Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(6): 26581
https://doi.org/10.31083/FBL26581

Review

Epigenetic Mechanisms in Neuroendocrine Neoplasms: Is There a Place for Inhibitors of DNA Binding Proteins?

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Academic Editors: Hongquan Wang and Claudia Pivonello
Submitted: 15 September 2024 Revised: 19 November 2024 Accepted: 13 December 2024 Published: 30 May 2025

Abstract

Inhibitors of DNA-binding (Id) proteins constitute a family of repressor factors that modulate a multitude of cellular processes and have been linked to tumor aggressiveness, resistance to chemotherapy, angiogenesis, and worse prognosis in numerous malignancies. This review explores the role of Id proteins in the pathogenesis of neuroendocrine neoplasms (NENs). The findings revealed that this family of proteins shows significant overexpression in tumors such as small cell lung carcinoma (SCLC), neuroendocrine prostate carcinoma (NEPC), and medullary thyroid carcinoma (MTC), although the role of epigenetics in regulating Id proteins within NENs remains poorly understood, with most evidence limited to NEPC. These results underscore the potential of Id proteins not only as diagnostic biomarkers and promising therapeutic targets for the management of NENs, but also highlight the need for further research to better understand their epigenetic regulation and broader role in these tumors.

Keywords: Id; Id protein; cancer; neuroendocrine neoplasm; epigenetics

1. Introduction

Inhibitors of DNA-binding (Id) proteins represent a family of crucial transcriptional regulators involved in numerous biological processes [1]. These proteins, characterized by their ability to interfere with the binding of specific transcription factors to DNA, play a key role in cell cycle regulation, differentiation, and apoptosis.

Among the diverse cancer types where Id proteins are implicated, neuroendocrine neoplasms (NENs) stand out as a heterogeneous group of malignancies originating in the diffuse endocrine cell system. Gastroenteropancreatic NENs (GEP-NENs) have the highest incidence, followed by bronchopulmonary neoplasms (BP-NENs), with approximately 3.56 new cases per 100,000 and 1.49/100,000 respectively [2]. These tumors display considerable heterogeneity in their biological behavior, ranging from well-differentiated, slow-growing forms to poorly differentiated, aggressive variants [3]. This diversity is driven, in part, by complex molecular mechanisms, including genetic and epigenetic alterations, which influence tumor progression, therapeutic resistance, and clinical outcomes.

Despite advances in the understanding of NENs, the involvement of Id proteins in their development remains poorly characterized. Given the established significance of Id proteins in other cancers, it is critical to investigate their contribution to the molecular mechanisms underlying NENs, including the potential role of epigenetic regulation, as such an exploration could reveal novel opportunities for the development of targeted diagnostic and therapeutic strategies. This research focuses on evaluating the role of Id proteins in the development of NENs, providing a basis for future explorations to better understand these molecular interactions and their clinical implications.

2. Structure and Homeostasis of Id Proteins

Inhibitors of DNA binding proteins represent a family of small size proteins (13–18 kDa) characterized by the presence of highly preserved helix-loop-helix (HLH) domain and their implication in gene expression by interacting with several proteins and transcription factors [4]. This peculiar structure is the key for understanding their main functions and their involvement in various cell growth and differentiation pathways.

Id proteins are not the only ones within the HLH superfamily. Among the seven subtypes described (I–VII), Id proteins belong to class V, which are characterized by lacking basic amino acids [5]. This leads to the impossibility of binding directly to specific regions of the DNA. Therefore,

their binding targets are mainly other HLH proteins, especially class I–IV, which do have basic amino acids (bHLH) and can bind directly to DNA. Within the Id proteins family, four subtypes (Id1-4) are currently distinguished. Although they have a high structural homology, they share different and sometimes even antagonistic functions. In fact, Id1-3 are usually recognized as tumor promoters, whereas Id4 appears to be tumor suppressor, being this, due probably to the presence of polyalanine segments in the N-terminal region of Id4 [6].

Id proteins, which were discovered in 1990, are encoded by four different genes located on separated chromosomes [7,8]. From among the multiple factors that modulate their expression the role of the members of the transforming growth factor-β (TGF-β), represented mainly by bone morphogenetic proteins (BMP) and their interaction with Smad transcription factors should be highlighted [9]. It seems that BMP can regulate their expression in a concentration-dependent way. Higher concentrations result in activation of the anaplastic lymphoma kinase type 1 (ALK1) receptor, whereas lower concentrations exert a suppressive role following activation of the ALK5 receptor [10]. The degradation mechanisms of Id proteins are crucial to control their activity and maintain balance in various biological processes. These proteins exhibit short half-life and are mainly degraded through the 26S-proteasome pathway [11,12]. This process is intimately regulated by ubiquitinases and it also depends on the interaction with other proteins and the formation of heterodimers [13,14].

3. Signaling Pathway and Functions of Id Proteins

Id proteins perform their function of modulating gene expression through binding to other proteins, as they cannot bind to DNA due to the absence of a basic region adjacent to the HLH motif (Fig. 1). The main targets for binding are HLH proteins, specifically class I and II proteins [15]. E proteins (mainly E2A, HeLa E-Box binding factor (HEB) and E2-2) are representative of class I HLHs and the formation of these heterodimers prevent their physiological binding to specific recognition sites known as E-box and N-box [16]. By the formation of this heterodimer, Id proteins prevent binding and therefore repress gene transcription that regulate various cellular processes such as angiogenesis, neurogenesis, myelopoiesis, regulation of the immune system, cell growth and tumorigenesis. Class II of HLH proteins are mainly composed of myogenic (MyoD) and neural (NeuroD/Beta2) regulatory factors [17].

On the other hand, the Id family not only establishes its functions by binding to HLH proteins, but also has the capacity to interact with different proteins and transcription factors [18]. A key target is the retinoblastoma protein (Rb), the inhibition of which mediates much of the effects on cell proliferation [19,20]. Other examples include paired-box (PAX) transcription factors, caveolin-1 transmembrane protein, Von-Hippel Lindau (VHL) syndrome-associated protein or the estrogen receptor beta-1 [21–24].

As Id proteins have multitude of interactions, the intracellular signaling mechanisms are complex (Fig. 2). Different stimuli at transmembrane receptors lead to a different signaling cascades. Binding of BMP2 or growth factors such as vascular endothelial growth factor (VEGF) or epidermal growth factor (EGF) leads to an increase in Id1 transcription via Smad1/5/8 and Src proto-oncogene (Src) tyrosine kinase respectively while TGB-β induces a repression via Smad3 [25]. Inhibiting differentiation and promoting proliferation are the two main functions of Id proteins and they can perform this by inhibiting tumor suppressors such as Rb or p53 and by inducing proliferation pathways such as Akt kinase (Akt), Raf or MEK1/2 [15,19,20,26]. Another important effect is the inhibition of p16 and p21, which inhibit cell-cycle regulators and enhance the cyclin/Cdk activity [27,28].

Within Id proteins, Id1 is mainly involved in the processes of endothelization and vascular proliferation due to its inhibition of the E2-2 protein, which is responsible for inhibiting endothelial cell proliferation through a decrease in the concentration of vascular endothelial growth factor receptor 2 (VEGFR2) [29–31]. It has also been linked to the development of atherosclerotic plaque and has been suggested as a possible therapeutic target [32,33]. Furthermore, alterations in Id proteins can lead to severe cardiac abnormalities, such as valvular defects in double/triple knockout mice or arrhythmias, both ventricular and atrial, in those with loss of Id2 function [34–37].

The relationship between the immune response and the Id family has also been extensively studied. While Sanjurjo *et al*. [38] showed the role of Id3 in M2 macrophague polarization, Deng *et al*. [39] demonstrated that Id3 promotes antitumour response by increasing phagocytosis of Kupfer cells by preventing the binding of transcription factors such as E2A and ELK to the signal regulatory protein-alpha locus (SIRPα), thereby increasing dectin-1 levels. Regarding adaptive immunity, it seems that Id3 knockout mice exhibit an increase in T_h17 response in asthmatic inflammation but upregulated Id3 expression leads to increased regulatory T cells (Treg) and hepatitis B virus (HBV) immune response [40,41]. This dynamic balance between E proteins and Id members is also essential not only for T-cell differentiation, both CD4 and CD8, but also for B-cell proliferation and IgM synthesis [42–44].

The Id family of proteins has been closely linked to neuronal development. Among the four members, Id2 and Id4 have been most closely linked to nervous system physiology. Indeed, they are key in the processes of oligodendrogenesis, proliferation and differentiation of oligodendrocyte precursor cells (OPCs) [45,46]. These effects of Id2 are mediated through inactivation of Rb or its interaction with oligodendrocyte lineage transcription factor (OLIG). Id2 is in turn regulated by multiple signals, such as BMP2

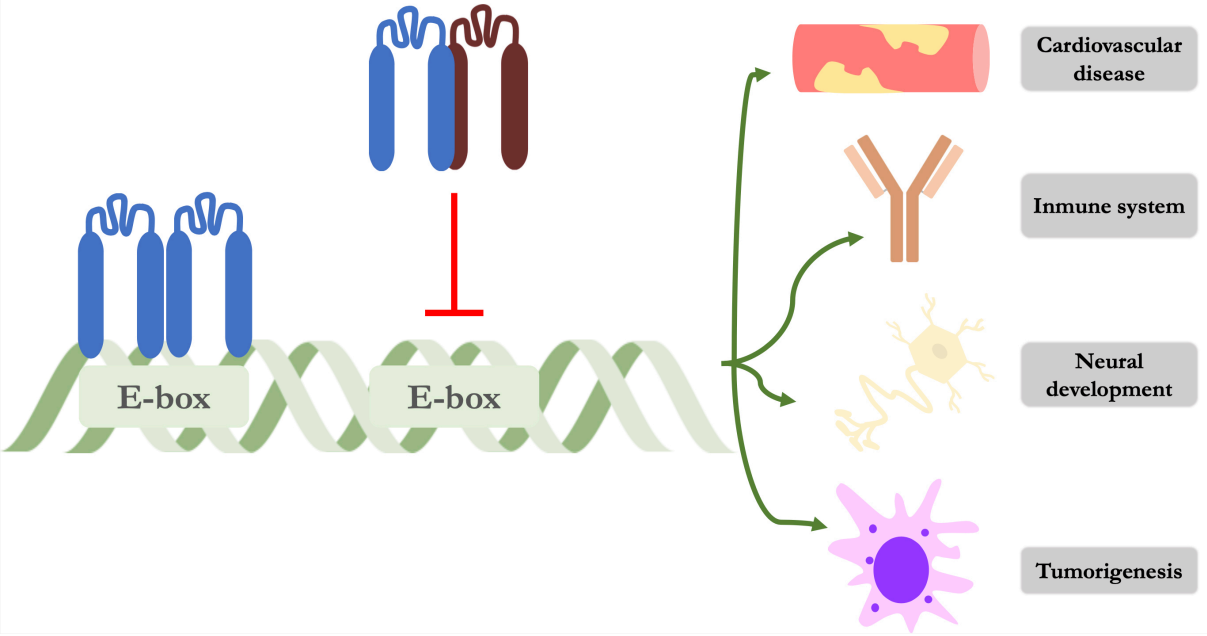

Fig. 1. Schematic representation of the mechanism of action of Id proteins. The left-hand side shows an E protein forming a homodimer and binding to its promoter region on DNA. On the right, an Id protein (dark red) is shown forming a heterodimer and preventing its binding and thus repressing gene transcription of various cellular processes. Id, inhibitor of DNA binding protein.

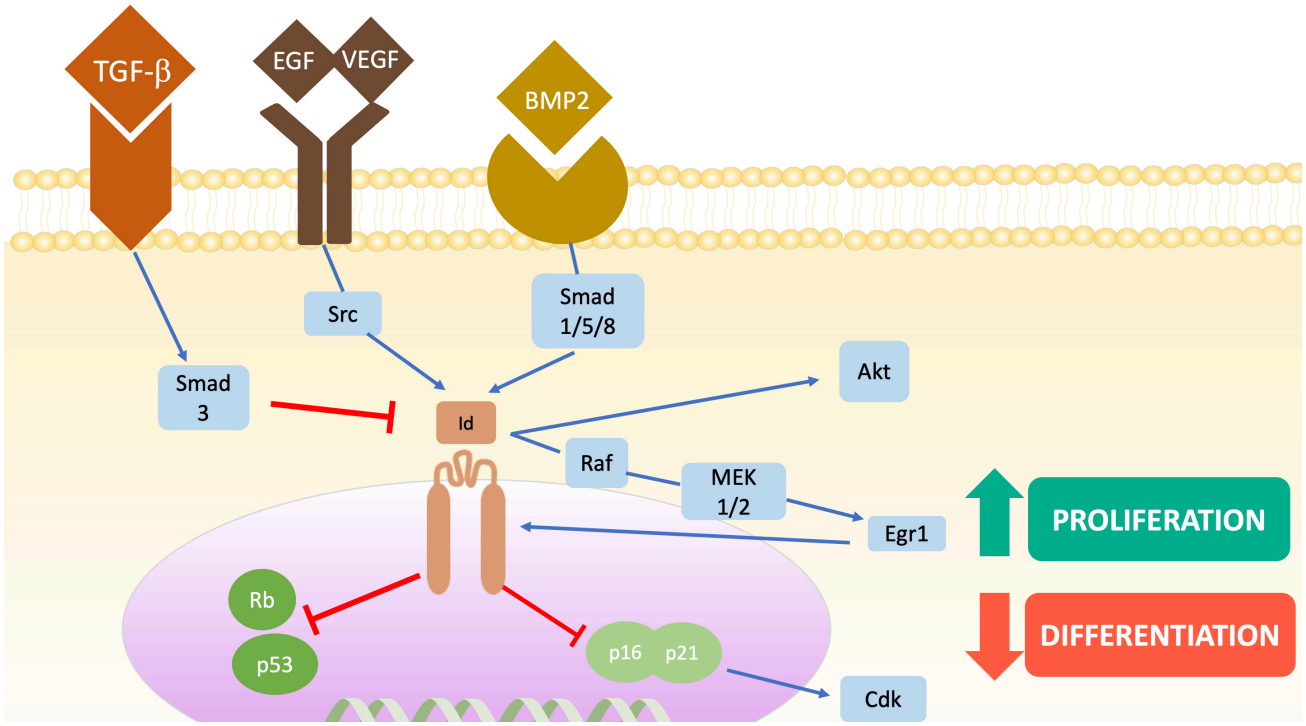

Fig. 2. Regulation of Id proteins and their main stimulation pathways. Blue arrows mean activation while red arrows represent metabolic pathway inhibition. Note that Egr1 establishes a positive feedback system, as it ultimately favours the transcription of Id proteins. TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; BMP2, bone morphogenetic protein type 2; Smad, suppressor of mothers against decapentaplegic; Raf, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; Egr1, early growth response protein 1; Rb, retinoblastoma protein; Cdk, cyclin-dependent kinases; Id, inhibitor of DNA binding protein; Akt, Akt kinase; Src, Src proto-oncogene.

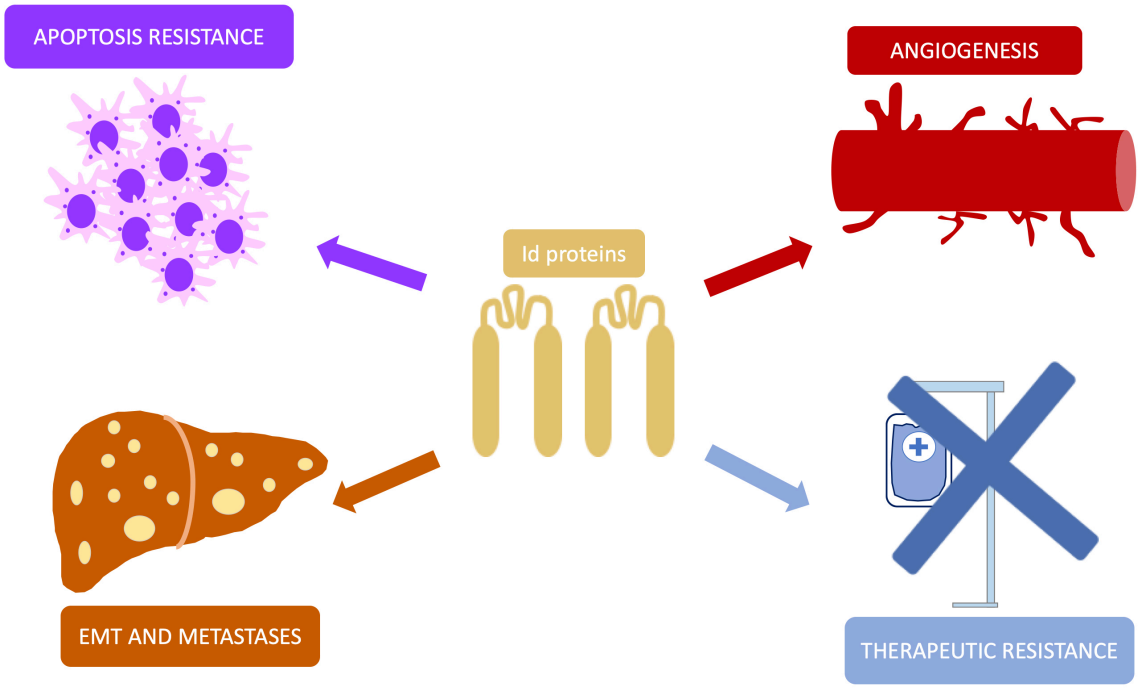

Fig. 3. Pathways of Id proteins involvement in carcinogenesis. This simplified representation shows the different pathways by which Id promotes the development and progression of malignant neoplasms. Id, inhibitor of DNA-binding; EMT, epithelial-mesenchymal transition.

or the Wnt/catenin pathway [47]. It has even been hypothesized that targeting their signaling could be of use in white matter damage as it has been shown in animal models to accelerate axonal regeneration and promote neuromuscular reinnervation [48,49]. Although these are the main processes in which the intervention of the Id proteins family has been studied, various aspects such as reproductive function, ocular disease, adipogenesis or disruption of the endocrine system are also the subject of study [50–56].

4. Id Proteins and Cancer

Although they do not fit the strict definition of oncogene, Id proteins are intimately involved in cell proliferation and differentiation, which therefore plays pivotal role in the tumorigenesis and development of malignant neoplasms. As previously discussed, loss of function of suppressors such as p53 or Rb allows cells to bypass their inhibitory signal, leave the quiescent state and initiate a continuous proliferative process. Nevertheless, not only are Id proteins related to the insensitivity to growth inhibitory signals but also this family of transcription factors are involved in more neoplastic processes (Fig. 3).

4.1 Enhancement of Neovascularization

Angiogenesis is another mainstay on which malignant tumors are built, being a key step in metastatic disease. Within this process, VEGF emerges as the most relevant molecule, and its regulation is closely linked to the increase in hypoxia-inducible factor 1-alpha (HIF-1α). In this context, Id proteins play a crucial role in mediating these angiogenic effects [57–59]. A study in animal model has shown that Id1 and Id3 knockdown mice do not develop tumors due to an inability to form neovessels, highlighting their relevance in the angiogenic process [60].

Id1 also actively participates in the mobilization and recruitment of endothelial progenitor cells from the bone marrow, an essential step for tumor neovascularization [61]. Moreover, these proteins not only promote the formation of new vessels, but also repress angiogenesis inhibitory factors, such as thrombospondin, promoting a vascular microenvironment that favors tumor growth [62]. On the other hand, Id1 potentiates the secretion of proinflammatory cytokines, such as interleukine-8 (IL-8) and chemokine growth-regulated protein alpha (GRO-α), which contribute both to the attraction of immune cells and to the amplification of the angiogenic and protumorigenic environment [63]. A particularly relevant case is glioblastoma multiforme, where overexpression of the Smad/Id1 pathway has been implicated in resistance to bevacizumab, a VEGF inhibitor [64]. This resistance could be due to the ability of tumor cells to compensate for VEGF inhibition through alternate Id1-mediated pathways. In this sense, it has been proposed that combined treatment with therapies directed against the Smad/Id pathway could improve the clinical efficacy of VEGF inhibitors, opening new therapeutic opportunities in the management of glioblastoma and other angiogenic tumors.

4.2 Treatment Desensitization

Resistance to conventional treatments is a major problem, as different types of cancer have developed strategies to counteract their cytotoxic effects. Among the cell subtypes within a neoplasm, tumor cells with stem-cell characteristics are a major focus of resistance because of their self-renewal skills and are favoured by the presence of Id proteins together with signal transducer and activator of transcription type 3 (STAT3) [65]. For example, Id1 together with c-Jun proto-oncogene (c-Jun) has been linked to resistance to etoposide-induced DNA damage in esophageal squamous cell carcinoma while in prostate carcinoma it is associated with resistance to taxane-induced damage due to Akt overexpression [24,66]. In hepatocellular carcinoma, Id1 activates the p16/IL6 axis, favoring resistance to sorafenib, and stimulates the pentose phosphate pathway, promoting chemoresistance to oxaliplatin [67, 68]. What is more, Id1 overexpression induces resistance to 5-Fluorouracil through activation of E2F1-dependent thymidylate synthase in colorectal cancer, whereas its inhibition restores sensitivity to treatment. These findings underscore the multifaceted role of Id1 in the regulation of therapeutic resistance [69].

4.3 Resistance to Apoptosis

Avoidance of pro-apoptotic signals is one of the significant mechanisms for tumor cell survival and the Id family has also been involved at this level [70]. In fact, suppression of apoptosis has been demonstrated in small cell lung carcinoma (SCLC) and prostate adenocarcinoma being the latter mediated through an increased nuclear factor kappa β (NF-kβ) signaling pathway [71,72]. What is more, targeting Id1 pathway with deubiquitylating enzyme ubiquitin-specific protease 1 (USP1) or Id1/3 inhibitors has shown induction of apoptosis in lymphoblastic leukaemia and breast cancer cells respectively [73,74]. In addition, Lin *et al*. [75] found that Id1 contributes to the survival of head and neck squamous cell carcinoma through activation of the NF-kappaβ/survivin and phosphoinositide 3-kinase/Akt signaling pathways.

4.4 Tissue Invasion and Metastasis Development

Multiple alterations are necessary for tissue invasion and the development of metastasis, such as overcoming cellular adhesion, eliminating the extracellular matrix and being able to settle in a distant organ. This process is known as epithelial-mesenchymal transition (EMT) and involves several molecules including Id1 and E47 [76–78]. This fact has clinical implications, such as the Id1-induced resistance to osimertinib in non-SCLC through an increase in EMT [79]. In addition, BMP4 and T-box transcription factor 3 (TBX3) are responsible for the increase in Id1 overexpression, EMT and metastatic disease in both gastric and cervical cancer respectively [80,81]. Id1 has also been identified as a critical regulator of breast cancer stem cell-like properties and metastatic colonization. Under the control of transforming growth factor beta (TGF-β) signaling, Id1 induces mesenchymal-epithelial transition (MET) at the metastatic site by antagonizing the activity of the transcription factor Twist1 [82].

5. Interrelation between Id Proteins and Epigenetics

As previously described, Id proteins play multiple roles in tumor development, acting as key regulators in various biological processes. These proteins are part of complex signaling cascades, interacting with multiple molecular pathways that contribute to cancer progression. Moreover, their activity is tightly regulated by epigenetic mechanisms, while they themselves influence and are modulated by these processes, establishing a bidirectional relationship that highlights their importance in the regulation of the tumor environment.

5.1 Interrelation with DNA Methylation Pattern

It has been shown that Id1 potentiates the E3 ligase activity of RING1b through Mel-18 and Bmi-1 proteins, which represent epigenetic repressor proteins that are part of Polycomb Repressive Complex 1 (PRC1), establishing a connection between Id1 and Polycomb-mediated epigenetic regulation [83]. It has also been described that inhibition of Id1 promoter methylation by demethylating agents, such as 5-AZA-2′-deoxycytidine, can increase its expression and, consequently, improve sensitivity to treatment in hepatocellular carcinoma [84]. Along the same lines, the BMP9-ID1 pathway has been implicated in the reduction of N6-methyladenosine methylation in CyclinD1, favoring cell proliferation in this type of cancer [85]. On the other hand, Id4 presents an apparently contradictory role: in glioblastoma, its epigenetic silencing seems to be associated with a better prognosis due to the inhibition of angiogenesis whereas its methylation pattern positions it as a potential tumor suppressor in leukemia [86,87].

5.2 Interrelation with Histones

Recent research has revealed significant interactions between Id proteins and histone modifications in various oncological contexts. Tamari *et al*. [88] demonstrated that polyamine efflux suppresses the activity of histone lysine demethylases, resulting in an accumulation of repressor epigenetic marks and increased Id1 expression in cancer stem cells. In addition, Zhang *et al*. [89] identified that targeted inhibition of lysine-specific demethylase 6 (KDM6) eradicates tumor-initiating cells in colorectal cancer through enhancer reprogramming, involving key genes such as Id1. On the other hand, it has also been observed that the histone deacetylase inhibitor trichostatin A induces Id1 expression and promotes apoptosis in human acute myeloid leukemic cells, indicating that histone acetylation can activate Id1 expression and trigger cell death in certain tumor contexts [90].

5.3 Interrelation with MicroRNAs

MicroRNAs (miRNAs) have emerged as important regulators of Id proteins, modulating their expression in different types of cancer and affecting both progression and therapeutic response. In colorrectal cancer, miRNA-885-3p blocks BMP/Smad/Id1 signaling by upregulating BMP receptor type 1A (BMPR1A), thereby suppressing angiogenesis and slowing tumor growth, while the miRNA-371~373 cluster represses metastatic initiation by inhibiting the TGF receptor type 2 (TGFBR2)/Id1 axis, highlighting their role as tumor suppressors [91,92]. In esophageal squamous cell carcinoma, circ-ATIC acts by sequestering miRNA-326, allowing Id1 overexpression and favoring tumor progression [93]. On the other hand, in papillary thyroid carcinoma, the long non-coding RNA NEAT1 captures miRNA-524-5p, reducing its regulatory capacity over Id1 and promoting tumor development [94]. The influence of miRNAs has also been related to EMT, such as the inhibitory influence of miRNA-29b in ovarian carcinoma and of miRNA-381 in lung cancer, resulting in both cases in reduced cell migration and invasiveness when these molecules were applied [95,96]. Finally, in the context of hematological malignancies, downregulation of miRNA-29b and subsequent overexpression of Id1 have been found to be involved in decitabine resistance, suggesting a direct connection between this pathway and therapeutic resistance [97]. These findings underscore the complexity of the interaction between miRNAs and Id proteins, highlighting their relevance in the regulation of tumor progression and their potential as therapeutic targets.

6. Epigenetic Mechanisms in NENs

Most cases of NENs occur sporadically but it is estimated that around 5% may occur in the context of a germline genetic mutation and are part of familial predisposing syndromes such as multiple endocrine neoplasia type 1 (MEN1), type 4 (MEN4), Von-Hippel-Lindau, Tuberous Sclerosis or Neurofibromatosis type 1 syndrome [98–101]. On the other hand, it is now widely recognised that epigenetic mechanisms are fundamental in the regulation of gene expression and the development of neoplasms [102]. Of course, NENs are no exception to this axiom and several regulatory processes at this level can be identified, which vary significantly depending on the location of the primary tumor (Fig. 4).

6.1 Alterations in DNA Methylation

In small intestine NENs (siNENs), higher hypermethylation of Ras association domain family member 1A (RASSF1A) promoter has been identified in metastases compared to the primary tumour, conferring a worse prognosis [103]. This finding is also present in pancreatic neuroendocrine neoplasms (panNENs), where the degree of hypermethylation is even more pronounced and potentially more significant [104]. In addition, lower levels of ubiquitin C-terminal hydrolase L1 (UCHL1), which acts as a p53 stabilizer, were observed in metastatic siNENs due to a hypermethylation in its promoter [105]. A relationship was also discovered between lower levels of semaphorin 3 (SEMA3F), methylation of its promoter, increased proliferation and tumour stage [106]. It seems that semaphoring 3 is somehow linked to the PI3K/Akt/mTOR pathway and its downregulation is associated with hypermethylation of its promoter gene SEMA3F.

Regarding panNENs, different mechanisms are described in the literature such as the aforementioned hypermethylation and downregulated expression of RASSF1A (up to 80% of panNENs), which is facilitated by death domain-associated protein (DAXX) and is related to apoptosis and cell cycle arrest by its interaction with a broad spectrum of proteins like including rat sarcoma virus (Ras) or c-Jun [107–110]. Another that appears to down-regulate the cell cycle is Hypermethylated in cancer 1 (HIC1) protein, which is frequently repressed because of its frequent (93%) hypermethylation in panNENs [111]. Further examples of tumour suppressors with lower activity in these neoplasms are adenomatous polyposis coli (APC) and cyclin-dependent kinase inhibitor 2A (CDKN2A), with findings of hypermethylation in 20–48%, being linked the latter to metastatic disease and worse prognosis [104,111–115]. Other physiological processes in which increased hypermethylation can be found are DNA damage repair by the enzyme O6-methylguanine-DNA methyltransferase (MGMT), extracellular matrix degradation by metalloproteinases or angiogenesis [116–119].

In relation to lung carcinoids, there is no large detailed study of the role of DNA methylation [120]. Although some alterations have been reported in the methylation profile, few have been confirmed. Among the identified alterations, RASSF1A appears to be the promoter with the highest frequency of methylation whereas CDKN2B promoter appeared methylated in 15% of cases [121,122]. Although lower expression of *MEN1* gene was associated to poorer prognosis in carcinoids, it seems that its hypermethylation was not the underlying mechanism [123]. With regard to small cell lung carcinoma (SCLC), selective hypermethylations of RASSF1A and caveolin-1 are present in up to 60% of cases [124,125]. Another protein whose function is altered due to hypermethylation is enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2), a chromatin modifier that is involved in smoke damage mechanisms [126,127].

Although less frequent, DNA hypomethylation also plays a role in NENs development. Indeed, hypomethylation in long interspersed element 1 (LINE1) and Arthrobacter luteus (ALU) homolog genes, confer a lower survival and a higher tumour stage in panNENs [117,128]. Furthermore, global hypomethylation has been described as a characteristic finding of SCLC [124,125].

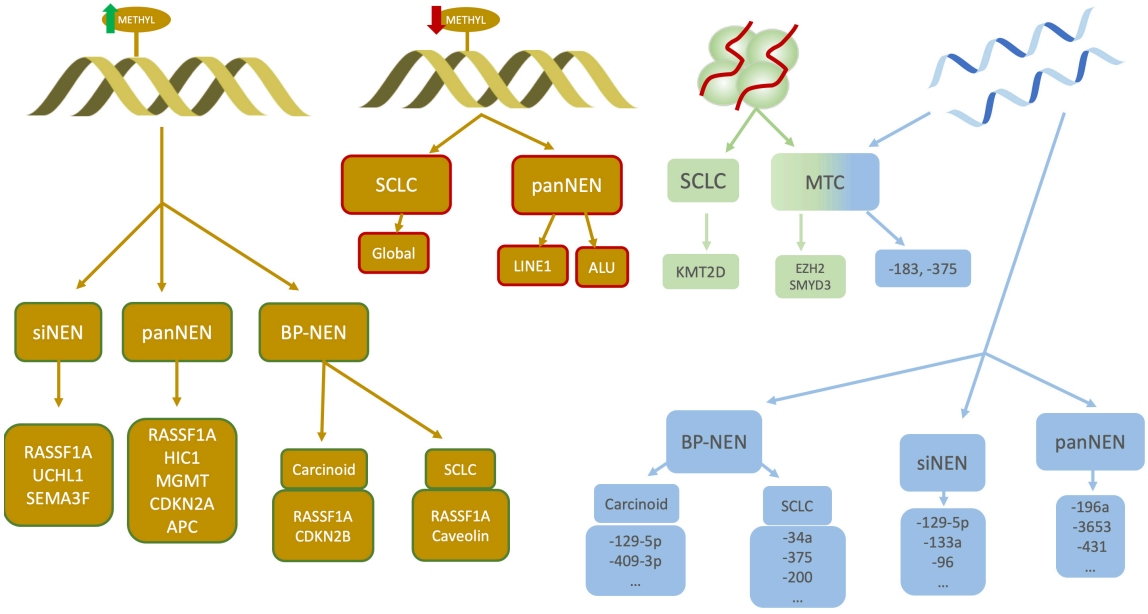

Fig. 4. Different epigenetic mechanisms involved in NENs. From left to right: hypermethylation, hypomethylation, histone modifications and miRNAs. Primary tumour and genes involved in hypermethylation are shown in yellow squares with green lines while those related to hypomethylation have red lines. Note the importance of RASSF1A in all NENs regardless of their location. siNEN, small intestine neuroendocrine neoplasm; panNEN, pancreatic neuroendocrine neoplasm; BP-NEN, bronchopulmonary neuroendocrine tumour; SCLC, small cell lung carcinoma; MTC, medullary thyroid carcinoma; RASSF1A, Ras association domain family member 1A; SEMA3F, semaphorin 3; APC, adenomatous polyposis coli; CDKN2A, cyclin-dependent kinase inhibitor 2A; MGMT, O6-methylguanine-DNA methyltransferase; LINE1, long interspersed element 1; ALU, Arthrobacter luteus; KMT2D, lysine methyltransferase 2D; CDKN2B, cyclin-dependent kinase inhibitor 2B; METHYL, methylation; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; SMYD3, SET and MYND domain containing 3; UCHL1, ubiquitin C-terminal hydrolase L1; HIC1, HIC ZBTB transcriptional repressor 1.

6.2 Histone Modifications

Histones play a crucial role in gene expression by regulating chromatin structure and accessibility, thus influencing transcriptional activity [129]. In this regard, it is essential to highlight the lysine methyltransferase 2D gene (KMT2D), responsible for regulating the methylation of histone 3 lysine 4 and CREB-binding protein (CREBBP), whose inactivation is associated with increased tumour growth in SCLC [130,131]. In addition, overexpression of histone methyltransferases EZH2 and SET and MYND domain containing 3 (SMYD3) has been described in metastatic medullary thyroid carcinoma (MTC) [132].

6.3 Differential Expression in MiRNAs

The role of miRNAs is fundamental in epigenetics, as they direct gene silencing by RNA interference, influencing chromatin modifications and maintaining genome stability [133]. In relation to siNENs, differential expression in miRNA between primary tumours and metastasic disease (for example, miRNA-129-5-p, -133a, -96, -183 or -204) has been described, but no other clinical implications are known for the moment [134]. Regarding miRNAs, a relationship between miRNA-196a and the mitotic index, Ki-67, lower disease-free survival and worse prognosis has been found, as well as between miRNA-3653 and the risk of metastasis, probably mediated by the interaction with alpha-thalassemia mental retardation X-linked (ATRX) protein [135,136]. In addition, miRNA-431 is also associated with metastasis, and appears to act through the degradation of disabled homolog 2-interacting protein (DAB2IP), inducing activation of the Ras/Erk pathway [137].

There has also been found that miRNA-129-5p, -409-3p, -409-5p, -185 and -497 are overexpressed in typical carcinoids compared to atypical neoplasm [138]. In reference to SCLC, the role of miR-34a as a tumour suppressor could be highlighted and its absence carries a worse prognosis [139]. In addition, miRNA-375 and miRNA-200 (includes miR-200a, miR-200b and miR-200c), are related to metastatic disease and chemotherapy resistance respectively [140,141].

Overexpression of miRNA-183 and miRNA-375 has been observed in sporadic cases of MTC compared to hereditary cases and is associated with a more aggressive behavior. Therefore, miRNA-375 may be associated with tumour stage, calcitonin levels and disease progression [142].

7. Id Proteins and Their Implications in NENs

Since Id proteins are an additional pathway in the vast compendium of processes involved in the development of carcinogenesis, it was decided to investigate their role in NENs development. Notably, evidence on the main epigenetic mechanisms involving Id proteins in NENs is particularly scarce, with the knowledge largely restricted to neuroendocrine prostate carcinoma (NEPC). In terms of molecular pathways and signaling mechanisms (excluding epigenetics), evidence on the role of Id proteins in NENs is notably limited for gastroenteropancreatic (GEP)-NENs. Although the gastroenteropancreatic site is the most frequent location of NENs, there is a paucity of research exploring the influence that Id proteins may have in such cases. Indeed, the only published information on GEP-NENs comes from a single article related to panNENs [143]. Overall, most of the literature discussing the molecular pathways involving Id proteins in NENs focuses on BP-NENs, MTC and NEPC.

7.1 Id Proteins and GEP-NENs

GEP-NENs are governed by a specific anatomopathological classification, where tumour grade is an important prognostic factor [144]. Within G3 tumours, well-differentiated or poorly differentiated tumours, also known as neuroendocrine carcinoma (NEC), can be distinguished with differences in management and survival [144,145]. In relation to pan-NENs, such is the difference that it is hypothesized whether there are differences in the cell lineage of origin, with NECs starting from an undifferentiated primitive stem cell and without clear neuroendocrine differentiation [146]. By studying a mouse model of islet cell carcinoma, Hunter *et al*. [143] discovered a tumour subtype with absent beta-cell marker expression and high mitotic grade that they called poorly differentiated invasive carcinoma (PDIC) and showed a high similarity to poorly differentiated human panNEN. In their work, they found that although both PDIC and well-differentiated insulinoma expressed neuroendocrine markers such as synaptophysin, only PDIC cells had a high staining intensity for Id1, showing the latter positivity for beta cell markers such as insulin or MafA. Therefore, when considering the similarity between PDIC and poorly differentiated panNENs, it could be intuited that Id1 is also highly expressed in the latter, although the reality is that neither histological nor molecular studies are available for panNENs.

7.2 Id Proteins and BP-NENs

Unlike GEP-NENs, the involvement of the Id family has been studied in BP-NENs in several studies. Increased expression of Id1, Id2 and Id3 was found in SCLC cell lines while an increased expression of all four subtypes in human tumour samples was detected [147]. Their cellular location showed significant differences, as a higher nuclear positivity of Id3 and Id4 was detected whereas the distribution of Id1 and Id2 resulted mainly cytoplasmic. In fact, the cytoplasmic expression of Id2 was positively correlated with patient survival, with a 3-month survival when Id2 was weakly expressed compared to 10 months when Id2 expression was strong. Although it may be contradictory, it is hypothesized that a higher cytoplasmic level translates into a leakage of Id2 from the nucleus and therefore less availability of this protein to inhibit tumour suppressors. In relation to other hystological types, Zhang *et al*. [148] demonstrated that SCLC shows an upregulation of Id2 and Id4, whereas lung squamous cell carcinoma exhibits lower Id2 expression. What is more, the study of Id2 target genes led to a second conclusion: Id2 plays different roles depending on the tumour lineage. Such is the case that in SCLC up-regulates genes involved in mitochondrial function and ATP production, whereas in squamous cell carcinoma Id2 stimulates T cell activity and leukocyte chemotaxis. These findings seem to explain the high growth and proliferation rate of SCLC as well as the ability to evade the immune response in the latter. The biological relevance of increased expression of Id family members in SCLC is that these cells show an increased proliferative state reminiscent of stem-cell like. Neuron-specific enolase (NSE) appears to be responsible for this, as it favours the BMP2-Smad1/5/8-Id1 cellular pathway through its ability to inhibit neuroblastoma suppressor of tumorigenicity 1 (NBL1), whose function is to antagonize the TGF-β pathway by inhibiting BMP2 [149]. As lung cancer cells exhibit an activated BMP/Smad/Id pathway, the association of 4-[4-(2-Pyridinyl)-2-pyrimidinylamino]phenol (DMH2), a BMP type I receptor inhibitor, resulted in reduced phosphorylation of Smad1/5/8 as well as reduced expression of Id1, Id2 and Id3 [149]. Furthermore, in SCLC and bronchial carcinoid cell lines with stem-cell markers overexpression, the addition of DMH2 not only resulted in the above-mentioned effects, but was also accompanied by a suppression of tumour growth. This opens the door to a promising future in the targeting of the BMP2-Smad1/5/8-Id1/3 axis [150].

7.3 Id Proteins and MTC

Thyroid cancer is the most frequent endocrine neoplasm and Id proteins inhibitors have been studied in this type of tumour [151,152]. However, most of the evidence comes from differentiated thyroid cancer. An upregulation of Id1 in malignant versus benign thyroid pathology has been shown and anaplastic carcinoma showed the highest Id1 expression from among them [153]. In papillary thyroid carcinoma, strong immunostaining of Id1 was detected but no correlation with tumor size, lymph node metastasis or tumor stage stage was found [154]. In addition, Id2 has recently been shown to play an influential role in proliferative capacity, stemness, EMT and metastasis development. These effects are presumed to be mediated by the phosphatidylinositol-3 kinase (PI3K)/Akt/mammalian tar-

get of rapamycin (mTOR) pathway [155]. In relation to tumour lineage of neuroendocrine origin, Kebebew *et al.* [156] found moderate-to-high immunostaining in patients with MTC in sporadic, familial MTC or MEN2A associated disease compared to normal tissue, which showed faint-to-absent intensity ($p = 0.002$). Additionally, they also characterized its gene expression in human cell cultures, finding a fourfold higher expression of the Id1 RNA transcript when cultured with growth factors, while lower gene expression was identified when inoculated with a redifferentiating agent.

7.4 Id Proteins and NEPC

Although an uncommon NEN, mechanisms involving the Id protein family have been described in NEPC. It is a rare entity, with an incidence of 35 per 10,000 per year and accounts for 1–2% of malignant tumours of the prostate gland [157,158]. However, there is increasing interest in this neoplasm because of its different prognostic and treatment behavior compared to prostate adenocarcinoma (PRAD) [159,160]. The origin of this neoplasm is not completely understood. Initially, it was thought that NEPC arises from prostatic neuroendocrine cells (1% of epithelial prostate cells) from the beginning of its development but evidence suggests that it derives from a castration-resistant prostate cancer (CRPC) that has enhanced mechanisms to change its lineage, transdifferentiate from PRAD and express neuroendocrine markers such as chromogranin, synaptophysin, CD56, neuron-specific enolase (NSE) or insulinoma-associated protein 1 [161–163]. A novel classification for these neoplasms was proposed in 2014 and in the latest 2022 WHO Classification of Urinary and Male Genital Tumors it has been recognised as treatment-related NEPC (t-NEPC) [164,165]. Firstly, Bishop *et al.* [166] studied the changes in protein synthesis and gene expression that occur in enzalutamide-resistant cancer cells that allow them to dedifferentiate and acquire a subsequent neuroendocrine phenotype. Among the many findings, an Id2 upregulation was found in those with neuroendocrine differentiation in comparison to absent expression in CRPC cells [166]. At an epigenetic level, Zhang *et al.* [167] recently demonstrated an increased level of Id2 transcripts in neuroendocrine cells compared to those with androgen receptors and also found intense Id2 positivity by immunofluorescence in the former with a weak signal for adenocarcinoma cells. They also identified an increased acetylation of histone 3 in lysine residue at N-terminal position 27 (H3K27) in NEPC cells, which may explain why the Id2 gene is more active in the neuroendocrine lineage. Furthermore, the increased acetylation at H3K27 appears to drive the downstream effects of Id2, including the greatest increase in *IFI6* and *IFI27* gene expression—both involved in apoptosis—a decrease in HOXB13, an androgen co-stimulatory factor, and an upregulation of the IL-6/Jak/Stat3 pathway, which is associated with stemness. With other members of the Id family, a relationship with histone modifications has also been observed. The MYST/Esa1-associated factor 6 (MEAF6), a component of the NuA4 histone acetyltransferase complex, plays a key role in promoting gene transcription through the acetylation of histones H4 and H2A, leading to the upregulation of Id1 and Id3 [168]. These proteins, in turn, mediate the proliferative effects associated with MEAF6. However, they seem to only increase NEPC progression, rather than favoring the transdifferentiation process.

8. Conclusions

Id protein family are essential transcription factors for the development of diverse types of neoplasms due to their perpetuating effects on the stem-cell state, tumor proliferation as well as their inhibitory effects on differentiation. NENs are no exception to this and are also regulated by these molecules. However, it may be striking that GEP-NENs have little evidence in this regard, despite being the most prevalent type. Among them, Id1 and Id2 have been most frequently linked to molecular processes in NENs, highlighting its prominent role in this context.

Selective targeting of Id proteins, particularly Id1, has shown promising results in reducing tumor proliferation and enhancing chemotherapy sensitivity in other cancer types. Within the field of NENs, inhibitors of the BMP receptor have demonstrated potential therapeutic benefits in SCLC. These findings pave the way for further exploration of Id proteins as actionable targets in NENs.

Additionally, epigenetic regulation is abundant within NENs and plays a pivotal role in their biology. However, when it comes to the involvement of Id proteins in these epigenetic mechanisms, most of the evidence stems from studies on NEPC. This reinforces the need for continued research, particularly in an era where understanding intracellular signaling pathways and epigenetic modulation holds the key to developing effective targeted therapies to challenge cancer.

Author Contributions

DP, MG, PA, SW, AH, JT: conceptualization, investigation, project administration, resources, supervision, visualization, writing, review and editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Nair R, Teo WS, Mittal V, Swarbrick A. ID proteins regulate diverse aspects of cancer progression and provide novel therapeutic opportunities. Molecular Therapy. 2014; 22: 1407–1415. https://doi.org/10.1038/mt.2014.83.

[2] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, *et al*. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncology. 2017; 3: 1335–1342. https://doi.org/10.1001/jamaoncol.2017.0589.

[3] Reccia I, Pai M, Kumar J, Spalding D, Frilling A. Tumour Heterogeneity and the Consequent Practical Challenges in the Management of Gastroenteropancreatic Neuroendocrine Neoplasms. Cancers. 2023; 15: 1861. https://doi.org/10.3390/cancers15061861.

[4] Massari ME, Murre C. Helix-loop-helix proteins: regulators of transcription in eucaryotic organisms. Molecular and Cellular Biology. 2000; 20: 429–440. https://doi.org/10.1128/MCB.20.2.429-440.2000.

[5] Cano A, Portillo F. An emerging role for class I bHLH E2-2 proteins in EMT regulation and tumor progression. Cell Adhesion & Migration. 2010; 4: 56–60. https://doi.org/10.4161/cam.4.1.9995.

[6] Sharma P, Chinaranagari S, Chaudhary J. Inhibitor of differentiation 4 (ID4) acts as an inhibitor of ID-1, -2 and -3 and promotes basic helix loop helix (bHLH) E47 DNA binding and transcriptional activity. Biochimie. 2015; 112: 139–150. https://doi.org/10.1016/j.biochi.2015.03.006.

[7] Benezra R, Davis RL, Lockshon D, Turner DL, Weintraub H. The protein Id: a negative regulator of helix-loop-helix DNA binding proteins. Cell. 1990; 61: 49–59. https://doi.org/10.1016/0092-8674(90)90214-y.

[8] Asirvatham AJ, Carey JPW, Chaudhary J. ID1-, ID2-, and ID3-regulated gene expression in E2A positive or negative prostate cancer cells. The Prostate. 2007; 67: 1411–1420. https://doi.org/10.1002/pros.20633.

[9] Korchynskyi O, ten Dijke P. Identification and functional characterization of distinct critically important bone morphogenetic protein-specific response elements in the Id1 promoter. The Journal of Biological Chemistry. 2002; 277: 4883–4891. https://doi.org/10.1074/jbc.M111023200.

[10] Souilhol C, Harmsen MC, Evans PC, Krenning G. Endothelial-mesenchymal transition in atherosclerosis. Cardiovascular Research. 2018; 114: 565–577. https://doi.org/10.1093/cvr/cvx253.

[11] Bounpheng MA, Dimas JJ, Dodds SG, Christy BA. Degradation of Id proteins by the ubiquitin-proteasome pathway. FASEB Journal. 1999; 13: 2257–2264.

[12] Trausch-Azar JS, Lingbeck J, Ciechanover A, Schwartz AL. Ubiquitin-Proteasome-mediated degradation of Id1 is modulated by MyoD. The Journal of Biological Chemistry. 2004; 279: 32614–32619. https://doi.org/10.1074/jbc.M403794200.

[13] Berse M, Bounpheng M, Huang X, Christy B, Pollmann C, Dubiel W. Ubiquitin-dependent degradation of Id1 and Id3 is mediated by the COP9 signalosome. Journal of Molecular Biology. 2004; 343: 361–370. https://doi.org/10.1016/j.jmb.2004.08.043.

[14] Williams SA, Maecker HL, French DM, Liu J, Gregg A, Silverstein LB, *et al*. USP1 deubiquitinates ID proteins to preserve a mesenchymal stem cell program in osteosarcoma. Cell. 2011; 146: 918–930. https://doi.org/10.1016/j.cell.2011.07.040.

[15] Ling F, Kang B, Sun XH. Id proteins: small molecules, mighty regulators. Current Topics in Developmental Biology. 2014; 110: 189–216. https://doi.org/10.1016/B978-0-12-405943-6.00005-1.

[16] De Masi F, Grove CA, Vedenko A, Alibés A, Gisselbrecht SS, Serrano L, *et al*. Using a structural and logics systems approach to infer bHLH-DNA binding specificity determinants. Nucleic Acids Research. 2011; 39: 4553–4563. https://doi.org/10.1093/nar/gkr070.

[17] Murre C, McCaw PS, Vaessin H, Caudy M, Jan LY, Jan YN, *et al*. Interactions between heterologous helix-loop-helix proteins generate complexes that bind specifically to a common DNA sequence. Cell. 1989; 58: 537–544. https://doi.org/10.1016/0092-8674(89)90434-0.

[18] Roschger C, Cabrele C. The Id-protein family in developmental and cancer-associated pathways. Cell Communication and Signaling. 2017; 15: 7. https://doi.org/10.1186/s12964-016-0161-y.

[19] Lasorella A, Iavarone A, Israel MA. Id2 specifically alters regulation of the cell cycle by tumor suppressor proteins. Molecular and Cellular Biology. 1996; 16: 2570–2578. https://doi.org/10.1128/MCB.16.6.2570.

[20] Iavarone A, Garg P, Lasorella A, Hsu J, Israel MA. The helix-loop-helix protein Id-2 enhances cell proliferation and binds to the retinoblastoma protein. Genes & Development. 1994; 8: 1270–1284. https://doi.org/10.1101/gad.8.11.1270.

[21] Roberts EC, Deed RW, Inoue T, Norton JD, Sharrocks AD. Id helix-loop-helix proteins antagonize pax transcription factor activity by inhibiting DNA binding. Molecular and Cellular Biology. 2001; 21: 524–533. https://doi.org/10.1128/MCB.21.2.524-533.2001.

[22] Lee SB, Frattini V, Bansal M, Castano AM, Sherman D, Hutchinson K, *et al*. An ID2-dependent mechanism for VHL inactivation in cancer. Nature. 2016; 529: 172–177. https://doi.org/10.1038/nature16475.

[23] Chen L, Qiu J, Yang C, Yang X, Chen X, Jiang J, *et al*. Identification of a novel estrogen receptor beta1 binding partner, inhibitor of differentiation-1, and role of ERbeta1 in human breast cancer cells. Cancer Letters. 2009; 278: 210–219. https://doi.org/10.1016/j.canlet.2009.01.008.

[24] Zhang X, Ling MT, Wang Q, Lau CK, Leung SCL, Lee TK, *et al*. Identification of a novel inhibitor of differentiation-1 (ID-1) binding partner, caveolin-1, and its role in epithelial-mesenchymal transition and resistance to apoptosis in prostate cancer cells. The Journal of Biological Chemistry. 2007; 282: 33284–33294. https://doi.org/10.1074/jbc.M705089200.

[25] Chu YH, Lin JD, Nath S, Schachtrup C. Id proteins: emerging roles in CNS disease and targets for modifying neural stemcell behavior. Cell and Tissue Research. 2022; 387: 433–449. https://doi.org/10.1007/s00441-021-03490-z.

[26] Tournay O, Benezra R. Transcription of the dominant-negative helix-loop-helix protein Id1 is regulated by a protein complex containing the immediate-early response gene Egr-1. Molecular and Cellular Biology. 1996; 16: 2418–2430. https://doi.org/10.1128/MCB.16.5.2418.

[27] O'Brien CA, Kreso A, Ryan P, Hermans KG, Gibson L, Wang Y, *et al*. ID1 and ID3 regulate the self-renewal capacity of human colon cancer-initiating cells through p21. Cancer Cell. 2012; 21: 777–792. https://doi.org/10.1016/j.ccr.2012.04.036.

[28] Zheng W, Wang H, Xue L, Zhang Z, Tong T. Regulation of cellular senescence and p16(INK4a) expression by Id1 and E47 proteins in human diploid fibroblast. The Journal of Biological Chemistry. 2004; 279: 31524–31532. https://doi.org/10.1074/jb

c.M400365200.
[29] Tanaka A, Itoh F, Nishiyama K, Takezawa T, Kurihara H, Itoh S, *et al*. Inhibition of endothelial cell activation by bHLH protein E2-2 and its impairment of angiogenesis. Blood. 2010; 115: 4138–4147. https://doi.org/10.1182/blood-2009-05-223057.
[30] Scharpfenecker M, van Dinther M, Liu Z, van Bezooijen RL, Zhao Q, Pukac L, *et al*. BMP-9 signals via ALK1 and inhibits bFGF-induced endothelial cell proliferation and VEGF-stimulated angiogenesis. Journal of Cell Science. 2007; 120: 964–972. https://doi.org/10.1242/jcs.002949.
[31] Wang H, Yu Y, Guo RW, Shi YK, Song MB, Chen JF, *et al*. Inhibitor of DNA binding-1 promotes the migration and proliferation of endothelial progenitor cells in vitro. Molecular and Cellular Biochemistry. 2010; 335: 19–27. https://doi.org/10.1007/s11010-009-0236-9.
[32] Wang G, Qiu J, Hu J, Tang C, Yin T. Id1: a novel therapeutic target for patients with atherosclerotic plaque rupture. Medical Hypotheses. 2011; 76: 627–628. https://doi.org/10.1016/j.mehy.2011.01.014.
[33] Qiu J, Li Y, Wang B, Sun X, Qian D, Ying Y, *et al*. The Role and Research Progress of Inhibitor of Differentiation 1 in Atherosclerosis. DNA and Cell Biology. 2022; 41: 71–79. https://doi.org/10.1089/dna.2021.0745.
[34] Fraidenraich D, Stillwell E, Romero E, Wilkes D, Manova K, Basson CT, *et al*. Rescue of cardiac defects in id knockout embryos by injection of embryonic stem cells. Science. 2004; 306: 247–252. https://doi.org/10.1126/science.1102612.
[35] Seyerle AA, Lin HJ, Gogarten SM, Stilp A, Méndez Giráldez R, Soliman E, *et al*. Genome-wide association study of PR interval in Hispanics/Latinos identifies novel locus at *ID2*. Heart. 2018; 104: 904–911. https://doi.org/10.1136/heartjnl-2017-312045.
[36] Springhorn JP, Ellingsen O, Berger HJ, Kelly RA, Smith TW. Transcriptional regulation in cardiac muscle. Coordinate expression of Id with a neonatal phenotype during development and following a hypertrophic stimulus in adult rat ventricular myocytes in vitro. The Journal of Biological Chemistry. 1992; 267: 14360–14365.
[37] Hu W, Xin Y, Hu J, Sun Y, Zhao Y. Inhibitor of DNA binding in heart development and cardiovascular diseases. Cell Communication and Signaling. 2019; 17: 51. https://doi.org/10.1186/s12964-019-0365-z.
[38] Sanjurjo L, Aran G, Téllez É, Amézaga N, Armengol C, López D, *et al*. CD5L Promotes M2 Macrophage Polarization through Autophagy-Mediated Upregulation of ID3. Frontiers in Immunology. 2018; 9: 480. https://doi.org/10.3389/fimmu.2018.00480.
[39] Deng Z, Loyher PL, Lazarov T, Li L, Shen Z, Bhinder B, *et al*. The nuclear factor ID3 endows macrophages with a potent anti-tumour activity. Nature. 2024; 626: 864–873. https://doi.org/10.1038/s41586-023-06950-4.
[40] Maruyama T, Li J, Vaque JP, Konkel JE, Wang W, Zhang B, *et al*. Control of the differentiation of regulatory T cells and T(H)17 cells by the DNA-binding inhibitor Id3. Nature Immunology. 2011; 12: 86–95. https://doi.org/10.1038/ni.1965.
[41] Liu C, Zeng X, Yu S, Ren L, Sun X, Long Y, *et al*. Up-regulated DNA-binding inhibitor Id3 promotes differentiation of regulatory T cell to influence antiviral immunity in chronic hepatitis B virus infection. Life Sciences. 2021; 285: 119991. https://doi.org/10.1016/j.lfs.2021.119991.
[42] Omilusik KD, Shaw LA, Goldrath AW. Remembering one's ID/E-ntity: E/ID protein regulation of T cell memory. Current Opinion in Immunology. 2013; 25: 660–666. https://doi.org/10.1016/j.coi.2013.09.004.
[43] Perry HM, Oldham SN, Fahl SP, Que X, Gonen A, Harmon DB, *et al*. Helix-loop-helix factor inhibitor of differentiation 3 regulates interleukin-5 expression and B-1a B cell proliferation. Arteriosclerosis, Thrombosis, and Vascular Biology. 2013; 33: 2771–2779. https://doi.org/10.1161/ATVBAHA.113.302571.
[44] Osinski V, Srikakulapu P, Haider YM, Marshall MA, Ganta VC, Annex BH, *et al*. Loss of Id3 (Inhibitor of Differentiation 3) Increases the Number of IgM-Producing B-1b Cells in Ischemic Skeletal Muscle Impairing Blood Flow Recovery During Hindlimb Ischemia. Arteriosclerosis, Thrombosis, and Vascular Biology. 2022; 42: 6–18. https://doi.org/10.1161/ATVBAHA.120.315501.
[45] Li H, He Y, Richardson WD, Casaccia P. Two-tier transcriptional control of oligodendrocyte differentiation. Current Opinion in Neurobiology. 2009; 19: 479–485. https://doi.org/10.1016/j.conb.2009.08.004.
[46] Gokhan S, Marin-Husstege M, Yung SY, Fontanez D, Casaccia-Bonnefil P, Mehler MF. Combinatorial profiles of oligodendrocyte-selective classes of transcriptional regulators differentially modulate myelin basic protein gene expression. The Journal of Neuroscience. 2005; 25: 8311–8321. https://doi.org/10.1523/JNEUROSCI.1850-05.2005.
[47] Chen XS, Zhang YH, Cai QY, Yao ZX. ID2: A negative transcription factor regulating oligodendroglia differentiation. Journal of Neuroscience Research. 2012; 90: 925–932. https://doi.org/10.1002/jnr.22826.
[48] Gou X, Tang Y, Qu Y, Xiao D, Ying J, Mu D. Could the inhibitor of DNA binding 2 and 4 play a role in white matter injury? Reviews in the Neurosciences. 2019; 30: 625–638. https://doi.org/10.1515/revneuro-2018-0090.
[49] Huang ZH, Feng AY, Liu J, Zhou L, Zhou B, Yu P. Inhibitor of DNA binding 2 accelerates nerve regeneration after sciatic nerve injury in mice. Neural Regeneration Research. 2021; 16: 2542–2548. https://doi.org/10.4103/1673-5374.313054.
[50] Ongaro L, Schang G, Ho CC, Zhou X, Bernard DJ. TGF-β Superfamily Regulation of Follicle-Stimulating Hormone Synthesis by Gonadotrope Cells: Is There a Role for Bone Morphogenetic Proteins? Endocrinology. 2019; 160: 675–683. https://doi.org/10.1210/en.2018-01038.
[51] Johnson AL, Haugen MJ, Woods DC. Role for inhibitor of differentiation/deoxyribonucleic acid-binding (Id) proteins in granulosa cell differentiation. Endocrinology. 2008; 149: 3187–3195. https://doi.org/10.1210/en.2007-1659.
[52] Gupta S, Fink MK, Kempuraj D, Sinha NR, Martin LM, Keele LM, *et al*. Corneal fibrosis abrogation by a localized AAV-mediated inhibitor of differentiation 3 (Id3) gene therapy in rabbit eyes in vivo. Molecular Therapy. 2022; 30: 3334. https://doi.org/10.1016/j.ymthe.2022.08.015.
[53] Gupta S, Martin LM, Sinha NR, Smith KE, Sinha PR, Dailey EM, *et al*. Role of *inhibitor of differentiation 3 gene* in cellular differentiation of human corneal stromal fibroblasts. Molecular Vision. 2020; 26: 742–756.
[54] Cutchins A, Harmon DB, Kirby JL, Doran AC, Oldham SN, Skaflen M, *et al*. Inhibitor of differentiation-3 mediates high fat diet-induced visceral fat expansion. Arteriosclerosis, Thrombosis, and Vascular Biology. 2012; 32: 317–324. https://doi.org/10.1161/ATVBAHA.111.234856.
[55] Svendstrup M, Vestergaard H. The potential role of inhibitor of differentiation-3 in human adipose tissue remodeling and metabolic health. Molecular Genetics and Metabolism. 2014; 113: 149–154. https://doi.org/10.1016/j.ymgme.2014.08.008.
[56] Murad JM, Place CS, Ran C, Hekmatyar SKN, Watson NP, Kauppinen RA, *et al*. Inhibitor of DNA binding 4 (ID4) regulation of adipocyte differentiation and adipose tissue formation in mice. The Journal of Biological Chemistry. 2010; 285: 24164–24173. https://doi.org/10.1074/jbc.M110.128744.
[57] Guo X, Niu Y, Han W, Han X, Chen Q, Tian S, *et al*. The ALK1 Smad1/5 ID1 pathway participates in tumour angiogenesis induced by low dose photodynamic therapy. International Jour-

nal of Oncology. 2023; 62: 55. https://doi.org/10.3892/ijo.2023.5503.

[58] Shen C. ID1 and IGFBP3: roles in cellular senescence, cardiac development, angiogenesis and cancer diagnosis. Journal of Translational Medicine. 2023; 21: 797. https://doi.org/10.1186/s12967-023-04701-7.

[59] Lee TK, Poon RTP, Yuen AP, Ling MT, Wang XH, Wong YC, *et al*. Regulation of angiogenesis by Id-1 through hypoxia-inducible factor-1alpha-mediated vascular endothelial growth factor up-regulation in hepatocellular carcinoma. Clinical Cancer Research. 2006; 12: 6910–6919. https://doi.org/10.1158/1078-0432.CCR-06-0489.

[60] Lyden D, Young AZ, Zagzag D, Yan W, Gerald W, O'Reilly R, *et al*. Id1 and Id3 are required for neurogenesis, angiogenesis and vascularization of tumour xenografts. Nature. 1999; 401: 670–677. https://doi.org/10.1038/44334.

[61] Mellick AS, Plummer PN, Nolan DJ, Gao D, Bambino K, Hahn M, *et al*. Using the transcription factor inhibitor of DNA binding 1 to selectively target endothelial progenitor cells offers novel strategies to inhibit tumor angiogenesis and growth. Cancer Research. 2010; 70: 7273–7282. https://doi.org/10.1158/0008-5472.CAN-10-1142.

[62] Volpert OV, Pili R, Sikder HA, Nelius T, Zaichuk T, Morris C, *et al*. Id1 regulates angiogenesis through transcriptional repression of thrombospondin-1. Cancer Cell. 2002; 2: 473–483. https://doi.org/10.1016/s1535-6108(02)00209-x.

[63] Dell'Orso S, Ganci F, Strano S, Blandino G, Fontemaggi G. ID4: a new player in the cancer arena. Oncotarget. 2010; 1: 48–58. https://doi.org/10.18632/oncotarget.108.

[64] Choi SH, Jang J, Kim Y, Park CG, Lee SY, Kim H, *et al*. ID1^{high}/activin A^{high} glioblastoma cells contribute to resistance to anti-angiogenesis therapy through malformed vasculature. Cell Death & Disease. 2024; 15: 292. https://doi.org/10.1038/s41419-024-06678-7.

[65] Ying QL, Nichols J, Chambers I, Smith A. BMP induction of Id proteins suppresses differentiation and sustains embryonic stem cell self-renewal in collaboration with STAT3. Cell. 2003; 115: 281–292. https://doi.org/10.1016/s0092-8674(03)00847-x.

[66] Zhao Y, Luo A, Li S, Zhang W, Chen H, Li Y, *et al*. Inhibitor of Differentiation/DNA Binding 1 (ID1) Inhibits Etoposide-induced Apoptosis in a c-Jun/c-Fos-dependent Manner. The Journal of Biological Chemistry. 2016; 291: 6831–6842. https://doi.org/10.1074/jbc.M115.704361.

[67] Niu LL, Cheng CL, Li MY, Yang SL, Hu BG, Chong CCN, *et al*. ID1-induced p16/IL6 axis activation contributes to the resistant of hepatocellular carcinoma cells to sorafenib. Cell Death & Disease. 2018; 9: 852. https://doi.org/10.1038/s41419-018-0926-x.

[68] Yin X, Tang B, Li JH, Wang Y, Zhang L, Xie XY, *et al*. ID1 promotes hepatocellular carcinoma proliferation and confers chemoresistance to oxaliplatin by activating pentose phosphate pathway. Journal of Experimental & Clinical Cancer Research. 2017; 36: 166. https://doi.org/10.1186/s13046-017-0637-7.

[69] Li B, Xu WW, Guan XY, Qin YR, Law S, Lee NPY, *et al*. Competitive Binding Between Id1 and E2F1 to Cdc20 Regulates E2F1 Degradation and Thymidylate Synthase Expression to Promote Esophageal Cancer Chemoresistance. Clinical Cancer Research. 2016; 22: 1243–1255. https://doi.org/10.1158/1078-0432.CCR-15-1196.

[70] Sun WZ, Li MH, Chu M, Wei LL, Bi MY, He Y, *et al*. Id1 knockdown induces the apoptosis and inhibits the proliferation and invasion of ovarian cancer cells. European Review for Medical and Pharmacological Sciences. 2016; 20: 2812–2818.

[71] Chen D, Forootan SS, Gosney JR, Forootan FS, Ke Y. Increased expression of Id1 and Id3 promotes tumorigenicity by enhancing angiogenesis and suppressing apoptosis in small cell lung cancer. Genes & Cancer. 2014; 5: 212–225. https://doi.org/10.18632/genesandcancer.20.

[72] Ling MT, Wang X, Ouyang XS, Xu K, Tsao SW, Wong YC. Id-1 expression promotes cell survival through activation of NF-kappaB signalling pathway in prostate cancer cells. Oncogene. 2003; 22: 4498–4508. https://doi.org/10.1038/sj.onc.1206693.

[73] Kuang X, Xiong J, Lu T, Wang W, Zhang Z, Wang J. Inhibition of USP1 induces apoptosis via ID1/AKT pathway in B-cell acute lymphoblastic leukemia cells. International Journal of Medical Sciences. 2021; 18: 245–255. https://doi.org/10.7150/ijms.47597.

[74] Mern DS, Hoppe-Seyler K, Hoppe-Seyler F, Hasskarl J, Burwinkel B. Targeting Id1 and Id3 by a specific peptide aptamer induces E-box promoter activity, cell cycle arrest, and apoptosis in breast cancer cells. Breast Cancer Research and Treatment. 2010; 124: 623–633. https://doi.org/10.1007/s10549-010-0810-6.

[75] Lin J, Guan Z, Wang C, Feng L, Zheng Y, Caicedo E, *et al*. Inhibitor of differentiation 1 contributes to head and neck squamous cell carcinoma survival via the NF-kappaB/survivin and phosphoinositide 3-kinase/Akt signaling pathways. Clinical Cancer Research. 2010; 16: 77–87. https://doi.org/10.1158/1078-0432.CCR-08-2362.

[76] Savagner P. The epithelial-mesenchymal transition (EMT) phenomenon. Annals of Oncology. 2010; 21: vii89–vii92. https://doi.org/10.1093/annonc/mdq292.

[77] Schmidt M, Asirvatham AJ, Chaudhary J. Inhibitor of differentiation 1 (ID1) promotes cell survival and proliferation of prostate epithelial cells. Cellular & Molecular Biology Letters. 2010; 15: 272–295. https://doi.org/10.2478/s11658-010-0007-3.

[78] Cubillo E, Diaz-Lopez A, Cuevas EP, Moreno-Bueno G, Peinado H, Montes A, *et al*. E47 and Id1 interplay in epithelial-mesenchymal transition. PLoS ONE. 2013; 8: e59948. https://doi.org/10.1371/journal.pone.0059948.

[79] Liu K, Chen X, Wu L, Chen S, Fang N, Cai L, *et al*. ID1 mediates resistance to osimertinib in EGFR T790M-positive non-small cell lung cancer through epithelial-mesenchymal transition. BMC Pulmonary Medicine. 2021; 21: 163. https://doi.org/10.1186/s12890-021-01540-4.

[80] Deng G, Chen Y, Guo C, Yin L, Han Y, Li Y, *et al*. BMP4 promotes the metastasis of gastric cancer by inducing epithelial-mesenchymal transition via ID1. Journal of Cell Science. 2020; 133: jcs237222. https://doi.org/10.1242/jcs.237222.

[81] Yang H, Sun Y, Jia X, Cai Y, Zhao X, Li N. TBX3 promotes the epithelial mesenchymal transition of cervical cancer by upregulating ID1. American Journal of Cancer Research. 2023; 13: 4115–4124.

[82] Teo WS, Nair R, Swarbrick A. New insights into the role of ID proteins in breast cancer metastasis: a MET affair. Breast Cancer Research. 2014; 16: 305. https://doi.org/10.1186/bcr3654.

[83] Qian T, Lee JY, Park JH, Kim HJ, Kong G. Id1 enhances RING1b E3 ubiquitin ligase activity through the Mel-18/Bmi-1 polycomb group complex. Oncogene. 2010; 29: 5818–5827. https://doi.org/10.1038/onc.2010.317.

[84] Meng J, Li S, Niu ZQ, Bao ZQ, Niu LL. The efficacy of sorafenib against hepatocellular carcinoma is enhanced by 5-aza-mediated inhibition of ID1 promoter methylation. FEBS Open Bio. 2024; 14: 127–137. https://doi.org/10.1002/2211-5463.13734.

[85] Chen H, Zhang M, Li J, Liu M, Cao D, Li YY, *et al*. BMP9-ID1 Pathway Attenuates N^6-Methyladenosine Levels of CyclinD1 to Promote Cell Proliferation in Hepatocellular Carcinoma. International Journal of Molecular Sciences. 2024; 25: 981. https://doi.org/10.3390/ijms25020981.

[86] Martini M, Cenci T, D'Alessandris GQ, Cesarini V, Cocomazzi A, Ricci-Vitiani L, *et al*. Epigenetic silencing of Id4 identifies a glioblastoma subgroup with a better prognosis as a consequence of an inhibition of angiogenesis. Cancer. 2013; 119: 1004–1012.

https://doi.org/10.1002/cncr.27821.
[87] Yu L, Liu C, Vandeusen J, Becknell B, Dai Z, Wu YZ, *et al*. Global assessment of promoter methylation in a mouse model of cancer identifies ID4 as a putative tumor-suppressor gene in human leukemia. Nature Genetics. 2005; 37: 265–274. https://doi.org/10.1038/ng1521.
[88] Tamari K, Konno M, Asai A, Koseki J, Hayashi K, Kawamoto K, *et al*. Polyamine flux suppresses histone lysine demethylases and enhances *ID1* expression in cancer stem cells. Cell Death Discovery. 2018; 4: 104. https://doi.org/10.1038/s41420-018-0117-7.
[89] Zhang J, Ying Y, Li M, Wang M, Huang X, Jia M, *et al*. Targeted inhibition of KDM6 histone demethylases eradicates tumor-initiating cells via enhancer reprogramming in colorectal cancer. Theranostics. 2020; 10: 10016–10030. https://doi.org/10.7150/thno.47081.
[90] Yu WP, Scott SA, Dong WF. Induction of ID1 expression and apoptosis by the histone deacetylase inhibitor (trichostatin A) in human acute myeloid leukaemic cells. Cell Proliferation. 2008; 41: 86–97. https://doi.org/10.1111/j.1365-2184.2007.00499.x.
[91] Xiao F, Qiu H, Cui H, Ni X, Li J, Liao W, *et al*. MicroRNA-885-3p inhibits the growth of HT-29 colon cancer cell xenografts by disrupting angiogenesis via targeting BMPR1A and blocking BMP/Smad/Id1 signaling. Oncogene. 2015; 34: 1968–1978. https://doi.org/10.1038/onc.2014.134.
[92] Ullmann P, Rodriguez F, Schmitz M, Meurer SK, Qureshi-Baig K, Felten P, *et al*. The miR-371∼373 Cluster Represses Colon Cancer Initiation and Metastatic Colonization by Inhibiting the TGFBR2/ID1 Signaling Axis. Cancer Research. 2018; 78: 3793–3808. https://doi.org/10.1158/0008-5472.CAN-17-3003.
[93] Zhang B, Chu W, Li Z, Zhang Y, Zhen Q, Lv B, *et al*. Circ-ATIC Serves as a Sponge of miR-326 to Accelerate Esophageal Squamous Cell Carcinoma Progression by Targeting ID1. Biochemical Genetics. 2022; 60: 1585–1600. https://doi.org/10.1007/s10528-021-10167-3.
[94] Liao G, Huang Z, Gan T, Wu C, Wang X, Li D. Long non-coding RNA nuclear enriched abundant transcript 1 (NEAT1) modulates inhibitor of DNA binding 1 (ID1) to facilitate papillary thyroid carcinoma development by sponging microRNA-524-5p. Bioengineered. 2022; 13: 13201–13212. https://doi.org/10.1080/21655979.2022.2076498.
[95] Teng Y, Zhao L, Zhang Y, Chen W, Li X. Id-1, a protein repressed by miR-29b, facilitates the TGFβ1-induced epithelial-mesenchymal transition in human ovarian cancer cells. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology. 2014; 33: 717–730. https://doi.org/10.1159/000358647.
[96] Rothschild SI, Tschan MP, Jaggi R, Fey MF, Gugger M, Gautschi O. MicroRNA-381 represses ID1 and is deregulated in lung adenocarcinoma. Journal of Thoracic Oncology. 2012; 7: 1069–1077. https://doi.org/10.1097/JTO.0b013e31824fe976.
[97] Ma J, Wen X, Xu Z, Xia P, Jin Y, Lin J, *et al*. Abnormal regulation of miR-29b-ID1 signaling is involved in the process of decitabine resistance in leukemia cells. Cell Cycle. 2023; 22: 1215–1231. https://doi.org/10.1080/15384101.2023.2200312.
[98] Das S, Dasari A. Epidemiology, Incidence, and Prevalence of Neuroendocrine Neoplasms: Are There Global Differences? Current Oncology Reports. 2021; 23: 43. https://doi.org/10.1007/s11912-021-01029-7.
[99] Chevalier B, Coppin L, Romanet P, Cuny T, Maïza JC, Abeillon J, *et al*. Beyond MEN1, When to Think About MEN4? Retrospective Study on 5600 Patients in the French Population and Literature Review. The Journal of Clinical Endocrinology and Metabolism. 2024; 109: e1482–e1493. https://doi.org/10.1210/clinem/dgae055.
[100] Ganeshan D, Menias CO, Pickhardt PJ, Sandrasegaran K, Lubner MG, Ramalingam P, *et al*. Tumors in von Hippel-Lindau Syndrome: From Head to Toe-Comprehensive State-of-the-Art Review. Radiographics. 2018; 38: 849–866. https://doi.org/10.1148/rg.2018170156.
[101] Manoukian SB, Kowal DJ. Comprehensive imaging manifestations of tuberous sclerosis. AJR. American Journal of Roentgenology. 2015; 204: 933–943. https://doi.org/10.2214/AJR.13.12235.
[102] Esteller M. Epigenetics in cancer. The New England Journal of Medicine. 2008; 358: 1148–1159. https://doi.org/10.1056/NEJMra072067.
[103] Zhang HY, Rumilla KM, Jin L, Nakamura N, Stilling GA, Ruebel KH, *et al*. Association of DNA methylation and epigenetic inactivation of RASSF1A and beta-catenin with metastasis in small bowel carcinoid tumors. Endocrine. 2006; 30: 299–306. https://doi.org/10.1007/s12020-006-0008-1.
[104] House MG, Herman JG, Guo MZ, Hooker CM, Schulick RD, Lillemoe KD, *et al*. Aberrant hypermethylation of tumor suppressor genes in pancreatic endocrine neoplasms. Annals of Surgery. 2003; 238: 423–431; discussion 431–432. https://doi.org/10.1097/01.sla.0000086659.49569.9e.
[105] Kleiman DA, Beninato T, Sultan S, Crowley MJP, Finnerty B, Kumar R, *et al*. Silencing of UCHL1 by CpG promoter hypermethylation is associated with metastatic gastroenteropancreatic well-differentiated neuroendocrine (carcinoid) tumors. Annals of Surgical Oncology. 2014; 21: S672–S679. https://doi.org/10.1245/s10434-014-3787-2.
[106] Bollard J, Massoma P, Vercherat C, Blanc M, Lepinasse F, Gadot N, *et al*. The axon guidance molecule semaphorin 3F is a negative regulator of tumor progression and proliferation in ileal neuroendocrine tumors. Oncotarget. 2015; 6: 36731–36745. https://doi.org/10.18632/oncotarget.5481.
[107] Mafficini A, Scarpa A. Genetics and Epigenetics of Gastroenteropancreatic Neuroendocrine Neoplasms. Endocrine Reviews. 2019; 40: 506–536. https://doi.org/10.1210/er.2018-00160.
[108] Zhang H, He J, Li J, Tian D, Gu L, Zhou M. Methylation of RASSF1A gene promoter is regulated by p53 and DAXX. FASEB Journal. 2013; 27: 232–242. https://doi.org/10.1096/fj.12-215491.
[109] Pizzi S, Azzoni C, Bottarelli L, Campanini N, D'Adda T, Pasquali C, *et al*. RASSF1A promoter methylation and 3p21.3 loss of heterozygosity are features of foregut, but not midgut and hindgut, malignant endocrine tumours. The Journal of Pathology. 2005; 206: 409–416. https://doi.org/10.1002/path.1784.
[110] Donninger H, Vos MD, Clark GJ. The RASSF1A tumor suppressor. Journal of Cell Science. 2007; 120: 3163–3172. https://doi.org/10.1242/jcs.010389.
[111] Arnold CN, Sosnowski A, Schmitt-Gräff A, Arnold R, Blum HE. Analysis of molecular pathways in sporadic neuroendocrine tumors of the gastro-entero-pancreatic system. International Journal of Cancer. 2007; 120: 2157–2164. https://doi.org/10.1002/ijc.22569.
[112] Zhao R, Choi BY, Lee MH, Bode AM, Dong Z. Implications of Genetic and Epigenetic Alterations of CDKN2A (p16(INK4a)) in Cancer. eBioMedicine. 2016; 8: 30–39. https://doi.org/10.1016/j.ebiom.2016.04.017.
[113] Liu L, Broaddus RR, Yao JC, Xie S, White JA, Wu TT, *et al*. Epigenetic alterations in neuroendocrine tumors: methylation of RAS-association domain family 1, isoform A and p16 genes are associated with metastasis. Modern Pathology. 2005; 18: 1632–1640. https://doi.org/10.1038/modpathol.3800490.
[114] Serrano J, Goebel SU, Peghini PL, Lubensky IA, Gibril F, Jensen RT. Alterations in the p16INK4a/CDKN2A tumor suppressor gene in gastrinomas. The Journal of Clinical Endocrinology and Metabolism. 2000; 85: 4146–4156. https://doi.org/10.1210/jcem.85.11.6970.

[115] Arnold CN, Nagasaka T, Goel A, Scharf I, Grabowski P, Sosnowski A, *et al*. Molecular characteristics and predictors of survival in patients with malignant neuroendocrine tumors. International Journal of Cancer. 2008; 123: 1556–1564. https://doi.org/10.1002/ijc.23690.

[116] Kulke MH, Hornick JL, Frauenhoffer C, Hooshmand S, Ryan DP, Enzinger PC, *et al*. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. Clinical Cancer Research. 2009; 15: 338–345. https://doi.org/10.1158/1078-0432.CCR-08-1476.

[117] Stefanoli M, La Rosa S, Sahnane N, Romualdi C, Pastorino R, Marando A, *et al*. Prognostic relevance of aberrant DNA methylation in g1 and g2 pancreatic neuroendocrine tumors. Neuroendocrinology. 2014; 100: 26–34. https://doi.org/10.1159/000365449.

[118] Wild A, Ramaswamy A, Langer P, Celik I, Fendrich V, Chaloupka B, *et al*. Frequent methylation-associated silencing of the tissue inhibitor of metalloproteinase-3 gene in pancreatic endocrine tumors. The Journal of Clinical Endocrinology and Metabolism. 2003; 88: 1367–1373. https://doi.org/10.1210/jc.2002-021027.

[119] Schmitt AM, Schmid S, Rudolph T, Anlauf M, Prinz C, Klöppel G, *et al*. VHL inactivation is an important pathway for the development of malignant sporadic pancreatic endocrine tumors. Endocrine-related Cancer. 2009; 16: 1219–1227. https://doi.org/10.1677/ERC-08-0297.

[120] Dreijerink KMA, Derks JL, Cataldo I, Scarpa A, Valk GD, Speel EJM. Genetics and Epigenetics of Pancreatic Neuroendocrine Tumors and Pulmonary Carcinoids. Frontiers of Hormone Research. 2015; 44: 115–138. https://doi.org/10.1159/000382138.

[121] Pelosi G, Fumagalli C, Trubia M, Sonzogni A, Rekhtman N, Maisonneuve P, *et al*. Dual role of RASSF1 as a tumor suppressor and an oncogene in neuroendocrine tumors of the lung. Anticancer Research. 2010; 30: 4269–4281.

[122] Chaussade L, Eymin B, Brambilla E, Gazzeri S. Expression of p15 and p15.5 products in neuroendocrine lung tumours: relationship with p15(INK4b) methylation status. Oncogene. 2001; 20: 6587–6596. https://doi.org/10.1038/sj.onc.1204798.

[123] Swarts DRA, Scarpa A, Corbo V, Van Criekinge W, van Engeland M, Gatti G, *et al*. MEN1 gene mutation and reduced expression are associated with poor prognosis in pulmonary carcinoids. The Journal of Clinical Endocrinology and Metabolism. 2014; 99: E374–E378. https://doi.org/10.1210/jc.2013-2782.

[124] Wu J, Di D, Zhao C, Pan Q, Liu Y, Zhang X, *et al*. Clinical Significance of Gli-1 And Caveolin-1 Expression in the Human Small Cell Lung Cancer. Asian Pacific Journal of Cancer Prevention. 2018; 19: 401–406. https://doi.org/10.22034/APJCP.2018.19.2.401.

[125] Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nature Reviews. Cancer. 2017; 17: 725–737. https://doi.org/10.1038/nrc.2017.87.

[126] Vaz M, Hwang SY, Kagiampakis I, Phallen J, Patil A, O'Hagan HM, *et al*. Chronic Cigarette Smoke-Induced Epigenomic Changes Precede Sensitization of Bronchial Epithelial Cells to Single-Step Transformation by KRAS Mutations. Cancer Cell. 2017; 32: 360–376.e6. https://doi.org/10.1016/j.ccell.2017.08.006.

[127] Chang CJ, Hung MC. The role of EZH2 in tumour progression. British Journal of Cancer. 2012; 106: 243–247. https://doi.org/10.1038/bjc.2011.551.

[128] Choi IS, Estecio MRH, Nagano Y, Kim DH, White JA, Yao JC, *et al*. Hypomethylation of LINE-1 and Alu in well-differentiated neuroendocrine tumors (pancreatic endocrine tumors and carcinoid tumors). Modern Pathology. 2007; 20: 802–810. https://doi.org/10.1038/modpathol.3800825.

[129] Martire S, Banaszynski LA. The roles of histone variants in fine-tuning chromatin organization and function. Nature Reviews. Molecular Cell Biology. 2020; 21: 522–541. https://doi.org/10.1038/s41580-020-0262-8.

[130] Augert A, Zhang Q, Bates B, Cui M, Wang X, Wildey G, *et al*. Small Cell Lung Cancer Exhibits Frequent Inactivating Mutations in the Histone Methyltransferase KMT2D/MLL2: CALGB 151111 (Alliance). Journal of Thoracic Oncology. 2017; 12: 704–713. https://doi.org/10.1016/j.jtho.2016.12.011.

[131] Jia D, Augert A, Kim DW, Eastwood E, Wu N, Ibrahim AH, *et al*. *Crebbp* Loss Drives Small Cell Lung Cancer and Increases Sensitivity to HDAC Inhibition. Cancer Discovery. 2018; 8: 1422–1437. https://doi.org/10.1158/2159-8290.CD-18-0385.

[132] Fussey JM, Vaidya B, Kim D, Clark J, Ellard S, Smith JA. The role of molecular genetics in the clinical management of sporadic medullary thyroid carcinoma: A systematic review. Clinical Endocrinology. 2019; 91: 697–707. https://doi.org/10.1111/cen.14060.

[133] Catalanotto C, Cogoni C, Zardo G. MicroRNA in Control of Gene Expression: An Overview of Nuclear Functions. International Journal of Molecular Sciences. 2016; 17: 1712. https://doi.org/10.3390/ijms17101712.

[134] Boons G, Vandamme T, Peeters M, Van Camp G, Op de Beeck K. Clinical applications of (epi)genetics in gastroenteropancreatic neuroendocrine neoplasms: Moving towards liquid biopsies. Reviews in Endocrine & Metabolic Disorders. 2019; 20: 333–351. https://doi.org/10.1007/s11154-019-09508-w.

[135] Lee YS, Kim H, Kim HW, Lee JC, Paik KH, Kang J, *et al*. High Expression of MicroRNA-196a Indicates Poor Prognosis in Resected Pancreatic Neuroendocrine Tumor. Medicine. 2015; 94: e2224. https://doi.org/10.1097/MD.0000000000002224.

[136] Gill P, Kim E, Chua TC, Clifton-Bligh RJ, Nahm CB, Mittal A, *et al*. MiRNA-3653 Is a Potential Tissue Biomarker for Increased Metastatic Risk in Pancreatic Neuroendocrine Tumours. Endocrine Pathology. 2019; 30: 128–133. https://doi.org/10.1007/s12022-019-9570-y.

[137] Zhang T, Choi S, Zhang T, Chen Z, Chi Y, Huang S, *et al*. miR-431 Promotes Metastasis of Pancreatic Neuroendocrine Tumors by Targeting DAB2 Interacting Protein, a Ras GTPase Activating Protein Tumor Suppressor. The American Journal of Pathology. 2020; 190: 689–701. https://doi.org/10.1016/j.ajpath.2019.11.007.

[138] Rapa I, Votta A, Felice B, Righi L, Giorcelli J, Scarpa A, *et al*. Identification of MicroRNAs Differentially Expressed in Lung Carcinoid Subtypes and Progression. Neuroendocrinology. 2015; 101: 246–255. https://doi.org/10.1159/000381454.

[139] Lee JH, Voortman J, Dingemans AMC, Voeller DM, Pham T, Wang Y, *et al*. MicroRNA expression and clinical outcome of small cell lung cancer. PLoS ONE. 2011; 6: e21300. https://doi.org/10.1371/journal.pone.0021300.

[140] Korbecki J, Simińska D, Gąssowska-Dobrowolska M, Listos J, Gutowska I, Chlubek D, *et al*. Chronic and Cycling Hypoxia: Drivers of Cancer Chronic Inflammation through HIF-1 and NF-κB Activation: A Review of the Molecular Mechanisms. International Journal of Molecular Sciences. 2021; 22: 10701. https://doi.org/10.3390/ijms221910701.

[141] Han Y, Li H. miRNAs as biomarkers and for the early detection of non-small cell lung cancer (NSCLC). Journal of Thoracic Disease. 2018; 10: 3119–3131. https://doi.org/10.21037/jtd.2018.05.32.

[142] Accardo G, Conzo G, Esposito D, Gambardella C, Mazzella M, Castaldo F, *et al*. Genetics of medullary thyroid cancer: An overview. International Journal of Surgery. 2017; 41: S2–S6. https://doi.org/10.1016/j.ijsu.2017.02.064.

[143] Hunter KE, Quick ML, Sadanandam A, Hanahan D, Joyce JA. Identification and characterization of poorly differentiated invasive carcinomas in a mouse model of pancreatic neuroendocrine tumorigenesis. PLoS ONE. 2013; 8: e64472. https://doi.org/10.1371/journal.pone.0064472.

[144] Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, *et al*. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020; 76: 182–188. https://doi.org/10.1111/his.13975.

[145] Alese OB, Jiang R, Shaib W, Wu C, Akce M, Behera M, *et al*. High-Grade Gastrointestinal Neuroendocrine Carcinoma Management and Outcomes: A National Cancer Database Study. The Oncologist. 2019; 24: 911–920. https://doi.org/10.1634/theoncologist.2018-0382.

[146] Reidy DL, Tang LH, Saltz LB. Treatment of advanced disease in patients with well-differentiated neuroendocrine tumors. Nature Clinical Practice. Oncology. 2009; 6: 143–152. https://doi.org/10.1038/ncponc1326.

[147] Kamalian L, Gosney JR, Forootan SS, Foster CS, Bao ZZ, Beesley C, *et al*. Increased expression of Id family proteins in small cell lung cancer and its prognostic significance. Clinical Cancer Research. 2008; 14: 2318–2325. https://doi.org/10.1158/1078-0432.CCR-07-4716.

[148] Zhang S, Li M, Ji H, Fang Z. Landscape of transcriptional deregulation in lung cancer. BMC Genomics. 2018; 19: 435. https://doi.org/10.1186/s12864-018-4828-1.

[149] Langenfeld E, Hong CC, Lanke G, Langenfeld J. Bone morphogenetic protein type I receptor antagonists decrease growth and induce cell death of lung cancer cell lines. PLoS ONE. 2013; 8: e61256. https://doi.org/10.1371/journal.pone.0061256.

[150] Langenfeld E, Deen M, Zachariah E, Langenfeld J. Small molecule antagonist of the bone morphogenetic protein type I receptors suppresses growth and expression of Id1 and Id3 in lung cancer cells expressing Oct4 or nestin. Molecular Cancer. 2013; 12: 129. https://doi.org/10.1186/1476-4598-12-129.

[151] Balajam NZ, Mousavian AH, Sheidaei A, Gohari K, Tavangar SM, Ghanbari-Motlagh A, *et al*. The 15-year national trends of endocrine cancers incidence among Iranian men and women; 2005-2020. Scientific Reports. 2023; 13: 7632. https://doi.org/10.1038/s41598-023-34155-2.

[152] Ciarrocchi A, Piana S, Valcavi R, Gardini G, Casali B. Inhibitor of DNA binding-1 induces mesenchymal features and promotes invasiveness in thyroid tumour cells. European Journal of Cancer. 2011; 47: 934–945. https://doi.org/10.1016/j.ejca.2010.11.009.

[153] Kebebew E, Peng M, Treseler PA, Clark OH, Duh QY, Ginzinger D, *et al*. Id1 gene expression is up-regulated in hyperplastic and neoplastic thyroid tissue and regulates growth and differentiation in thyroid cancer cells. The Journal of Clinical Endocrinology and Metabolism. 2004; 89: 6105–6111. https://doi.org/10.1210/jc.2004-1234.

[154] Kebebew E, Treseler PA, Duh QY, Clark OH. The helix-loop-helix protein, Id-1, is overexpressed and regulates growth in papillary thyroid cancer. Surgery. 2003; 134: 235–241. https://doi.org/10.1067/msy.2003.227.

[155] Deng Z, Xu M, Ding Z, Kong J, Liu J, Zhang Z, *et al*. ID2 promotes tumor progression and metastasis in thyroid cancer. Endocrine. 2024; 84: 1051–1063. https://doi.org/10.1007/s12020-023-03674-3.

[156] Kebebew E, Treseler PA, Duh QY, Clark OH. The helix-loop-helix transcription factor, Id-1, is overexpressed in medullary thyroid cancer. Surgery. 2000; 128: 952–957. https://doi.org/10.1067/msy.2000.111082.

[157] Aggarwal R, Zhang T, Small EJ, Armstrong AJ. Neuroendocrine prostate cancer: subtypes, biology, and clinical outcomes. Journal of the National Comprehensive Cancer Network. 2014; 12: 719–726. https://doi.org/10.6004/jnccn.2014.0073.

[158] Komiya A, Yasuda K, Watanabe A, Fujiuchi Y, Tsuzuki T, Fuse H. The prognostic significance of loss of the androgen receptor and neuroendocrine differentiation in prostate biopsy specimens among castration-resistant prostate cancer patients. Molecular and Clinical Oncology. 2013; 1: 257–262. https://doi.org/10.3892/mco.2013.69.

[159] Bhagirath D, Liston M, Akoto T, Lui B, Bensing BA, Sharma A, *et al*. Novel, non-invasive markers for detecting therapy induced neuroendocrine differentiation in castration-resistant prostate cancer patients. Scientific Reports. 2021; 11: 8279. https://doi.org/10.1038/s41598-021-87441-2.

[160] Arnold P, Penaloza-Ramos MC, Adedokun L, Rees S, Lockhat M, Spary L, *et al*. Clinical characteristics and outcomes for patients with non metastatic castration-resistant prostate cancer. Scientific Reports. 2021; 11: 22151. https://doi.org/10.1038/s41598-021-01042-7.

[161] Beltran H, Demichelis F. Therapy considerations in neuroendocrine prostate cancer: what next? Endocrine-Related Cancer. 2021; 28: T67–T78. https://doi.org/10.1530/ERC-21-0140.

[162] Thoreson GR, Gayed BA, Chung PH, Raj GV. Emerging therapies in castration resistant prostate cancer. The Canadian Journal of Urology. 2014; 21: 98–105.

[163] Quicios-Dorado C, Bolufer-Moragues E, Gomis-Goti C, Cabello-Benavente R, Cannata-Ortiz PJ, González-Enguita C. Aggressive variants of castration resistant prostate cancer (CRPC): neuroendocrine prostate cancer. Archivos Espanoles De Urologia. 2018; 71: 721–734.

[164] Epstein JI, Amin MB, Beltran H, Lotan TL, Mosquera JM, Reuter VE, *et al*. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. The American Journal of Surgical Pathology. 2014; 38: 756–767. https://doi.org/10.1097/PAS.0000000000000208.

[165] Surintrspanont J, Zhou M. Prostate Pathology: What is New in the 2022 WHO Classification of Urinary and Male Genital Tumors? Pathologica. 2022; 115: 41–56. https://doi.org/10.32074/1591-951X-822.

[166] Bishop JL, Sangha B, Gleave M, Zoubeidi A. Immune evasion strategies of neuroendocrine-like Enzalutamide resistant prostate cancer. Journal for Immunotherapy of Cancer. 2013; 1: P147. https://doi.org/10.1186/2051-1426-1-S1-P147.

[167] Zhang J, Chen Z, Mao Y, He Y, Wu X, Wu J, *et al*. ID2 Promotes Lineage Transition of Prostate Cancer through FGFR and JAK-STAT Signaling. Cancers. 2024; 16: 392. https://doi.org/10.3390/cancers16020392.

[168] Lee AR, Li Y, Xie N, Gleave ME, Cox ME, Collins CC, *et al*. Alternative RNA splicing of the MEAF6 gene facilitates neuroendocrine prostate cancer progression. Oncotarget. 2017; 8: 27966–27975. https://doi.org/10.18632/oncotarget.15854.