances its expression through a MEK-dependent mechanism. Furthermore, EGR1 expression significantly reduces the number and size of metastases and decreases vascular density and osteolytic lesions in metastatic regions. Additionally, EGR1 regulates the expression of numerous angiogenic and osteoclastogenic factors, including PDGF-A, transforming growth factor β1 (TGF-β1) and interleukin 6, which are implicated in prostate cancer metastasis (7). Peritoneal metastasis of GC is one of the most common forms of metastasis in advanced GC (81). GC cells with upregulated HOXA11 expression activate EGR1 expression in peritoneal mesothelial cells by secreting PDGF-BB and TGF-β1, a mechanism regulated by miR-181a-5p. EGR1 also facilitates peritoneal mesothelial fibrosis and enhances the migration and peritoneal dissemination of GC cells, establishing a feed-forward amplification loop that accelerates the progression of peritoneal metastasis (81). The role of osteoblast protein, osteopontin (OPN; an essential glycoprotein involved in cell signalling, immunological response and tissue remodelling), in tumour invasion and metastasis has attracted considerable attention (82). OPN helps tumour cells breakthrough *in situ* restriction and metastasise to other organs by facilitating cancer cell migration and survival (82). The role of EGR1 in cancer stem cells and metastasis in lung cancer has received considerable attention. A previous study has demonstrated that the transcription factor octamer-binding transcription factor 4 (Oct4) facilitates the upregulation of EGR1 by activating the EGR1 promoter, which in turn, together with OPN, forms an Oct4/EGR1/OPN axis and enhances the metastatic ability of lung cancer cells (82). Lymph node metastasis is a common feature of numerous malignant tumours and is closely associated with cancer progression and poor prognosis. Thyroid cancer, the most common endocrine tumour, has a high rate of lymph node metastasis (83). Long non-coding PTP receptor type C1 transcriptional splicing (LNCPTCS), a tumour suppressor long non-coding RNA, has significantly reduced expression in thyroid cancer, especially in metastatic lymph nodes. Inflammatory cytokines, including TNF-α and CXCL10, modulate the binding of EGR1 to the LNCPTCTS promoter, thereby reducing LNCPTCTS expression (84).

Angiogenesis. Tumour angiogenesis is an important mechanism for tumour growth and metastasis, and the inhibition of angiogenesis has emerged as an effective strategy for cancer treatment. A number of cancer cells secrete extracellular vesicles that facilitate vascular endothelial cell migration by upregulating EGR1, hence markedly enhancing angiogenesis (7). The rapid growth of tumours frequently results in hypoxia in their central region, and hypoxia is a potent angiogenesis-stimulating factor. Under hypoxic conditions, hypoxia-inducible factor (HIF) is upregulated, leading to increased expression of the vascular endothelial growth factor (VEGF) protein family, which stimulates angiogenesis and promotes tumour cell survival (85) (Fig. 1). EGR1 expression in prostate cancer is regulated by the inhibition of androgen receptor signalling and PTEN deletion, facilitating angiogenesis by upregulating HIF1 expression through activation of the HIF1 promoter under hypoxic conditions (86). In lung cancer, EGR1 directly binds to and activates the VEGFA promoter, thereby enhancing angiogenesis by enhancing HIF1α-dependent VEGFA expression (87). In addition, EGR1 transcriptionally activates the angiogenic factor, C-C motif chemokine ligand 2, which subsequently forms a

positive feedback loop through the CCR2/ERK/ELK1/EGR1 pathway (88). Programmed cell death ligand 1 (PD-L1) is abundantly distributed in the nucleus of malignant tumours. Furthermore, nuclear nPD-L1 is an endogenous accelerator of cancer angiogenesis; it promotes the binding of phosphorylated STAT3 to the EGR1 promoter, resulting in EGR1-mediated angiogenic activation (89).

EGR3 vs. EGR1 in tumour angiogenesis. In vascular endothelial cells, the EGR transcription factor family is essential in regulating vascular function. EGR1 is essential in several vascular-related diseases, including ischaemia/reperfusion-induced lung injury, atherosclerosis and fibroblast growth factor-2 (FGF-2)-dependent angiogenesis and tumour growth (90-92). EGR3 primarily regulates several downstream effects of VEGF, including promoting inflammatory responses, enhancing cell proliferation and migration *in vitro*, and facilitating neovascularisation in Matrigel and tumour growth *in vivo* (93). VEGF, thrombin and TNF-α rapidly activate endothelial cells and induce high expression levels of EGR family members, particularly EGR1 and EGR3. VEGF-induced upregulation of EGR3 is more pronounced and persists for a longer duration than that of EGR1 (93), whereas negative feedback pathways are essential for the temporal regulation of endothelial cell activation. For example, VEGF upregulates Down syndrome critical region 1 (DSCR-1) expression through activation of the calmodulin phosphatase/nuclear factor of activated T cells (NFAT) pathway, while DSCR-1 subsequently inhibits NFAT activity through a negative feedback mechanism (94,95). In endothelial cells, NFAT is essential in the specific induction of EGR3 expression by VEGF, while EGR3 further enhances DSCR-1 expression in VEGF-treated endothelial cells, establishing a self-limiting regulatory circuit that preserves the dynamic balance of the pathway by inhibiting NFAT-dependent EGR3 activation through DSCR-1 (93). NAB1 and NAB2 synergistically inhibit EGR1 activity in endothelial cells, with NAB acting as a direct negative feedback inhibitor of EGR1. However, EGR3 overexpression upregulates NAB1 and NAB2 expression, while NAB2 inhibits EGR3 activity independently and may facilitate its delayed negative feedback regulation (93). Additionally, EGR3 exhibits a dual feedback control mechanism in response to VEGF stimulation: VEGF induces EGR3 expression while simultaneously activating the upregulation of NAB2 and DSCR-1, which collaboratively inhibit EGR3 activity and expression through a feedback mechanism that regulates the functional state of endothelial cells (93). EGR3 assumes a more significant role than EGR1 in certain specific angiogenesis and tumourigenesis, such as VEGF-induced endothelial cell activation, neovascularisation in Matrigel and tumour growth *in vivo*.

Vasculogenic mimicry (VM) is an essential phenomenon in tumours, characterised by the formation of capillary-like channels composed of cancer cells within tumour tissues that are anatomically and physiologically similar to blood vessels and are essential in alternative angiogenesis in tumours (96). In triple-negative breast cancer cells, EGR1 expression is upregulated and localised to the nucleus during VM formation, while EGR1 knockdown markedly reduces VM formation (96). Additionally, Krüppel-like factor 4 (KLF4), a gene regulated by EGR1, exerts a positive regulatory role in VM formation. EGR1 regulates KLF4 expression by binding to its promoter region, while the functions of ERK and p38 kinase further affect VM formation by regulating EGR1 and KLF4 expression (96). Although much attention has been directed toward the role of EGR1 in VM, the impact of EGR3 on tumour angiogenesis is frequently neglected; however, its role may surpass that of EGR1.

Anti-carcinogenic regulation

Apoptosis. Apoptosis is the process by which cells eliminate themselves through programmed death mechanisms under physiological conditions, and EGR1 promotes apoptosis in cancer cells through multiple pathways. However, EGR1 can synergistically enhance TGF-β1, fibronectin (FN), p21Waf1/Cip1 and focal adhesion kinase (FAK) to inhibit apoptosis, thereby reducing caspase activity (97). Additionally, EGR1 facilitates apoptosis by enhancing the PTEN-mediated downregulation of AKT expression (98). EGR1 directly binds to the promoters of various apoptosis-inducing factors, including BCL2-associated X (BAX), NSAID-activated gene 1 (NAG1) and PTEN, to enhance their expression (99). D-tocotrienol induces apoptosis in pancreatic cancer cells by activating EGR1 through the JNK/c-Jun pathway and promoting BAX expression by binding to the BAX promoter (99,100). PTEN is a key tumour suppressor gene whose expression is directly regulated by EGR1. A study has demonstrated that EGR1 induces apoptosis in cancer cells by binding to the PTEN promoter region to enhance its transcription (101). Insulin-like growth factor-II upregulates EGR1, which subsequently increases PTEN expression; unconjugated bilirubin regulates EGR1 through activation of the apyrimidinic endodeoxyribonuclease 1/redox factor-1 pathway, which affects PTEN levels; and vitamin D significantly increases PTEN expression through synergistic interaction with the vitamin D receptor, EGR1, and p300 PTEN expression, further inducing apoptosis in cancer cells (101). EGR1 expression is lower in lung and liver cancer tissues than in normal tissues (101,102). In NSCLC, EGR1 facilitates cell cycle arrest and apoptosis through the regulation of tumour suppressor pathways, including PTEN. Moreover, TGF-β1 downregulates EGR1-induced EMT, while high EGR1 expression significantly inhibits EMT through the regulation of SNAIL, SLUG and E-cadherin expression (102). In uterine cancer, Wilms tumour 1-associated protein (WTAP) downregulation reduces EGR1 mRNA stability by decreasing its m6A modification, which subsequently reduces the expression of EGR1 and the tumour suppressor gene, PTEN, to promote tumourigenesis, while combined WTAP, EGR1 and PTEN upregulation significantly inhibits tumourigenicity of endometrial cancer cells and their stem cells (103). EGR2 is essential in mediating the anti-proliferative function of PTEN (104). In various cancer cell lines, including two endometrial cancer cell lines (Ishikawa and HEC-1A), one ovarian cancer cell line (SKOV3) and two colon cancer cell lines (HCT116 and HT29), EGR2 expression significantly inhibits cell colony formation (104). A further study demonstrated that EGR2 induces apoptosis in cancer cells and upregulates the transcriptional activity of the apoptosis-related genes, BCL2 interacting protein 3-like and BAK (105). NAG1 belongs to the TGF-β superfamily and can prevent tumour cell growth (106). A previous study demonstrated that EGR1 induces apoptosis

by upregulating NAG1 in cancer (106). However, NSAIDs promote apoptotic signalling through the peroxisome proliferator-activated receptor (PPAR)γ/EGR1/NAG1 pathway and can directly boost EGR1-mediated NAG1 expression in a cyclo-oxygenase-2 (COX-2)-independent manner, further promoting apoptosis (107).

The TP53 gene, an anticancer gene, is closely associated with various human tumours. The p53 protein encoded by the gene is a tetrameric transcription factor that primarily monitors DNA damage, preserving genome stability. Recently, the anticancer activity of p53-deficient cells has offered new perspectives for tumour therapy (108). p21, a major target of p53, facilitates cell cycle regulation after DNA damage and induces the apoptosis of cancer cells through a p53-independent mechanism after its expression is enhanced by EGR1 (109). Mutations in the p53 gene have been detected in numerous cancer types, and specific mutation sites (point mutations at 156, 246, 247 and 273) exhibit a high affinity for EGR1 activation (110). EGR1 is essential in DNA repair and its aberrant activation following p53 mutation may exacerbate tumour progression (111). In p53-deficient prostate cancer cells, EGR1 promotes apoptosis by inducing TNF-α expression. Additionally, EGR1 induces p21Waf1/Cip1 expression independently of p53 through the ERK and JNK MAPK/ELK1/EGR1 pathways, initiating DNA repair and enhancing apoptosis, indicating that EGR1 is a potential therapeutic target for p53-mutant tumours. Furthermore, mutant p53 initiates the ERK1/2 pathway to mediate EGR1 upregulation, further activating the EGR1/EGFR/ERK feedback loop (112).

Oncogene-induced senescence (OIS). OIS is an important endogenous tumour suppressor mechanism that induces cell cycle arrest by sensing oncogenic signals, hence inhibiting the transformation of normal cells to cancer cells (113,114). OIS, or apoptosis, is induced by the activation of key anticancer pathways, including the alternate reading frame/p53 pathway and cyclin-dependent kinase inhibitor 2A/retinoblastoma protein pathway, thereby inhibiting cancer initiation and progression. The transcription factor, CCAAT/enhancer-binding protein β (C/EBPβ), is essential for OIS regulation (113-115). EGR1, EGR2 and EGR3 recognise and transiently bind to specific sites on the C/EBPβ promoter and are closely associated with the inducible expression of C/EBPβ. However, the simultaneous knockdown of all three genes inhibits C/EBPβ expression, impairing the antitumour effect of OIS (115). Accordingly, the EGR family (namely EGR1, EGR2 and EGR3) facilitates tumour suppression through the regulation of OIS, and its impaired function may contribute to cancer development and progression.

Inhibition of cancer-promoting mechanisms. The antitumour function of EGR1 involves the inhibition of angiogenesis and invasive metastasis. The sustained expression of EGR1 upregulates several anti-angiogenic genes, including CXCL14, tissue inhibitor of metalloproteinase (TIMP)1, TIMP2, TIMP3 and Fms-related receptor tyrosine kinase 1, which inhibits tumour angiogenesis (116). In nasopharyngeal carcinoma, the transcription factor, EGR1, binds to the promoter region of nasopharyngeal carcinoma-associated gene 6 (NGX6) and upregulates its expression, thereby inhibiting tumour angiogenesis and impeding tumour progression (117). Fluorouracil upregulates EGR1 and inhibits angiogenesis through the p38 MAPK pathway, while EGR1 enhances thrombospondin 1 (TSP1) expression by binding to the TSP1 promoter, further diminishing tumour angiogenesis (117) (Fig. 1). A colon cancer study demonstrated that EGR1 controls the expression of Mindin by binding to its promoter, which inhibits HIF1α and VEGFA expression and reduces VEGFR2 phosphorylation in endothelial cells, resulting in an anti-angiogenic effect (118). In head and neck squamous cell carcinoma, oxytocin upregulates EGR1 through EGFR and ERK-dependent pathways and inhibits tumour invasion and metastasis, which may be related to E-cadherin upregulation (119). In leukaemia, thalidomide and LY294002 upregulate EGR1, inhibit cell invasion and metastasis and are not dependent on the PI3K/AKT pathway (120). In fibrosarcoma, EGR1 upregulation markedly inhibits tumour invasion by modulating TIMP2 expression (121).

5. Regulatory roles of EGR in tumour immunity

T cells. EGR family members are essential in numerous aspects of T cell function, including the regulation of T-cell activation, energy metabolism and antigen-driven T cell proliferation as well as effector function differentiation. For instance, EGR1 facilitates T helper cell type 2 (Th2) differentiation by upregulating IL-4 expression, while EGR2 and EGR3 inhibit Th1-type differentiation by repressing T-bet expression. Additionally, EGR4 is a key and non-redundant regulator of T-cell differentiation (27,122-125).

EGR and regulation of T cell function. The activation and effector functions of T lymphocytes are regulated by EGR1 and other essential transcription factors, including nuclear factor for activated T cells, which collectively regulate the transcriptional processes of IL-2 and TNF-α following T cell receptor (TCR) stimulation. The zinc finger protein binding region (ZIP) is an important regulatory element in the IL-2 promoter. ZIP is bound by the Sp1 transcription factor in resting T cells and by EGR1 in activated T cells, thereby regulating IL-2 expression (126,127). Additionally, promoter regions containing the ZIP region and the NFAT binding element promote IL-2 and TNF-α transcription. This region) in the human IL-2 and TNF-α promoters is a binding site for EGR1, NFAT and Sp1, which synergistically regulate the expression of key cytokines through heterodimer formation (126,127). EGR proteins (excluding EGR4) typically contain a repressor binding domain regulated by NAB (NAB1 and NAB2). NAB2 regulates target gene expression by binding to EGR1, while EGR1 concurrently regulates NAB2, forming a negative feedback loop to balance EGR1 activity (31,32). NAB1 can effectively inhibit EGR1; however, the role of NAB2 is more complex. NAB2 is upregulated during T-cell activation in response to co-stimulatory signals and collaborates with EGR1 to enhance IL-2 expression (27). IL-2 transcription is dependent on NAB2, which is recruited to the EGR1 binding site of the IL-2 promoter upon TCR stimulation, further enhancing EGR1 activity and facilitating IL-2 and IL-2β receptor synthesis (128). Moreover, EGR1 expression is correlated with CD40 ligand transcription in $CD4^+$ T cells and collaborates with NFAT proteins to regulate CD40 ligand expression, a process dependent on CD28 signalling. EGR1 is significantly upregulated upon CD28 stimulation and may act as an adaptor for TCR and CD28 signalling, facilitating

full activation of T cells and their co-stimulatory function with antigen-presenting cells (129,130).

During tumour growth, $CD8^+$ T cells progressively lose their ability to release inflammatory cytokines due to prolonged antigen exposure, accompanied by the upregulation of inhibitory receptor expression, a condition known as T-cell exhaustion (131-134). Although this phenomenon may have evolved as a mechanism to mitigate immune-mediated pathological damage, prolonged T-cell exhaustion weakens the immune system and hence promotes tumour growth (135). Antigen-induced NFAT-dependent regulatory mechanisms regulate the energy metabolism of $CD4^+$ T cells and the depletion process of $CD8^+$ T cells (136). Th expression of EGR2, a key energy-regulating transcription factor, is also induced upon TCR activation of NFAT (137). EGR2 inhibits T cell function in response to energy requirements by directly enhancing the expression of factors that reduce TCR signalling, including casitas B-lineage lymphoma b (Cbl-b) (125). Certain studies have demonstrated that the EGR2 expression level is significantly increased in $CD8^+$ T cells in a depleted state, indicating that EGR2 may be crucial in the regulation of T cell depletion (133,134). Additionally, EGR3 is more likely to collaborate with EGR2 in regulating the tolerance response. These two factors can bind the FasL regulatory element in the FasL promoter and enhance the transcriptional expression of FasL following TCR stimulation (138). EGR2 and EGR3 are essential regulators of FasL expression, which is upregulated in $CD4^+$ T cells following TCR signalling and sustains immunological homeostasis by inducing apoptosis (Fig. 2). NFAT mediates the regulation of FasL expression through EGR2 and EGR3, which are upregulated in an NFAT-dependent manner in $CD4^+$ T cells in the inactivated state. The upregulation of EGR2 and EGR3 inhibits the expression of the T-cell activators, EGR1 and NAB2, and inhibits T-cell secretion of IFN-γ and IL-2, while enhancing the expression of the E3 ubiquitin ligase, Cbl-b, an important mechanism for inducing T-cell tolerance and anergic states (27,139,140) (Fig. 2). Obstructing inhibitory receptors while simultaneously activating exhausted T-cell responses has become one of the key targets of immunotherapy, exhibiting significant clinical efficacy in cancer treatment (135).

Functions of EGR1 and EGR4 in store-operated calcium channel (SOCE) regulation. EGRs are prominent regulators of SOCE components, with EGR1 and EGR4 capable of driving and co-regulating STIM1 expression in T cells. However, EGR2 and EGR3 lack this function. EGR4 knockdown significantly reduced EGR1 binding to the STIM1 promoter, indicating a synergistic influence of both factors on STIM1 expression during T-cell activation (28). The main driver of calcium signalling during T-cell activation is TCR-mediated phospholipase C (PLC) activity, which facilitates Orai activation by increasing the expression of potassium channels, further amplifying the calcium influx response (141-143). The TCR is activated upon binding to antigenic peptides on antigen-presenting cells, initiating a signalling cascade response. This process activates PLCγ, which induces the release of Ca^{2+} from the endoplasmic reticulum through the inositol 1,4,5-trisphosphate receptor, while Orai1-mediated calcium influx sustains intracellular calcium concentrations (144,145). Subsequently, the zinc finger transcription factors, EGR1 and EGR4, are activated to modulate the expression of Ca^{2+} homeostasis-associated proteins (such as STIM1 and plasma membrane calcium ATPase 4), facilitating the long-term maintenance of Ca^{2+} signalling (28). This calcium signalling subsequently activates the calmodulin/calcineurin complex, facilitating NFAT translocation to the nucleus, where it regulates the expression of genes associated with T cell differentiation and proliferation (28) (Fig. 3). However, EGR4 deficiency disrupts the expression and function of potassium channels, causing a persistent excessive influx of calcium ions that abnormally activates the NFAT signalling pathway, significantly impacting T-cell function (122).

Although SOCE relies on the upregulation of STIM1, its functionality is significantly enhanced with a synchronous increase in Orai1 expression. Previous studies have demonstrated that SOCE inhibits tumour growth by facilitating apoptosis in prostate cancer (146,147), clarifying why SOCE deficiency may accelerate tumour progression. However, SOCE exhibits pro-carcinogenic effects in some cases, including promoting tumour angiogenesis by upregulating VEGF in cervical cancer and driving activation of COX-2 (148) and NFAT in other pathological responses (149,150). Additionally, high expression of STIM1 and Orai1 has been associated with several cancer types, including lung, liver and colorectal cancer (147). In prostate cancer, a negative feedback regulation mechanism exists between Orai1 and the androgen receptor, affecting their expression levels, while STIM1 and Orai1 expression is negatively correlated with the Gleason score (151). In breast cancer, STIM1 and Orai1 expression is significantly associated with focal adhesion formation; however, SOCE inhibition reduces the number of focal adhesions while paradoxically enhancing metastasis *in vivo* (152).

Repressor of EGR1 in SOCE regulation: WT1. WT1 is a tumour suppressor gene that notably overlaps with EGR1 in consensus targets; however, it is not a member of the EGR family. Unlike the direct early genes of the EGR family, WT1 expression is predominantly developmentally regulated and generates >20 isoforms through several mechanisms, including numerous transcription start sites, selective splicing and RNA editing (153). The specific splicing of exon 9 results in a lysine-threonine-serine insertion, a modification that significantly affects the DNA binding capacity and functional properties of WT1 (153). WT1 and EGR1 possess numerous transcriptional targets, with WT1 typically inhibiting the gene upregulation function of EGR1 by binding to these loci. This disparity illustrates the significant differences between the two in target recognition and transcriptional regulatory mechanisms (154). In mammalian genomes, cytosines at most CpG sites are methylated, leading to reduced EGR1 binding and downregulation of its target genes in some cases. The zinc finger structural domains of EGR1 and WT1 exhibit similar binding affinities to fully methylated DNA and are insensitive to methylation (155). However, they significantly differ in their ability to bind 5-carboxycytosine, an intermediate state of epigenetic reprogramming. Glutamate residues in EGR1 inhibit this binding, while glutamine residues in WT1 facilitate it (156). This binding preference may explain the difference in target function between the two in tumours, including breast cancer and glioma, where 5-carboxycytosine is significantly elevated and may serve as a unique epigenetic marker.

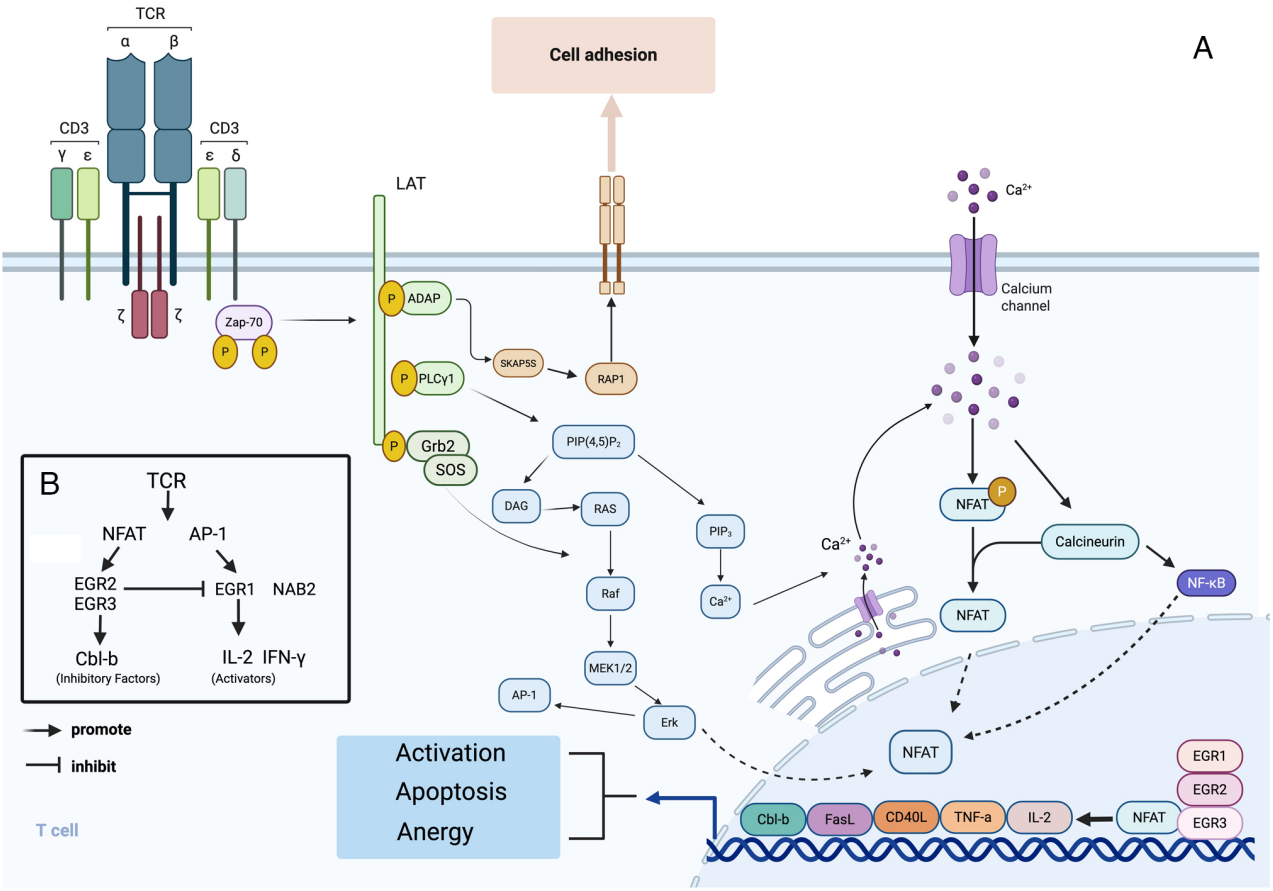

Figure 2. (A) EGR transcription factors are essential in the functional regulation of T cells. Upon the TCR stimulation of T cells, the transcriptional activation of EGR factors can trigger different cell fate decisions, a process modulated by the synergistic action of NFAT and EGR in the promoter region. Regulators in the promoter region include cytokines (such as IL-2 and TNF-α), co-stimulatory molecules (such as CD40L) and several regulatory molecules, such as FasL and the ubiquitin ligase Cbl-b, These factors do not bind directly to gene promoters; they activate downstream signalling pathways (such as JAK-STAT, NF-κB and MAPK) by interacting with their respective cell surface receptors, which in turn modulate the binding of nuclear transcription factors (including STATs, NF-κB, AP-1 and NFAT) to bind to promoters, which ultimately affects the transcriptional activity of genes indirectly. (B) EGR2 and EGR3 are essential negative regulators in the NFAT pathway and play key regulatory roles within the cell. EGR3 upregulates EGR2 expression, and collectively, they inhibit T cell function by increasing negative regulatory molecule expression (such as Cbl-b) and inhibiting the expression of T-cell activators, EGR1 and NAB2. TCR, T-cell receptor; NFAT, nuclear factor of activated T cells; JAK, Janus kinase; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; AP-1, activator protein 1; Cbl-b, casitas b-lineage lymphoma proto-oncogene-b; NAB2, NGFI-A binding protein 2.

Moreover, examining the effect of methylation on other EGR isoforms will elucidate the complex role of the EGR family in epigenetic regulation (157,158).

In Wilms tumour cells, WT1 expression is significantly associated with reduced STIM1 levels and SOCE activity. EGR1 positively regulates STIM1 expression, while WT1 regulates intracellular Ca^{2+} homeostasis by inhibiting STIM1 expression (159). In addition, aberrant expression of STIM1-independent calcium channels (such as CaV2.3) promotes Wilms tumour recurrence through the MAPK pathway (160). Furthermore, reduced EGR levels are significantly associated with a suboptimal patient response to chemotherapy (161). Thus, the action of WT1 may suppress tumours by inhibiting Ca^{2+} signalling, while EGR1 upregulation and enhancement of Ca^{2+} signalling may promote tumour recurrence and progression.

EGR2-mediated regulation of progenitor-exhausted T cell differentiation. The role of EGR in differentiation is significant in the immune escape mechanism of tumours. T cell factor 1 (TCF1) and Slamf6-depleted progenitor T cell populations are essential in cancer immune evasion, while EGR2 expression in these T cells regulates their differentiation process. Sustained antigen recognition induces high EGR2 expression in depleted and effector $CD8^+$ T cells, while selective EGR2 expression in $TCF1^+$ progenitor cells is progressively lost as these cells transition to a more differentiated state. EGR2 maintains the identity of progenitor-type depleted T cells and plays a vital role in tumour immune escape by regulating transcriptional and epigenetic networks (162). Specifically, EGR2 works with TCF1 to preserve the self-renewal capacity of progenitor-exhausted T cells (Tpex cells; $TCF1^+PD\text{-}1^+$) by regulating stem cell-related genes, including Slamf6 (163,164). Under chronic antigenic stimulation, EGR2 prevents premature Tpex differentiation into terminally depleted $Tim\text{-}3^+PD\text{-}1^+$ cells by inhibiting the expression of genes associated with terminal differentiation such as inhibitor of DNA binding 3, nuclear receptor subfamily 4 group A member 1 and thymocyte selection-associated high mobility group box (163,165). This regulation depends on EGR2 interaction with chromatin remodelling factors (such as lysine-specific histone demethylase 1) to preserve progenitor cell identity through the inhibition of epigenetic modifications, including H3K4me2 (162,166). In the

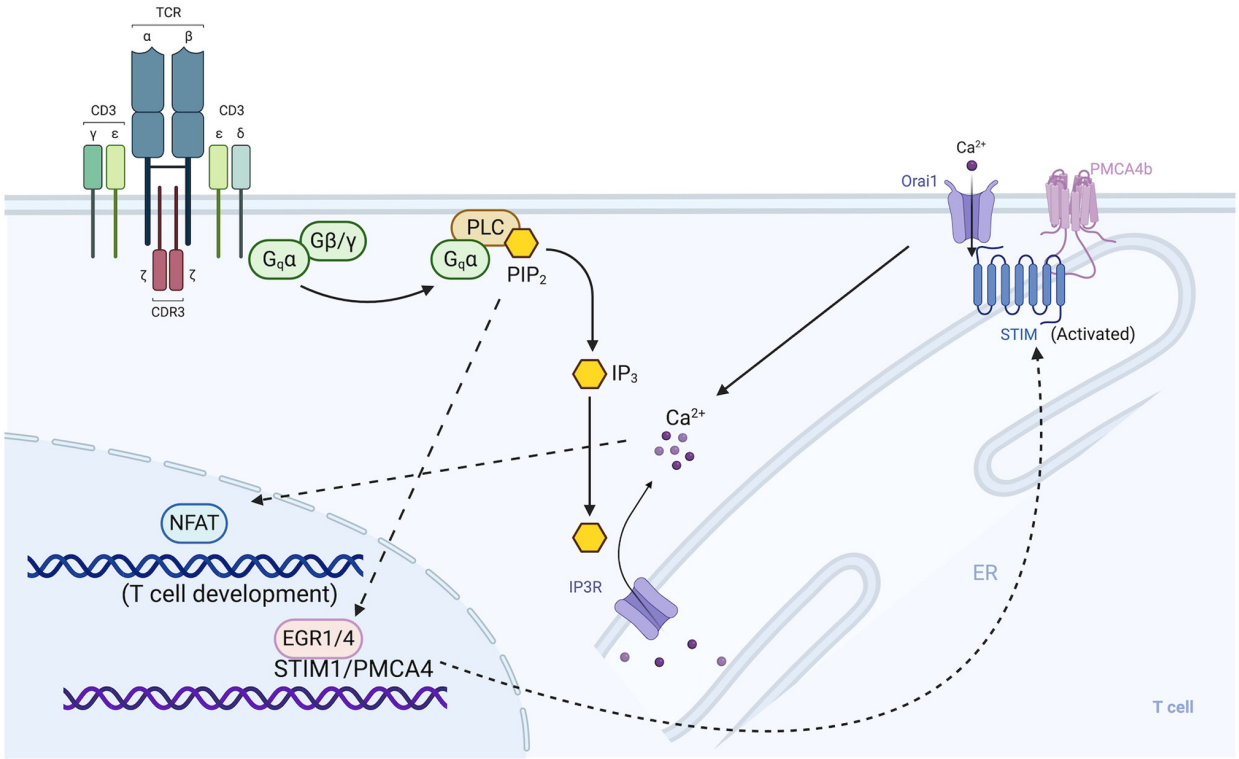

Figure 3. Regulation of Ca^{2+} signalling in EGR1/4-mediated T-cell activation. STIM1 functions by modulating the influx and efflux of Ca^{2+}.When Ca^{2+} are depleted within the ER, STIM1 oligomerises and translocates to the plasma membrane, facilitating the influx of Ca^{2+} through Orai channels. In addition, STIM1 interacts with PMCA through its serine- and threonine-rich structural domains, hence impeding its functionality. ER, endoplasmic reticulum; STIM1, stromal interaction molecule 1; PMCA, plasma membrane calcium ATPase.

TME, high EGR2 expression exacerbates immune escape by enhancing an immunosuppressive phenotype while sustaining progenitor-depleted T cell survival; EGR2 deficiency results in accelerated functional exhaustion of $CD8^+$ tumour-infiltrating lymphocytes and uncontrolled tumour growth (167); however, EGR2 mitigates immunopathological damage induced by T cell overactivation by modulating the expression of inhibitory receptors including PD-1 and lymphocyte-activation gene 3 (168,169). This balance may determine that therapies targeting EGR2 must be precisely regulated.

B cells. In B lymphocyte responses, EGR1 expression is directly regulated by antigen activation through the B cell receptor (BCR) activation of protein kinase C signalling. The maturity level of the B cell significantly regulates BCR signalling; in mature B cells, EGR1 expression is often correlated with cellular proliferative and growth responses, while in immature B cells, it may provide contrary effects (170). The expression of EGR2 and EGR3 are induced in B cells by chronic antigenic stimulation through the NFAT pathway (170). Deletion of EGR2 and EGR3 may result in an abnormal accumulation of B1 cells; for instance, in mouse models, EGR2 and EGR3 defective mice exhibit significantly increased B1 cells inside the peritoneal cavity, spleen and bloodstream, and this accumulation is closely associated with CLL pathogenesis (16). EGR2 inhibits the differentiation of B cells into plasma cells by modulating the expression of specific genes (such as PR domain containing 1, with zinc finger/B-lymphocyte-induced maturation protein 1). However, when EGR2 mutations disrupt this regulation, B cells may undergo aberrant proliferation and differentiation, contributing to CLL development and progression. Further analysis has revealed that EGR2 mutations in CLL can impair the normal function of B cells by modifying their regulation of key target genes, hence facilitating leukaemia onset (16). In addition, B cells mitigate autoimmunity by secreting IL-10 and TGF-β, which are characteristic features of regulatory B cells (Bregs) and central mediators of their immunosuppressive effects (171,172). IL-10 and TGF-β facilitate the development of anti-inflammatory cells (Tregs), thus effectively mitigating autoimmune diseases (173). Bregs are a subset of specialised B cells with immunomodulatory roles, and hypoxic conditions inside the TME influence their differentiation. Under hypoxic conditions, B cells upregulate EGR1 and EGR3 expression through activation of the MAPK pathway, which modulates the synthesis of the downstream immunosuppressive factors, TGF-β1 and IL-10. This pathway facilitates the conversion of B cells into Bregs and enhances the differentiation and immunosuppressive capabilities of Tregs through the TGF-β1, IL-10 and TNF secreted by Bregs, promoting immune escape of tumours (29).

Macrophages. The EGR gene is activated in myeloid cells through cytokine regulation. Preliminary studies in leukaemia cell lines demonstrated that EGR1 expression was upregulated in response to IL-3, granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF), although only M-CSF has been shown to induce EGR1 expression in normal bone marrow progenitor cells (174). Additionally, EGR1 and EGR2 expression is increased during monocyte

differentiation in response to phorbol 12-myristate 13-acetate stimulation. EGR1 is essential in macrophage differentiation by rapidly responding to M-CSF stimulation in mouse bone marrow progenitors; however, it is insensitive to G-CSF (175). In leukaemia cell lines and bone marrow progenitor cells, the use of EGR1 antisense oligonucleotides inhibits macrophage differentiation; however, it has no effect on granulocyte differentiation (174). Further studies have demonstrated that EGR1 overexpression in cell lines and primary myeloid cells promotes macrophage differentiation; however, this differentiation is counterbalanced by inhibiting other myeloid lineages (174-176). EGR1 is not essential for macrophage differentiation, as myeloid cells in EGR1-deficient mice still differentiate into macrophages upon M-CSF stimulation, indicating that other EGR proteins may substitute for EGR1 function (175). Additionally, another study demonstrated that PU.1 re-expression in PU.1-deficient myeloid cells induced EGR2 upregulation and promoted macrophage differentiation. During macrophage differentiation, EGR1 and EGR2 were upregulated in immature foetal liver myeloid progenitors or bone marrow common myeloid progenitors, while no significant changes were observed in EGR3 and EGR4 (176). However, subsequent a study demonstrated that EGR1 and EGR3 expression levels were significantly increased in myeloid cells when M-CSF induced myeloid differentiation into macrophages, while EGR2 was weakly induced and EGR4 could not be detected (177). EGR2, in particular, may play a key role in monocyte differentiation into macrophages, and the expression of this transcription factor is fine-tuned during this process (178). Additionally, the role of EGR1 in monocyte development is critical, especially in enhancer regions that regulate monocyte developmental genes (such as colony stimulating factor 1 receptor); however, differentiated macrophages exhibit a different EGR1 binding pattern than undifferentiated monocytes. Furthermore, in mature macrophages, EGR1 upregulation inhibits the activation state of macrophages by reducing cytokine secretion, inhibiting the expression of stimulatory ligands, including CD86, and increasing the expression of immune checkpoint molecules such as CTLA4 and PD-1 (179). Although EGR1 expression levels are decreased in mature macrophages, especially after lipopolysaccharide (LPS) stimulation, similar to other EGR family members, including EGR2, they still play important regulatory roles in mature myeloid cells (179).

Macrophages can be classified into two polarised states: M1- and M2-like phenotypes. M1-like macrophages are induced by Th1-associated cytokine (such as IFN-γ) and microbial products (including LPS) and exhibit high levels of major histocompatibility complex (MHC) class II and CD86, which efficiently stimulate $CD4^+$ T cells and drive a potent pro-inflammatory response, including nitric oxide production and IL-1β, IL-6 and TNF-α pro-inflammatory cytokines (180,181). However, M2-like macrophages are induced by Th2-associated cytokines (such as IL-4 or IL-13), express low levels of CD86 and typically act as promoters of tissue repair during the resolution phase of inflammation. Characteristic markers of M2 macrophages include arginase, found in inflammatory zone 1 (Fizz1) and chitinase-like protein 3, and M2 macrophages also produce anti-inflammatory cytokines, including IL-10 and TGF-β1. M1- or M2-like phenotypes have pro-inflammatory and anti-cancer or pro-cancer and anti-inflammatory roles, respectively (181,182) (Fig. 4). EGR2 is regarded as a novel M2-type marker that is essential for the selective activation of macrophages, and its expression plays a key role in the polarisation state of macrophages (183). EGR2 is expressed to some extent in inactivated M0 macrophages, while it is regulated in M2-type macrophages; however, EGR2 expression is significantly reduced in M1-type macrophages, and its expression level remains low after stimulation (17). EGR2 plays a significant role in regulating M1 and M2 markers, particularly under M2 stimuli (including IL-4 and IL-13), where the upregulation of EGR2 promotes the expression of M2 signature markers and the upregulation of M1 markers during M2 to M1 transition. Conversely, EGR2 expression is downregulated under M1 stimuli (including IFNγ and LPS), and low levels of EGR2 are associated with the maintenance of M1 markers and weak upregulation of M2 markers, while EGR2 knockdown results in the decreased expression of M1 markers (17). The PPARγ transcription factor is involved in M2 polarisation, while its upstream transcription factor, CCAAT/enhancer-binding protein (CEBPβ), regulates the expression of markers in response to direct stimulation of M1 and M2 phenotypes (181). Additionally, EGR2 expression is regulated by CEBPβ, which is highly expressed and negatively regulates EGR2 levels in M1 macrophages. CEBPβ knockdown results in the upregulation of EGR2 expression, which affects the expression of M1 and M2 markers. However, EGR2 positively regulates CEBPβ expression, and EGR2 knockdown results in decreased CEBPβ levels (182,183) (Fig. 4B). Therefore, the reciprocal regulatory relationship between EGR2 and CEBPβ is essential for macrophage activation and polarisation. EGR2 promotes the expression of M1 and M2 markers by regulating CEBPβ, and this mechanism is correlated with the ability of macrophages to respond to inflammatory stimuli. However, low levels of EGR2 expression indicate that macrophages are less responsive to activation signals.

The selective polarisation of macrophages by IL-4 is essential for maintaining immune homeostasis *in vivo*. IL-4 activates the signal transducer and activator of the transcription 6 (STAT6) signalling pathway by binding to the IL-4 receptor (IL-4Rα). Although STAT6 activation is transient following IL-4 stimulation, it can initiate several sustained transcriptional changes (184) (Fig. 4A). EGR2 was identified as an important factor in IL-4/IL-13-induced alternative activation of macrophages, with its expression significantly upregulated in these cells. IL-4 promotes EGR2 expression through the STAT6 pathway, while EGR2 upregulation relies on self-regulatory mechanisms. EGR2 is essential in late enhancer activation during IL-4-mediated processes, specifically in maintaining BRD4, the switch/sucrose non-fermentable complex and RNA polymerase II binding to enhancers and in regulating H3K27ac modification and chromatin accessibility (30,75). Within 24 h of IL-4 stimulation, EGR2 selectively occupies persistent and late enhancers, particularly those sites that regulate the IL-4 response. After peak STAT6 activity, EGR2 binds to these late enhancers, forming a self-sustaining feedback loop that allows the expression of IL-4-responsive genes to be maintained even when STAT6 is dissociated from chromatin (30,75). EGR2 is essential in the transcriptional regulation of IL-4-responsive

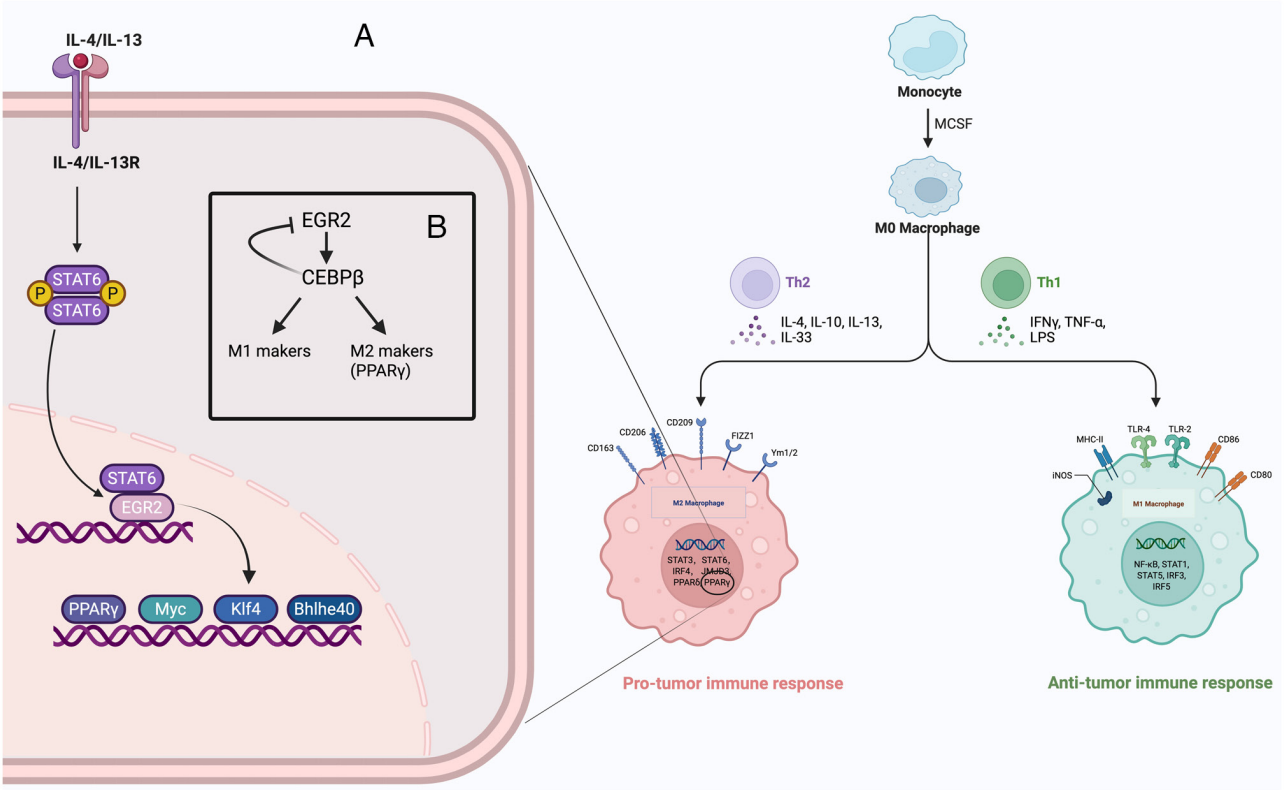

Figure 4. (A) Following IL-4 or IL-13 stimulation of macrophages, STAT6 is phosphorylated and translocated to the nucleus, where it binds to enhancers associated with the EGR2 regulatory site, activating EGR2 expression. EGR2 subsequently binds to *de novo* enhancers in its target genes and promotes downstream effector gene activation (such as PPARγ, MYC, Klf4 and Bhlhe40), which triggers a specific polarised transcriptional programme. (B) In M1 and M2 type macrophages, EGR1 promotes M1 or M2 marker expression by upregulating CEBPβ, which promotes M1 or M2 marker expression. In M1 macrophages, high levels of CEBPβ inhibit EGR2 expression. IL, interleukin; STAT6, signal transducer and activator of transcription 6; EGR, early growth response; PPARγ, peroxisome proliferator-activated receptor γ; MYC, myelocytomatosis oncogene; KLF4, Krüppel-like factor 4; BHLHE40, basic helix-loop-helix family member e40; C/EBPβ, CCAAT/enhancer-binding protein β.

genes, and almost all IL-4-induced and repressed gene expression is dependent on EGR2 involvement (174). Unlike STAT6, EGR2 is not directly involved in STAT6 regulation; instead, it binds to late enhancer regions devoid of STAT6 binding sites, which affects gene expression. EGR2 can activate and inhibit several downstream transcription factors, including PPARγ, Klf4, MYC and basic helix-loop-helix family member e40, which is essential in alternative activation (185,186) (Fig. 4A). There may be synergistic effects between EGR2 and alternative activators including PPARγ and retinoid X receptor (RXR), especially in response to IL-4 stimulation, where PPARγ upregulation enhances the binding of RXR heterodimers to *de novo* enhancers, which regulates IL-4-responsive gene expression and facilitates the strong binding of STAT6 in response to repeated stimulation (185-187). Additionally, EGR2 may regulate the inhibition of LPS- or IFN-γ-induced inflammatory responses in IL-4-treated macrophages (188,189).

NK cells. The functional inhibitory effect of the TME on NK cells is an essential mechanism of tumour immune escape. Hypoxia, metabolic stress and the accumulation of immunosuppressive cells result in diminished NK cell activity, which weakens their ability to kill tumour cells (190). In tumours, including acute myeloid leukaemia and glioma, high EGR2 and diacylglycerol kinase α (DGKα) levels are correlated with poor patient prognosis, while low levels of expression indicate improved survival. In xenograft tumour models, NK cell dysfunction is closely associated with high EGR2 and DGKα expression (190). The EGR2 and DGKα transcription factors play key negative regulatory roles in inhibiting NK cell function, particularly in preserving the inactive and tolerogenic state of NK cells (Fig. 5). Inhibiting the expression of EGR2 and DGKα markedly enhances NK cell activity, as evidenced by an increased degranulation response, ERK phosphorylation and intracellular calcium signalling (190). Furthermore, silencing EGR2 reduces the expression of the immune checkpoint molecule, PD-1, further enhancing NK cell activity (190) (Fig. 6). These results indicate that targeted modulation of the EGR2 and DGKα pathways restores NK cell function and serves as an important therapeutic strategy to counteract tumour immunosuppression.

MDSCs and cancer-associated fibroblasts (CAFs). In the TME, EGR family members, especially EGR1, have relatively complex interactions with MDSCs and CAFs (191,192). EGRs are essential in regulating tumour immune escape, stromal remodelling and angiogenesis. EGR1 serves as an essential regulatory factor in the differentiation of MDSCs; it facilitates the differentiation of MDSCs by directly interacting with the promoter region of the MyoG gene while simultaneously inhibiting their proliferation (191). This process entails

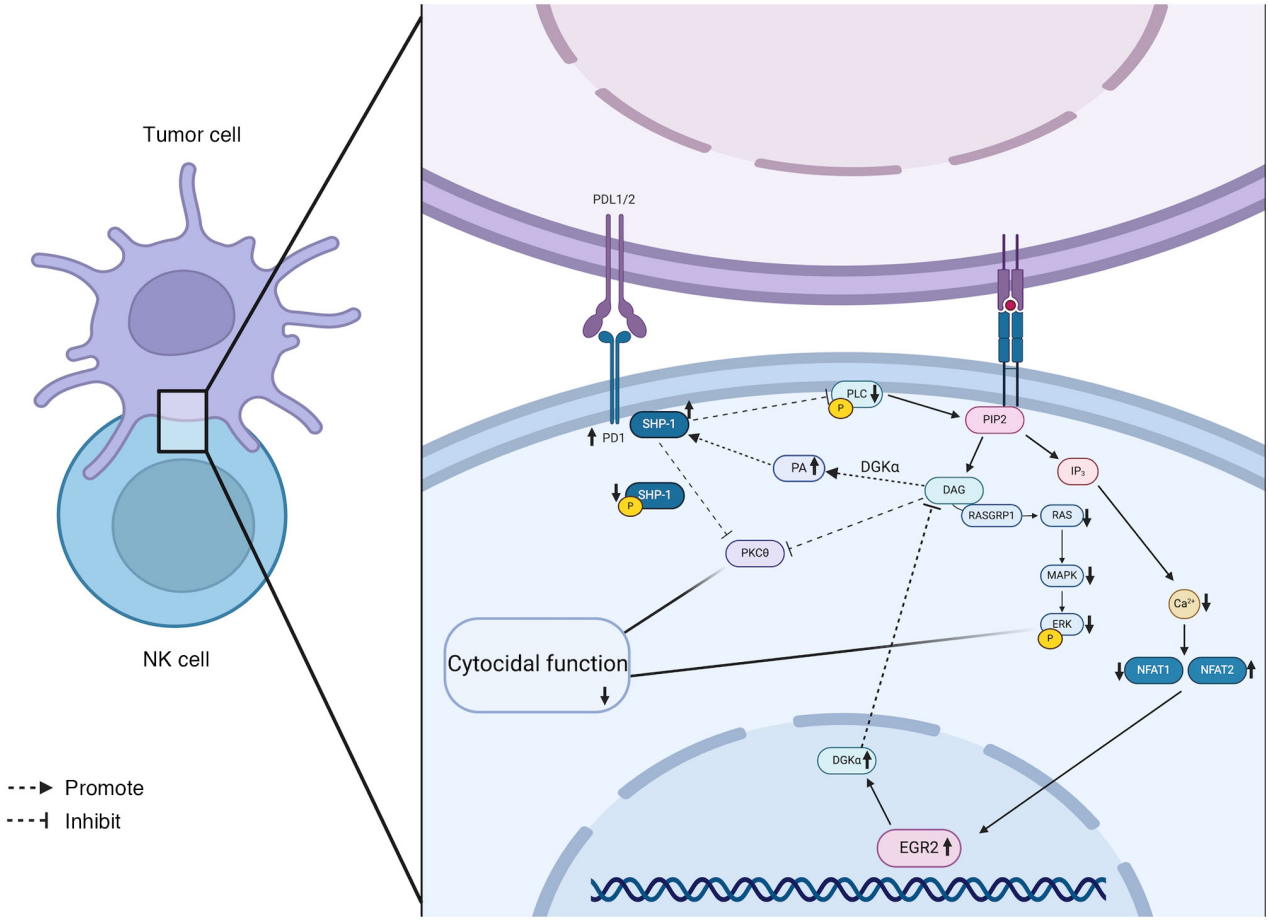

Figure 5. Schematic diagram of the signalling pathway in anergic NK cells. In anergic NK cells, the EGR2 expression level is elevated, which subsequently triggers an increase in DGKα. This change prompts the conversion of DAG to phosphatidic acid, which subsequently recruits more SHP-1 to the cell membrane. Therefore, DAG availability is limited, thereby inhibiting protein kinase Cθ activity and preventing the regulation of SHP-1 function. Dephosphorylation of SHP-1 further inhibits the phosphorylation of linker for activation of T cells and PLCγ1/2, blocking the initiation of downstream signalling. Additionally, DAG deficiency inhibits DAG-mediated activation of the Ras/Raf/MEK/ERK signalling pathway and IP3-mediated calcium influx. SHP-1, Src homology 2 domain-containing phosphatase-1; PLCγ1/2, phospholipase C γ 1/2; NK, natural killer; DGKα, diacylglycerol kinase α; DAG, diacylglycerol; SHP-1, Src homology 2 domain-containing phosphatase-1; PKCθ: protein kinase C θ; LAT, linker for activation of T cells; PLCγ1/2, phospholipase C γ 1/2; IP_3, inositol 1,4,5-triphosphate.

a negative regulation of the Toll-like receptor signalling pathway, subsequently triggering the abnormal accumulation of MDSCs in the context of chronic inflammation or chemotherapy-induced cellular senescence [for instance, in high-risk myeloid malignancies where del(5q) results in EGR1 haploinsufficiency] (191). In addition, EGR2 promotes crosstalk between MDSCs and immune cells, including T cells and macrophages, by regulating cytokine networks, including IL-8, thereby contributing to an immunosuppressive microenvironment (192). Additionally, EGR1 is essential in CAFs. In placental site trophoblastic tumours, high EGR1 expression in CAFs activates VEGFA, facilitating angiogenesis and expediting tumour metastasis (193). In ovarian cancer, EGR1 synergistically drives the process of EMT with high mobility group AT-hook 1, while IL-6 secreted by CAFs further enhances tumour invasiveness through the EGR/Runx1 axis (194). In adult T-cell leukaemia/lymphoma, a subset of CAFs display high levels of EGFR-related transcripts, particularly EGR1 and EGR2, which stimulate $CD4^+$ T-cell proliferation through the FGF7/FGF1 and PDGFA-PDGFRA/B pathways, which may drive tumour malignant progression (195). In colorectal cancer, EGR4 expression is significantly associated with the abundance of CAFs, which promotes CAF activation and extracellular matrix remodelling through activation of the TNFα/NF-κB pathway, enhancing the proliferation and invasive ability of cancer cells, altering the CAF phenotypes and exacerbating the tumour-promoting effects, possibly by modulating inflammatory factor secretion and chromatin assembly-related pathways (65).

6. Regulatory role of EGR in tumour metabolism

Glycolysis. Cancer is increasingly recognised as a metabolic disease, and the abnormal alteration of energy metabolism in cancer cells is one of the hallmarks of cancer (196). The Warburg (aerobic glycolysis) effect is a major pathway of energy acquisition in cancer cells and is regarded as an important marker of tumourigenesis (197). Among the underlying mechanisms of the Warburg effect, TAp73, a homologue of the tumour suppressor p53, is essential in regulating phosphofructokinase L (PFKL) expression, which in turn promotes glycolysis and facilitates tumour cell proliferation (198).

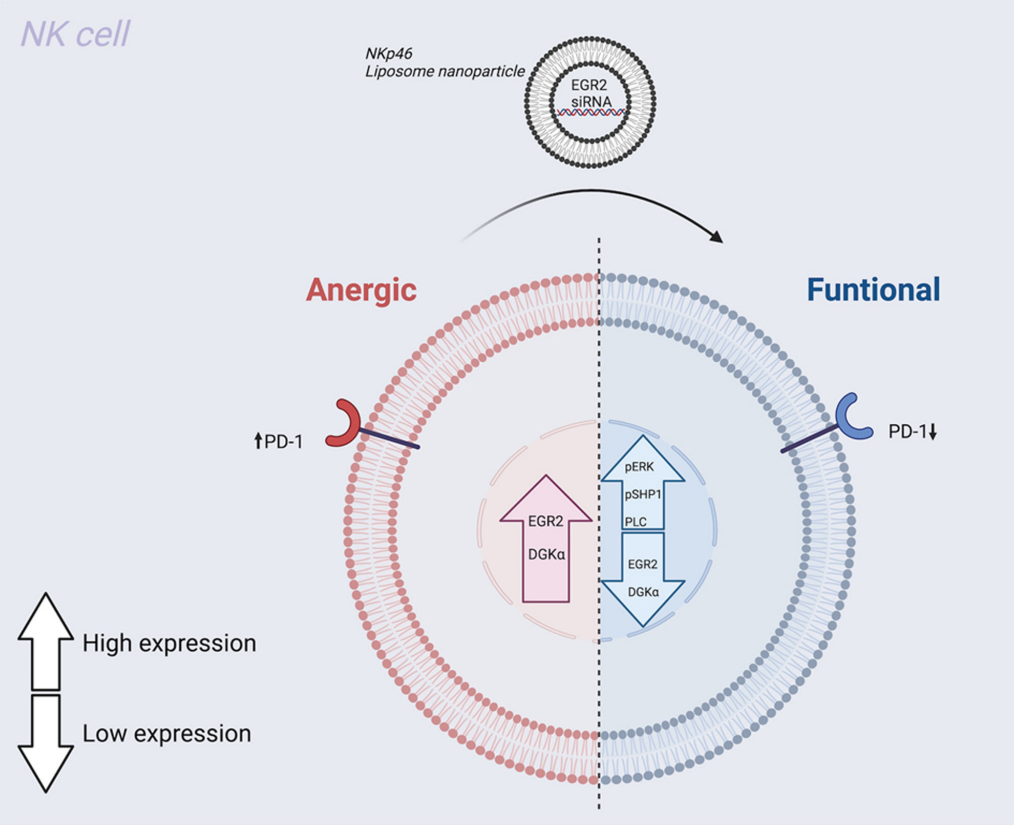

Figure 6. Functional reprogramming of anergic NK cells. NK, natural killer; EGR2, early growth response 2; DGKα, diacylglycerol kinase α; SHP-1, Src homology 2 domain-containing phosphatase-1; PKCθ, protein kinase C θ; LAT, linker for activation of T cells; PLCγ1/2, phospholipase C γ 1/2.

Additionally, targeted inhibition of PFKL is considered an effective antitumour strategy. In HCC models, the downregulation of EGR1 expression enhances glycolysis in tumour cells, while EGR1 overexpression binds to the promoter region of PFKL, resulting in transcriptional repression of PFKL and subsequent inhibition of glycolysis, reducing glucose consumption and lactic acid production, significantly inhibiting tumour proliferation and growth (199).

Circadian rhythms: Lipid metabolism and glucocorticoid rhythmicity. Complex interactions exist between circadian imbalances and cancer processes across various cancer types, and the biological clock, an evolutionarily highly conserved mechanism, is responsible for regulating the synchronisation of physiological processes and behaviour with the circadian cycle (200). Molecular clocks, focused on the transcription factors, brain and muscle arnt-like 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK), regulate the rhythmic expression of most protein-coding genes in the mammalian genome, thereby affecting various key physiological activities, including sleep, feeding, hormone secretion, metabolism and immune function (200,201). In a healthy physiological condition, EGR1 modulates rhythm by interacting with the feedback loop of the biological clock. Following stimulation of EGR1 by signals from the master clock, EGR1 binds to the promoter of the period circadian regulator 1 (Per1) gene and activates Per1 transcription, which inhibits Per2 and reverse-Erb A (Rev-erbs) expression. Rev-erbs repression contributes to significant rhythmic fluctuations in BMAL1, which interacts with EGR1 to activate its transcription, forming an EGR1/Per1/BMAL1 feedback loop that helps to synchronise the hepatic biological clock with the master biological clock, thereby ensuring circadian stability (202). EGR1 dysregulation in this process can result in aberrant cell cycle regulation, thereby facilitating cancer cell proliferation. In cancer cells, essential clock genes, including BMAL1 and CLOCK, are commonly dysregulated or mutated. For instance, in HCC, BMAL1 and CLOCK facilitate tumour cell proliferation by modulating cell cycle-related factors. Furthermore, inhibition of BMAL1 and CLOCK expression results in increased toxicity in HCC cells, activates apoptotic pathways and impedes normal cell cycle progression (203).

EGR1 and BMAL1/CLOCK complexes modulate the transcription of lipid metabolism genes [including cell death-inducing DFFA-like effector A (Cidea)], acting as a bridge between circadian rhythms and metabolic homeostasis in peripheral organs (202). EGR1 deficiency or dysfunction can disrupt lipid metabolism, which affects the energy supply and proliferation of tumour cells. Additionally, by regulating fatty acid uptake and lipid droplet formation, EGR1 may facilitate tumour growth and metastasis (202). During ageing, the circadian rhythmic expression of EGR1 is modified, leading to a change in the timing of its peak expression, which affects the expression of lipid metabolism genes, specifically the delayed phase of Cidea expression. Without EGR1, triglycerides accumulate in the liver due to increased fatty acid uptake and lipid droplet formation, while the rhythmic expression of lipid metabolism genes is disrupted, resulting in metabolic dysfunction in the liver. Ageing leads to decreased EGR1 expression,

and the dysregulation of circadian rhythms leads to a decoupling of the metabolic stability of peripheral organs (the liver) from the rhythms of the master biological clock, resulting in a decline in metabolic function (202).

EGR3 functions as a circadian gene within the suprachiasmatic nucleus and may exhibit a similar rhythmic regulatory mechanism with EGR1 (203). Considering that circadian rhythms are closely related to glucocorticoid secretion, the two may affect glucocorticoid secretion rhythms by regulating the expression of core biological clock genes (such as BMAL1 and Per1). In humans, glucocorticoids exist mainly as cortisol, while in rodents, they are primarily corticosterone; however, corticosterone is secreted in lower amounts in humans and is more likely to function as metabolic intermediates of cortisol (204). Rhythmic cortisol secretion is now recognised as an important predictor of survival in lung and breast cancer (200). The secretion of glucocorticoids (such as cortisol and corticosterone) is regulated by core biological clock genes (including BMAL1 and Per1), and their rhythmic release is critical for maintaining a stable circadian rhythm. Disruption of the secretion of these hormones can disrupt the biological clock system, which provides favourable conditions for tumourigenesis and tumour progression. Additionally, disruption of glucocorticoids (such as cortisol and corticosterone) can alter EGR1 and EGR3 expression, thereby interfering with the normal functioning of circadian rhythms and destabilising the biological clock, which triggers various responses, including metabolic changes that facilitate tumour cell development (205). However, differences exist between cortisol and corticosterone, with cortisol potentially regulating EGR family members (EGR1) in humans through a more complex mechanism that encompasses a broader transcriptional network through the dual action of the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) (206). The inhibition of T-cell activation and pro-inflammatory cytokine secretion by the GR may indirectly affect the immunoregulatory pathways in which the EGR family is involved. For instance, the role of EGR1 in oxidative stress and aldosterone synthesis may be inhibited by cortisol-GR signalling, thereby facilitating tumour immune escape (207,208). However, the role of rodent corticosterone has received less attention due to its diminished affinity for the GR and possibly weaker regulation of the EGR family. Corticosterone is more likely to be metabolised into its active form by 11β-hydroxysteroid dehydrogenase or to bind to the MR, thereby activating specific signalling pathways and indirectly regulating EGR1-related genes (209,210). In a tongue squamous cell carcinoma model, corticosterone promotes cancer cell migration and invasion by downregulating EGR1, while EGR1 overexpression inhibits these behaviours by regulating dual-specificity phosphatase 1 (211). Accordingly, the relationship between EGR and circadian rhythms, especially the interaction with the secretion of glucocorticoids (such as cortisol and corticosterone), may affect cancer development, progression and recurrence through multiple mechanisms.

7. Regulation of differentiation mechanisms by EGR in tumours

The interaction between neurones and cancer cells is one of the key processes in tumourigenesis and tumour progression, and cancer neurogenesis has been proposed as a new hallmark of cancer (212-214). The nervous system is extensively distributed throughout the body; it regulates organ development, maintains homeostasis and promotes cellular plasticity and damage repair by innervating tissue nerves while ensuring normal tissue function. However, the nervous system plays an essential regulatory role in tumour growth and metastasis (215-217). Colorectal cancer stem cells (CSCs) can differentiate into neurones, and these neurones can synapse with nerve fibres within the tumour (218). This process is essential for tumour onset and progression, and EGR2 serves as a key regulator of tumour neurogenesis. EGR2 ensures the survival of CSCs and enhances tumour progression by modulating the expression of homeobox genes, which are master transcription factors in embryonic development, and SRY-box (SOX) genes, which regulate neural stem cell fate (218). In the leukaemia environment, normal HSPCs protect themselves by assuming a quiescent state; however, their differentiation is significantly inhibited. EGR3 and EGR1 have been identified as key genes regulating this suppressed state. EGR3 is highly expressed in leukaemia bone marrow, and its ectopic upregulation induces cell cycle arrest and diminishes the remodelling capacity of HSPCs. EGR3 deletion enhances the proliferation and implantation potential of HSPCs and mitigates their quiescent state, indicating that EGR3 is a potent proliferation suppressor. Similarly, EGR1 upregulation significantly inhibits HSC function and modulates the state of HSPCs in leukaemia (219). Additionally, EGR3 can induce melanoma cell differentiation toward Schwann cell-like differentiation to inhibit tumour progression, mimicking nevus maturation, which causes significant changes in cellular morphology, decreased motility and reduced melanin production. These effects are achieved by modulating myelin protein zero (MPZ) and collagen type I α 1 chain (COL1A1) expression levels and involving SOX10-dependent and SOX10-independent regulatory mechanisms (220).

8. EGRs: A family of key regulators in tumour therapy

Combined targeted therapy and natural compounds. A clinical trial has demonstrated that regimens combining calcium channel blockers (CCBs) with CD20-targeted agents yield shorter progression-free survival and overall survival times compared with patients receiving CD20-targeted therapies alone (221). CD20-targeted therapies, including rituximab and obilizumab, induce cell death by facilitating the calcium ion influx through various mechanisms, which increases EGR1 expression. CCBs significantly inhibit EGR1 activation by preventing the influx of calcium ions, which attenuates the efficacy of CD20-targeting drugs (221). Thus, EGR1 may be a potential biomarker for predicting response to CD20-targeted therapy.

Natural compounds can modulate EGR1 expression, which affects the behaviour of tumour cells. For instance, quercetin induces apoptosis in colon cancer cells by increasing EGR1 levels and promoting NAG1 gene expression; the EGR1 binding site is located in the NAG1 promoter region, which is one of the central mechanisms of this process (222). Similarly, resveratrol induces apoptosis in cancer cells by upregulating EGR1. Resveratrol can synergistically inhibit lung cancer cell

proliferation by driving the expression of suicide gene therapy vectors through the EGR1 promoter (223). Berberine affects macrophage polarisation processes by regulating EGR2, consequently modifying the composition and function of immune cells in the TME. Macrophages transitioned from an M2-like polarised state with reduced immunosuppressive capacity and significantly enhanced antitumour immune responses after exposure to berberine. For instance, in the TME, conditioned medium (CM) induced bone marrow-derived macrophages to polarise towards M2-type TAMs, accompanied by an upregulation of EGR2 mRNA expression levels. This polarisation process could be inhibited by berberine treatment, which effectively inhibited CM-induced EGR2 mRNA upregulation (224).

Resistance to chemotherapy and radiotherapy. Cisplatin is the primary chemotherapeutic agent for NSCLC; however, chemoresistance significantly affects treatment efficacy and patient prognosis. Recently, researchers have endeavoured to explore new strategies, and the potential of natural compounds to overcome drug resistance has attracted widespread attention. For instance, the natural compound α-hederin, extracted from *Nigella sativa*, plays an important role in reversing cisplatin resistance in NSCLC. Specifically, α-hederin enhances the nuclear localisation of EGR1, inhibits the transcription of miR-96-5p and alleviates its inhibition of DDIT3, thereby activating the DDIT3/ATF3 pathway and inducing ferroptosis (225). Notably, EGR1 does not act in isolation, and the synergistic effect of EGR1 and p53 in cisplatin treatment can enhance its anticancer effect in NSCLC (226). This finding suggests that co-regulation of EGR1 and other key molecules may offer additional therapeutic strategies to overcome chemotherapeutic resistance.

In addition, the role of EGR1 extends beyond NSCLC, with emerging studies in other types of cancer indicating its diverse functions. For instance, in bladder cancer, EGR1 reduces tumour invasion and gemcitabine resistance by directly inhibiting LINC00839 expression; it regulates cancer cell migration, invasion and drug resistance through the LINC00839/miR-142 axis and its downstream target, SOX5 (227). In breast cancer, medication resistance significantly impairs the therapeutic efficacy. In tamoxifen (Tam)-sensitive and Tam-resistant (TamR) breast cancer cell models, recombinant glial cell line-derived neurotrophic factor (rGDNF) treatment can activate the GDNF/RET/EGR1 signalling pathway, leading to the binding of phosphorylated ELK1 to the EGR1 promoter, thereby increasing EGR1 expression. Subsequently, EGR1 further binds to the GDNF and Cyclin D1 (CCND1) promoters, forming a positive feedback loop and upregulating CCND1 expression, driving cell proliferation and drug resistance (228). EGR3 is essential in TamR breast cancer. EGR3, as an estrogen receptor α responsive factor, significantly upregulates oestrone (E1) expression and Tam in TamR cells and promotes their transcription by directly binding to the promoter region of the MCL1 anti-apoptotic gene, thereby increasing cellular resistance to apoptosis and facilitating drug resistance. Additionally, E1 significantly reduces Tam-induced apoptosis by upregulating EGR3 expression (20). This mechanism further highlights the potential of targeting EGR in breast cancer therapy. Gemcitabine is a key drug in the treatment of all stages of pancreatic cancer; however, drug resistance remains a significant challenge. EGR1 regulates multidrug resistance protein 1 (MDR1) expression in pancreatic cancer cells by binding to its promoter, facilitating resistance to gemcitabine. EGR1 knockdown inhibits MDR1 expression, which enhances apoptosis, attenuates tumour proliferation and significantly improves the chemotherapeutic efficacy of gemcitabine (229). These findings provide a new research direction for combination therapy in pancreatic cancer. A similar drug resistance issue has been observed in advanced thyroid cancer, where B-raf proto-oncogene (BRAF) mutations are commonly found in advanced thyroid cancers, such as papillary thyroid carcinoma and anaplastic thyroid carcinoma), and a significant increase in invasiveness is observed in BRAF inhibitor (BRAFi) resistant thyroid cancer cells. The expression of the extracellular matrix protein, FN, is significantly upregulated after BRAFi treatment, which increases the invasiveness of cancer cells. Moreover, the BRAFi-induced increase in invasiveness is dependent upon the expression of the EGR1 transcription factor, which is downregulated by BRAF/ERK1/2 co-inhibitory treatment, and deletion of EGR1 inhibits the BRAFi-induced increase in invasiveness (22). This indicates that EGR1 inhibition may be a potential strategy to mitigate BRAFi resistance. In glioblastoma, temozolomide is a commonly employed chemotherapeutic agent whose mechanism of action involves inhibiting the activity of LINC00470. A previous study demonstrated that LINC00470 activates SOX4 expression through EGR2, while temozolomide further inhibits SOX4 expression by inhibiting the transcriptional activation of EGR2 by LINC00470, thereby effectively preventing glioblastoma progression (22) (Table I).

Additionally, radiotherapy, an important treatment for NSCLC, depends on the modulation of molecular mechanisms to improve efficacy. Ionising radiation (IR) induces lipid peroxidation and ferroptosis in cancer cells by inducing ROS, a process regulated by multiple factors (230). Additionally, miR-139 may be a novel radiosensitiser in NSCLC by inhibiting the nuclear factor erythroid 2-related factor 2 (NRF2) pathway. Furthermore, miR-139 disrupts NRF2 signalling by directly targeting c-Jun and karyopherin α2, enhancing IR-induced lipid peroxidation and ferroptosis. IR induces miR-139 expression through the EGR1 transcription factor, which binds to the miR-139 promoter and activates its transcription (230) (Table I). These findings indicate that the multifunctionality of EGRs offers new targets for improving the efficacy of chemotherapy and radiotherapy in cancer.

Nanodelivery to reprogramme immune cell function. The functional status of macrophages and NK cells within the tumour immune microenvironment is essential for antitumour therapy. Recently, research teams have explored strategies to target the EGR family (EGR2 and EGR3) using nanodelivery systems, offering new ideas for tumour therapy. First, by constructing a vitamin E and sphingomyelin (VitE:SM) nanoemulsion delivery system, the polarisation state of macrophages can be effectively reprogrammed. Specifically, the expression of M2-type markers (such as EGR2) was significantly decreased and the expression of M1-type markers was significantly increased after treatment of macrophages with this nanoemulsion, thereby converting macrophages

Table I. Mechanisms of EGRs in chemotherapy and radiotherapy of various cancer types.

Cancer type	Drug/Treatment	Mechanism of action	(Refs.)
Non-small cell lung cancer	Cisplatin	α-Hederin enhances nuclear localization of EGR1, inhibits miR-96-5p transcription, activates the DDIT3/ATF3 pathway and induces ferroptosis. EGR1 synergizes with p53 to enhance anticancer effects.	(225,226)
Non-small cell lung cancer	Radiotherapy (IR)	IR induces ROS, triggering lipid peroxidation and ferroptosis. miR-139 suppresses the NRF2 signalling pathway, enhancing IR efficacy. EGR1 induces miR-139 expression by binding to its promoter and activating transcription.	(230)
Bladder cancer	Gemcitabine	EGR1 suppresses LINC00839 expression, reducing tumour invasion and drug resistance. Through the LINC00839/miR-142 axis, EGR1 regulates SOX5, affecting cancer cell migration, invasion and drug resistance.	(227)
Breast cancer	Tamoxifen	EGR1: rGDNF activates the GDNF/RET/EGR1 loop, increasing EGR1 expression and forming a positive feedback loop that upregulates CCND1, promoting cell proliferation and drug resistance. EGR3: Upregulated in resistant cells, it directly binds to the MCL1 promoter, enhancing its transcription, increasing anti-apoptotic capacity and conferring drug resistance.	(20,228)
Pancreatic cancer	Gemcitabine	EGR1 binds to the MDR1 promoter to regulate its expression, promoting drug resistance. Knockdown of EGR1 suppresses MDR1 expression, enhances apoptosis and improves chemotherapy efficacy.	(229)
Thyroid Cancer	BRAFi	BRAFi upregulates fibronectin expression, enhancing cancer cell invasiveness. EGR1, a downregulated gene in BRAF/ERK1/2 inhibition therapy, is required for BRAFi-induced invasiveness. Loss of EGR1 suppresses BRAFi-induced invasiveness.	(22)
Glioblastoma	Temozolomide	Temozolomide inhibits LINC00470-mediated transcriptional activation of EGR2, further suppressing SOX4 expression and preventing tumour progression.	(22)

NSCLC, non-small cell lung cancer; IR, ionizing radiation; ROS, reactive oxygen species; NRF2, nuclear factor erythroid 2-related factor 2; miR, microRNA; GDNF, glial cell line-derived neurotrophic factor; rGDNF, recombinant GDNF; RET, rearranged during transfection receptor tyrosine kinase; CCND1, Cyclin D1; LINC00839, long intergenic non-protein coding RNA 00839; MCL1, myeloid cell leukemia sequence 1; MDR1, multidrug resistance protein 1; BRAFi: BRAF inhibitor; LINC00470, long intergenic non-protein coding RNA 00470; SOX, SRY-box; EGR, early growth response; DDIT3, DNA damage inducible transcript 3; ATF3, activating transcription factor 3.

from M2-type to M1-type and enhancing their antitumour activity. Additionally, TGF-βR1 inhibitor encapsulated in VitE:SM nanoemulsions administered to tumour cells inhibited the growth of primary tumours and significantly reduced the level of TAM infiltration in the liver (231). Second, since targeting EGR2 can restore the ability of NK cells, another research team effectively administered EGR2 small interfering (si)RNA into NK cells utilising a nanoparticle-based siRNA delivery system. The anti-tumour function of NK cells was effectively activated using anti-NKp46-labelled liposome nanoparticles within a 3D organ sphere model, illustrating that this delivery system can reprogramme *in situ* NK cells, thereby enhancing their antitumour activity (Fig. 6) (190). Third, considering the role of EGR3 in differentiation, a team of researchers designed a therapeutic recombinant mRNA vaccine for melanoma utilising a P2A peptide linking the CD86 and EGR3 genes, administered through lipid nanoparticles. The vaccine significantly induced an extensive influx of immune cells, especially T cells, and facilitated the recruitment of NK cells and DCs. Similarly, serum concentrations of IFN-γ and TNF-α were significantly increased in treated mice, significantly prolonging the survival time of hormone-treated mice. Additionally, NK cells are essential in the initial immune response activation; after treatment, the expression levels of MPZ and COL1A1 were significantly upregulated in tumour tissue, while the expression of Ki-67 was reduced, indicating that the tumours exhibited Schwann cell-like features (220).

Therefore, nanodelivery strategies targeting EGR2 and EGR3 exhibit strong immunomodulatory potential and can enhance antitumour immune responses by reprogramming the functional state of macrophages and NK cells. These studies provide new insights into the role of the EGR family in tumour therapy and lay the foundation for developing nanotechnology-based precision immunotherapy strategies.

9. Future perspectives: Cutting-edge strategies to enhance the antitumour activity of TCR-T and chimeric antigen receptor (CAR)-T cells

Adoptive T-cell therapy has become an essential strategy for cancer immunotherapy. Engineered TCR-T and CAR-T cell therapies are two core immunotherapeutic platforms that precisely direct T cells against tumour antigens and have emerged as two of the most innovative and effective cancer treatments today. TCR-T cell therapy is indicated for treating solid tumours and recognises antigens on the cell membrane and intracellular tumour antigens presented by the peptide MHC, thereby eliminating the dependence on antigen expression on the surface of the target cells and allowing a broader target tumour antigen spectrum (232). TCR-T cells can be activated by a single target antigen molecule and are more sensitive to low antigen expression levels than CAR-T cells. Upon recognition of tumour cells, TCR-T cells are activated and secrete cytokines, telomerase and perforin, leading to effective tumour cell destruction (233). Previously, the regulatory mechanisms of the EGR family in T cells were examined, using EGR2 as an example, which is a crucial transcription factor regulating T cell unresponsiveness (anergy) (133,134,137). In TCR-T cell therapy, anergy is a common problem in the TME, severely compromising the ability of T cells to kill tumour cells (232,233). Regulating the signalling pathway associated with EGR2 is expected to enhance the functionality of TCR-T cells within the TME. Inhibiting TCR-T cells from entering an unresponsive state may enhance their ability to recognise and kill tumour cells, thereby increasing the anticancer efficacy of TCR-T cell therapy.

CAR-T cell therapy has demonstrated good efficacy in haematological cancer; however, drug resistance is often encountered in treating solid tumours, and results are more limited. CAR-T cells activate type I IFN signalling in response to prolonged stimulation, inducing epigenetic changes and inhibiting their antitumour effects (233,234). Knocking down the EGR2 transcription factor blocks the type I IFN-mediated inhibitory effect and enhances early memory CAR-T cell expansion, which could improve therapeutic efficacy against liquid and solid tumours. In addition, IFN-β exposure reverses the protective effect against chronic antigen-induced immune failure associated with EGR2 deficiency, indicating that EGR2 knockdown mitigates CAR-T cell dysfunction by inhibiting the type I IFN pathway (234). A further study demonstrated that the genetic characterisation of EGR2 is correlated with type I IFN-induced CAR-T cell failure and shortened patient survival, making the EGR2/type I IFN signalling pathway a new target and strategy for solid tumour treatment (234).

At present, to the best of our knowledge, there are no studies that systematically evaluate the feasibility of nanoparticle-based siRNA delivery systems for the precise introduction of EGR2 siRNA into TCR-T or CAR-T cells and their impact on antitumour function. However, this strategy has promising applications. For example, the use of liposomal nanoparticle carriers to deliver EGR2 siRNA into TCR-T cells is expected to successfully reverse the unresponsive state of T cells and enhance their killing activity in the TME. Similarly, antibody-modified nanoparticle systems have been used in CAR-T cells, and targeted EGR2 inhibition is expected to improve the durable activity and tolerability of CAR-T cells. Furthermore, in 3D tumour models, antibody-labelled liposome nanoparticles are expected to repair exhausted CAR-T and CAR-T cells through efficient delivery of EGR2 siRNA, and also significantly enhance their tumour recognition and lysis. These nanotechnology-based delivery platforms demonstrate the notable immune potential of targeting the EGR gene and open new avenues for the next generation of personalised cancer immunotherapies.

10. Conclusion

The EGR family, as key zinc finger transcription factors, exhibits complex dual regulatory roles in tumour onset, progression and treatment. In the present review, the multiple functions of the EGR family in the regulation of tumour cell proliferation, apoptosis, metastasis, angiogenesis and the immunological milieu have been systematically summarized, highlighting their important roles in tumour metabolism, differentiation and neurogenesis. EGR1, the most extensively researched member of this family, demonstrates dual pro-cancer and anticancer functions in tumour cells and influences tumour immune escape and the efficacy of immunotherapy by regulating the functional status of immune cells (including T cells, B cells, macrophages and NK cells). Additionally, the roles of EGR2, EGR3 and EGR4 in tumours, especially their unique functions in immune regulation and metabolic regulation, have been progressively clarified, offering new targets for tumour therapy. Based on the regulatory mechanism of the EGR family, the present review investigated the potential of combined targeted therapies, natural compounds, chemotherapy, radiotherapy and nanodelivery systems in tumour therapy, particularly focusing on the enhancement of the antitumour efficacy of CAR-T and CAR-T cells by modulating members of the EGR family, which represents a new strategy for overcoming tumour drug resistance and immunosuppression. In the future, in-depth studies on the molecular mechanisms of the EGR family in tumours and its interaction with other signalling pathways will facilitate the development of more precise and effective tumour therapeutic regimens and advance the development of personalised immunotherapy.

Acknowledgements

Not applicable.

Funding

This research topic has been sponsored by Yancheng Science and Technology Bureau (grant no. YCBE202421), The Special Funds for Science Development of the Clinical Teaching

Hospitals of Jiangsu Vocational College of Medicine (grant no. 20209113). The 2021 Jiangsu Provincial Health and Health Commission Medical Research Guidance Project (grant no. Z2021087), The Special Funds for Science Development of the Clinical Teaching Hospitals of Jiangsu Vocational College of Medicine (grant no. 20219105), The 2021 Yancheng Medical Science and Technology Development Plan Project (grant no. YK2021060) and the Nantong University's 2023 Academic Level Research Project (Special Project of Yancheng Third Institute; grant no. YXY-Z2023008).

Availability of data and materials

Not applicable.

Authors' contributions

RG, RW, WZ, YL, YW, HW, XL and JS conceptualized the study. RG wrote the manuscript. JS and XL reviewed the manuscript. RG, RW, WZ, YL, YW, HW, XL and JS contributed to manuscript editing. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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.

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