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Review

Insulin-Degrading Enzyme, an under-estimated potential target to treat cancer?

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Abstract: Insulin-degrading enzyme (IDE) is a multi-functional protease due to the variety of its substrates, its various cellular locations, its conservation between species and its many non-proteolytic functions. Numerous studies have successfully demonstrated its implication in two main therapeutic areas: metabolic and neuronal diseases. In recent years, several reports have underlined the overexpression of this enzyme in different cancers. Still, the exact role of IDE in the physiopathology of cancer remains to be elucidated. Known as the main enzyme responsible for the degradation of insulin, an essential growth factor for healthy cells but also for cancer cells, IDE has also been shown to behave like a chaperone and to interact with the proteasome. The pharmacological modulation of IDE (siRNA, chemical compounds ...) has demonstrated interesting results in cancer models. All these results point towards IDE as a potential target in cancer. In this review, we will discuss evidences of links between IDE and cancer development or resistance, IDE's functions, catalytic or non-catalytic, in the context of cell proliferation, cancer development and the impact of the pharmacomodulation of IDE as cancer therapeutics.

Keywords: insulin-degrading enzyme; cancer; target

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1. Introduction

Insulin-degrading enzyme (IDE), also called insulysin, is a ubiquitous 110kDa zinc metalloprotease belonging to the M16 family of metalloproteases. As the name suggests, this enzyme was discovered for its ability to degrade insulin but it was soon shown to be implicated in the hydrolysis of many other amyloidogenic peptides such as the amyloid- β peptide, IGF-II, glucagon or amylin. Its roles in diabetes mellitus, insulin resistance, and Alzheimer's disease have been explored for several years and suggest that IDE could be a potential target in these diseases [1–3]. IDE is a remarkable enzyme [4] as it 1) is expressed in all tissues, included non-insulin-sensitive tissues, 2) has various subcellular localizations either at the membrane or in the cytosol or in various organelles, 3) acts differently depending on the organ and 4) has a unique 3D structure.

Furthermore, IDE is found in many subcellular environments, mainly in the cytosol but also in endosomes [5,6], mitochondria [7], peroxisomes [8], nucleus [7,9] and at the plasma membrane [10]. It is also found extracellularly [11–13] and acts as a receptor for varicella virus [14]. These elements, along with evidences of activities beyond proteolysis suggest that IDE is a key multifunctional protein [15].

In addition to the physiological and physiopathological roles of IDE in the above mentioned diseases, we review here the potential roles of IDE in cancer via both substrate hydrolysis activities and other functions.

2. An atypical structure at the basis of IDE's multiple roles

IDE displays two homologous 50 kDa domains joined by a short hinge loop, defining a large inner chamber [16]. One domain contains the conserved HXXEH zinc ion-binding motif [17]. IDE adopts two conformations, an open-conformation which allows internalization of the substrate and release of the products, and a closed-conformation that reconstitutes the catalytic site for the substrate hydrolysis. The displacement of a subdomain, called "swinging door", that unveils an opening towards the enclosed catalytic chamber, has been recently evidenced by both X-Ray and CryoEM [18,19].

X-Ray crystallography and SAXS studies have revealed that IDE can form a dimer. This dimer also undergoes an open-to-closed transition promoted by substrate binding [19]. IDE uses its catalytic chamber to trigger the unfolding of substrates as proven by X-Ray structures that show the substrates in a partially unfolded state inside IDE [20]. IDE uses the size and the electrostatic properties of the catalytic chamber to selectively bind peptides that are less than 80 amino-acids in length and have a high dipole moment (Figure 1). Hydrophobic and aromatic residues of the active site are essential for peptide hydrolysis [21].

IDE is found and evolutionary conserved in a vast number of eukaryotes, including plants and lower organisms such as yeast, even though most of them do not produce cognate substrates, suggesting a key role in cell biology, yet to be fully understood. In particular, IDE has a well conserved exosite (Figure 1). By binding to the N-terminal end of IDE substrates, this exosite facilitates the unfolding of substrates [22] which allow multiple cleavage sites by IDE. Also, the binding of short substrates to the exosite seems to play a regulatory role by reducing the size of the IDE catalytic chamber, and thus entropically favors the binding of a second molecule of substrate at the catalytic site [23]. Also, IDE has an allosteric regulatory site at IDE-C where ATP attaches and selectively accelerates the degradation of the short peptides [24–26] (Figure 1).

Several important studies have also identified key amino-acids for IDE interactions with $\alpha 3$ -20S proteasome subunit (residues R674; R782; F486; E962; E964) [27] or ubiquitin C-term (residues F529 E606 E653) [28].

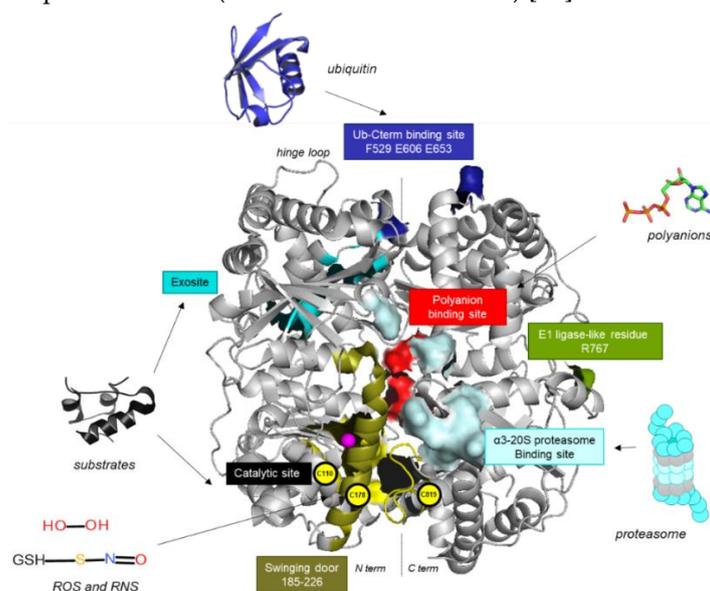


Figure 1. Structure of IDE (from 4NXO). Catalytic site in black, Zn²⁺ ion in magenta; Swinging door in olive exosite in cyan [19]; 20S proteasome binding in light blue [27]; E1 ligase like activity important residue in green [29]; Ub-Cterm binding in marine [28]; polyanion binding site in red [25]; Cysteins sensitive to reactive oxygen species (ROS) or reactive nitrogen species (RNS) in yellow spheres [30].

3. A long list of substrates

IDE behaves primarily as a proteolytic enzyme involved in the degradation of many substrates, amongst which several are of interest in cancer biology (Table 1).

Table 1. Properties of main substrates of IDE involved in cancer.

Substrates	Substrate characterization				Cancer effect ¹		
	Length (Residues)	Affinity (Km in μ M)	PDB codes	References	Pro	Anti	Ref.
<u>Hormones</u>							
Insulin	51	0.070	2G54 ; 2G56; 2WBY; 6BF8; 6BFC ; 6B3Q	[31]	X		[32]
Glucagon	29	3.5	2G49	[33]	X		[34]
Somatostatin	14/28	7.5	-	[35]		X	[36]
ANP	28	<i>nd</i>	3N57	[37]		X	[38,39]
CNP	22	<i>nd</i>	-	[40]		X	[38,39]
<u>Neuropeptides</u>							
B-endorphine	31	13	-	[41]	X	X	[42]
Dynorphin(B9)	9	27	-	[41]		X	[43]
Bradykinine	9	4200	3CWW	[23]	X		[44]
CGRP	37	<i>nd</i>	-	[45]	X		[46]
<u>Growth Factors</u>							
IGF-2	67	<i>nd</i>	3E4Z	[47]	X		[48]
TGF- α	50	<i>nd</i>	3E50	[49,50]	X		[51]
<u>Cytokines</u>							
CCL3	70	<i>nd</i>	3H44	[52,53]	X	X	[54]
CCL4	69	<i>nd</i>	4RAL	[52,53]	X	X	[54]
<u>Others</u>							
ubiquitin	76	<i>nd</i>	3OFI	[55]		X ²	[56]
amyloid β	40-42	2	2G47 ; 2WK3	[57]		X	[58–60]

¹ Main effect of the substrate in cancer describes in the literature. Pro and anti-tumor effects, direct or indirect can include all stages of cancer initiation, promotion and propagation. References referred to general review on the role of the substrate in cancer or if it is not available on an article.

² Perturbation of ubiquitination system in cancer, effect depends on substrates.

nd: not determined

IDE is the main enzyme responsible for the intracellular hydrolysis of insulin[31], glucagon [33] and amylin [61], other peptidic hormones secreted by the pancreas, are also substrates of IDE. Noteworthy, however, is the large difference in Km between insulin, on the one hand, and glucagon and amylin, on the other hand. This questions the biological relevance of IDE-mediated hydrolysis of glucagon and amylin, as no proof of involvement of IDE in the clearance of these peptides *in vivo* exists. Most of reported Km are far above normal plasma concentrations of these substrates, even for insulin which peaks at 2nM, roughly 30-times lower than the Km. However there are indirect proof of the involvement of IDE in insulin degradation. Indeed pharmacological inhibition of IDE increases insulin concentration in plasma and insulin signaling in target organs [62]. To interpret the biological relevance of IDE activity in degrading its substrates, it still needed to measure their actual concentrations, possibly in all possible subcellular location where both substrate and IDE are found and compare them with their Km. In 1994, studies in rats by Kurochkin et al. showed that IDE interacts with radiolabeled A β in both liver and brain[57]. IDE was then proposed as one the enzymes involved in the catabolism of A β . Hydrolysis of CGRP by IDE was evidenced in spinal cord lysates of mice [45]and this

hydrolytic clearance was shown to be entirely IDE-dependent. Many other peptides with various lengths and affinities have been reported as substrates of IDE like somatostatin[35], IGF-2[47], TGF- α [49], β -endorphin[41], dynorphins[41], bradykinin[23], atrial natriuretic peptide (ANP)[37], chemokine ligand (CCL)3 and CCL4 [52,53] and ubiquitin [55]. The involvement of IDE in the degradation of all these substrates suggests its potential role in processes modulated by these peptides. Interestingly, most substrates of IDE share a propensity to be amyloidogenic peptides [63], with a few exceptions like-HIV-1 p6 [64].

IDE has been thus shown to hydrolyze more than 15 different substrates that are involved to cancer pathophysiology. More specifically, insulin, IGF-2 and CCL3 will be detailed below.

4. IDE: a chaperone-like protein?

More and more observations point towards functions of IDE in cells beyond its catalytic activity. In particular, many studies have evidenced interactions with some key proteins and have suggested a chaperone-like activity of IDE. IDE is indeed overexpressed in different human cell lines cancerous and non-cancerous, after environmental stress such as heat-shock, oxidative stress and serum-starvation, in a parallel way to HSP70. This suggests that IDE could be a heat-shock protein. The chaperone effect of IDE is supported by the presence of heat shock elements (HSE) in the IDE gene promotor and by the presence of high affinity binding sites for the heat shock factor [54]. Moreover, it was observed that during a heat-shock response, newly synthesized IDE is translocated from the cytosol toward the ER, an important sub-cellular compartment for protein folding [66]. In the viral context of VZV, IDE bound the non-glycosylated precursor of glycoprotein E in the reticulum endoplasmic [67]. In particular, recombinant soluble IDE is able to induce a conformational change of the glycoprotein E that enhances infectivity and stability of the virus [68]. Some authors have described IDE as “dead-end” chaperone that forms highly stable complexes with amyloid peptides A β and α -synuclein [69,70]. Independently, it was also observed that IDE is able to block the amyloid pathway by promoting non-fibrillar aggregates formation in a non-catalytic way [70,71]. Interestingly, α -synuclein would have a dual effect in cancer, by promoting tumorigenicity but also by inhibiting cancer growth, according to the models studied in the different studies [72]. Ramaraju et al., describes the kinetic model of two IDE-bound states, one used for proteolysis and the other as a kinetic trap to differentiate non-amyloidogenic and amyloidogenic substrates [64]. Finally, IDE interacts with intermediate filaments, vimentin and nestin complexes during mitosis. These interactions modulate its catalytic activity, in a substrate-dependent manner [73]. Vimentin and nestin are described as playing an active role in tumorigenesis, in particular in metastasis and tumor growth [74].

5. IDE's close link with the proteasome

The ubiquitin-proteasome system (UPS) and autophagy are the two main pathways for protein degradation in cells [75,76]. Several studies show a strong functional link between IDE and the UPS. In particular, ubiquitin has been shown by Ralat et al to bind to IDE and to behave as a substrate, several amide bonds being sequentially hydrolyzed, starting with the cleavage of two C-terminal glycines [55,77,78]. Conversely, Grasso et al show that IDE can form K48 and K63 ubiquitin dimers like an E1-like ubiquitin-activating enzyme. However IDE would not assemble poly-ubiquitin chains [28,29]. Beside the direct observations of ubiquitin dimerization and catalytic hydrolysis of ubiquitin, another study by Tundo et al shows that transfection of SY5Y cells with an IDE siRNA reduces the amount of poly-ubiquitylated proteins [65]. This last observation could also be explained by the modulation of the proteasome by the IDE. Indeed, IDE interacts with the 26S and 20S proteasomes and behaves as a competitor of the 19S proteasome to bind to 20S [27,65,79]. The activity of the 20S proteasome is then impacted by

IDE in a bimodal manner explained by the existence of two binding sites displaying different affinities for IDE. Binding of IDE to the site of high affinity (13 nM) is consistent with the hypothesis that IDE could efficiently modulate h20S gating mechanisms [27]. Moreover, transfection of SHSY5Y cells with an IDE siRNA increases all three activities of the 26S proteasome, chymotrypsin, trypsin and caspase, and this modulation does not involve IDE catalytic activity [66]. Fawcett et al showed the inhibition of the proteasome by insulin. Binding of insulin to IDE would limit the activating interaction between IDE and the low affinity binding site on the 20S proteasome [79,80].

The proteasome is an important therapeutic target that led to the development of bortezomib almost twenty years ago, followed by other inhibitors (carfilzomib, ixazomib, oprozomib) in a variety of hematologic malignancies [81]. In this context, a pharmacological intervention targeting IDE could possibly increase the efficacy and/or the potency of antiproliferative activity of proteasome inhibitors.

6. Expression of IDE in human cancers

First protein expression of IDE was measured by cell microarray in more than thirty human tumor cell lines by Schmitt et al. Expression of IDE was confirmed in all tested lines from solid and blood tumors, except two cell lines (Raji lymphoma cells and HL-60 leukemia cells) [82,83]. More interestingly, overexpression of IDE was observed by immunochemistry in malignant human breast [84]. In the same way, Tundo et al showed by immunochemistry that IDE is overexpressed in tumors of the central nervous system (similarly high in grade III and IV malignant glioma cells and olfactory neuroblastoma tumors cells), in comparison to normal nerve cells, suggesting a role of IDE in tumor progression [65]. Recently, in a study of expression of genes related to the insulin and inflammatory pathways in breast cancers, IDE overexpression appears to be a risk factor of relapse and contributes to disease-free survival [85]. In another breast cancer cohort, IDE protein content in the cytoplasm of cells was found increased in tumor, compared to normal mammary gland [84]. In the latter study, a higher proportion of loss of heterozygosity in the locus harboring the ide gene has been found in high grade tumors. Despite the variety of modalities used to measure differences of IDE expression in disease tissues versus controls (mRNA or protein content using antibodies), these studies point out IDE as potential pharmacological target to treat cancer.

7. IDE and the insulin/insulin-growth factor signaling (IIS) pathway

Insulin and IGF, two genuine substrates of IDE control critical pathways in energy metabolism and growth, especially for cancer cells [86–88]. Dietary and lifestyle factors that impact this pathway are identified as cancer risk factors. In line with this observation, obesity itself is a cancer risk factor mediated by insulin resistance, hyperinsulinemia, adipokines secretion by adipose tissue, increasing IGFs expression and chronic inflammation [89]. The International Agency for Research on Cancer (IARC) working group reported from meta-analyses or pooled analyses that the relative risk of cancer for obese people was 1.5 to 1.8 for colon, gastric cardia, liver, gallbladder, pancreas and kidney cancers [90]. In addition to being a risk factor, in a prospective cohort study, people with a body mass index superior to 40, had 52% for men and 62% for women higher risk of death from all cancer than people with normal weight [91]. In the same way, type-2 diabetes, dyslipidemia, hyperglycemia, metabolic syndrome constitutes also a cancer risk factors [92,93].

Insulin binds two receptors isoforms, insulin-receptor A (IRA) or B (IRB). IGF-I binds the IGF1 receptor (IGF1-R) or the hybrid IR/IGF1-R, while IGF-II binds IRA, IGF1R, the hybrid IR-IGF1R and the IGF2 receptor (IGF2-R). For the latter, ligand binding is followed by internalization, lysosomal degradation and downregulation of IGF2. All other receptors when bound to an agonist, transduce a signal with IRS (Insulin Receptor

substrate), which activates the MAPKinase and PI3K/AKT pathways. IGFBP (IGF binding proteins) bind the IGF and in most of cases limits its activities (Figure 2A).

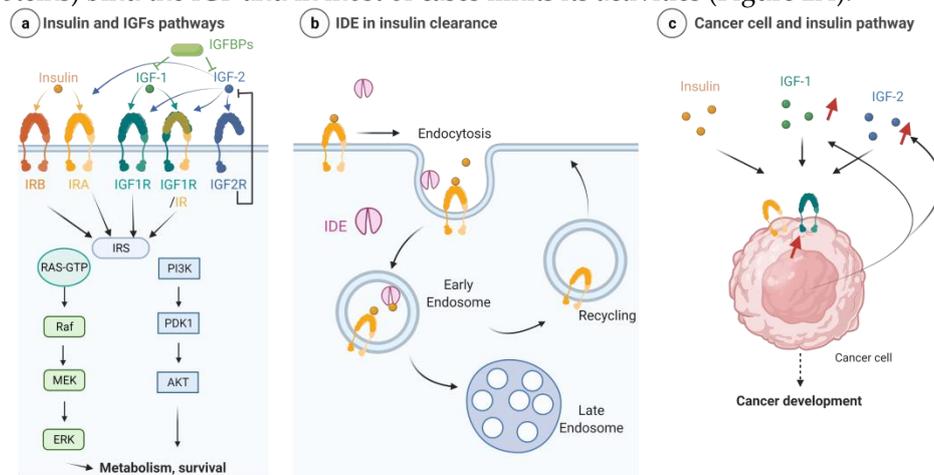


Figure 2. (a) Condensed representation of the insulin and IGFs pathways. After ligand binding and activation, insulin and IGF1 receptors induce a signal through IRS via MAPK and AKT pathways to control cell metabolism and survival. IGFBPs proteins bind IGFs and reduce its signals. The binding of IGF2 to IGF2-R leads to internalization and lysosomal degradation. (b) IDE is involved in insulin clearance, particularly in endosome after activation of insulin receptor by its ligand. (c) Cancer cells overexpress insulin and IGF1 receptors. Cancer cells can produce IGF proteins that act as autocrine and paracrine manner. Insulin and IGFs pathways contribute to cancer development. Red arrows mean overexpression. Created with BioRender.com

IDE has been shown to play a significant role in downstream signaling of insulin. It is indeed involved in insulin clearance in the extracellular compartment, at the plasma membrane, in the endosome and in the cytosol. Receptor-bound insulin is internalized into early-endosomes where IDE can hydrolyze insulin in this non-acidic environment. The recruitment of IDE in endosome can be promoted through phosphatidylinositol phosphates binding at its polyanion site [6]. In the acid late endosome, insulin is dissociated from its receptor and is degraded; the role of IDE in this context is discussed [6]. Then, the insulin receptor can be recycled back to the plasma membrane [94,95] (Figure 2b).

While Miller et al, in a rodent model of *Ide* deficiency failed to detect hyperinsulinemia [96], Farris et al showed that *Ide* gene ablation in mice reduces insulin clearance, induces glucose intolerance and moderate hyperinsulinemia [97]. Recently, a specific deletion of the *Ide* gene in the mouse liver did not show hyperinsulinemia as expected, but an impairment of insulin signaling by downregulating the insulin receptor expression at the plasma membrane [98]. This study suggests a more complex role of IDE in both insulin clearance and trafficking. The transmembrane glycoprotein CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) is involved in the endocytosis of the insulin-receptor activated by insulin. Najjar et al. proposed a cooperative role between IDE and CEACAM1 for insulin trafficking [99]. The ambiguous role of CEACAM1 in human malignancies, reported both as a tumor suppressor or as a tumor progression, angiogenesis, immune evasion factor, depending of malignancies could be explained by variations in IDE expression or catalytic activity in different pathological settings [100].

While IDE regulate both insulin level and signaling in multiple ways, insulin in return appears to regulate IDE expression. Indeed, in hippocampal neurons, insulin up-regulates the expression of IDE through the PI3K/AKT pathway [101]. However in HepG2 cells, a 24h treatment with insulin increases IDE activity without changing its expression (mRNA and protein levels) and this modulation is affected by glucose con-

centration [102]. These findings suggest that insulin signaling modulates IDE expression and/or activity depending on cell type and environment.

Cancer cells express insulin and IGFs receptors. Several studies demonstrated an overexpression of insulin receptors (IR), preferentially IR-A, and IGF1 receptors (IGF1-R) in malignant cells [103,104]. Unlike insulin which is secreted exclusively by pancreatic β cells, IGFs which are produced mainly by liver, can also be produced by cancer tissues and act through paracrine and autocrine mechanisms [105]. Insulin and IGFs participate in pathogenesis, progression and prognosis of cancer by increasing cancer cell proliferation (Figure 2C). In this way, preclinical studies of drugs that target IGF1 and/or insulin pathway suggest that modulating this pathway could find applications in cancer [86]. In breast cancer, an insulin signature based on differential expression of 15 genes has been observed and associated to 8-year disease-free survival. In this list, overexpression of IDE constitutes a high risk factor [85]. Some cancerous animal models displayed a decrease of systemic insulin that can be due in part to high IDE release by tumors cells. In this case, treatment of mice with insulin improves the cardiomyopathy associated to these models and decreases tumor growth [106].

At last, metabolism of cancer cells is characterized by the Warburg effect, which consists in aerobic glycolysis and production of lactate. It has been described that in liver lysates, L-lactate indirectly regulates IDE activity [107]. It would be interesting to know how IDE is modulated by cancer cell metabolism.

In all, how insulin modulates IDE expression levels or activity in cancer cells in different models, with and without the microenvironment, and how IDE inhibition in cancer cells affects the insulin/IGFs pathways and as a consequence tumor metabolism and survival, are key questions worth exploring.

8. IDE and sex hormones

Beside metabolic control of cell growth by insulin and IGFs, some tumors such as prostate or breast cancer are driven by sex hormones. Several teams have reported a close link between IDE expression and sex hormones even though the molecular mechanisms underlying this interplay and its functional consequences remain elusive. Indeed, IDE expression can be induced by estrogen in brain-region specific manner [108]. Another study demonstrates that testosterone and estrogen upregulate IDE expression in rat prostate and uterus [109]. An increased of IDE expression has been observed after dexamethasone plus testosterone treatment in castrated rats, suggesting an important role of IDE for tissue remodeling [110]. At least, IDE enhances the DNA binding of androgen and glucocorticoid receptors, but the consequences of these interactions, notably on transcription, remain to be described in detail [9]. So, the link between sex hormones and IDE evidenced so far deserves further studies in the field of cancer.

9. IDE, tumor suppression and proliferation

Cancer cells are the result of genetic alterations that activate oncogenes and/or inactivate tumor suppressor genes. Among the latter, the retinoblastoma protein (Rb) is a tumor suppressor which inhibits cell cycle progression by interacting with E2F transcription factors. A study by Radulescu *et al* shows that IDE can be co-purified with Rb from proteasomal preparation in two cancer cell lines [111]. They hypothesized that IDE could protect Rb from inactivation by insulin [111,112].

Another tumor suppressor that interplay with IDE is PTEN (Phosphatase and Tensin homolog deleted from chromosome 10). PTEN inhibits cell growth by antagonizing the PI3K-AKT-mTOR pathway and as such is frequently mutated and inactive in cancers. A study demonstrated that under nutritional starvation, IDE contributes with SIRT4 to PTEN degradation, inducing increased autophagy and cells survival [113]. In this study knock-out of IDE in cancer cells has minimal effect on cell cycle profile, cell

migration and cell growth, but upon serum starvation the absence of IDE decreases proliferation and migration. In the same way, the knock-down of *Ide* in neuroblastoma cells decreases also cell proliferation and induces cell apoptosis [65]. The same observation was made in HepG2 cells where IDE knockdown decreases cell proliferation [114].

10. IDE, tumor microenvironment and stress

Cancer cells are submitted to various environment stresses that force them to adapt. Interestingly, IDE expression and functions are sensitive to environmental stress including oxidative stress, serum starvation, proteotoxic stress, and heat stress [65,113,115] (Figure 3). It is hypothesized that IDE improves cell survival under stress conditions, a context highly relevant to tumor cells. In this way, IDE appears to play a role in the cell response to endoplasmic reticulum stress referred to as the Unfolded Protein Response (UPR). The UPR is an adaptive response to the accumulation of unfolded proteins in the ER that can restore cell homeostasis, but also can drive cell death if the stress is not rapidly resolved. This natural balance is involved in normal and pathological situations, particularly in cancer where cancer cells need to adapt and survive under stressful environmental conditions [116]. Minchenko *et al* have recently shown that IDE expression is modulated by the IRE1 α sensor of the UPR pathway in glioma cells [115]. The IDE homologue Iph1 in yeast participates to the ER stress response induced by tunicamycin [117]. In line with these observations, a potential binding site for XBP1 and HIF transcription factors in the IDE promoter region has been identified [115].

Autophagy, a catabolic process that involves the formation of autophagosome and the lysosomal degradation of proteins is another response to intrinsic or extrinsic stresses. Because it is involved in cancer pathogenesis, the modulation of autophagy has been proposed as a cancer therapy [118]. Interestingly, it was demonstrated that IDE secretion increases with autophagy flux in astrocytes [12,119]. However, the link between IDE and autophagy in a tumor context and the relevance of an increased secretion of IDE in this context has not yet been studied.

Also, cancer cells can escape recognition and destruction by T-cells. In this way, IDE could impact the antigen presentation on major histocompatibility complex (MHC) class I molecules, in an independent way of proteasome. Indeed IDE can process a tumor protein MAGE-A3 and so participate to cytotoxic T lymphocyte recognition of tumor cells [120]. In another study, IDE did not affect presentation on five epitopes from ovalbumin, envelope protein of HIV, type-1 diabetes autoantigen IGRP, proinsulin and beta-amyloid, nor MHC class one expression [121]. So, it seems that the role of IDE in antigen presentation remains only occasional. However, given the fact that IDE is a peptide processing protease, its role in antigen presentation, specifically in cancer warrants further study [122].

Inflammation -extrinsic or intrinsic- is often associated to tumorigenesis [123]. In this way CCL3 (also known as macrophage inflammatory protein-1 α , i.e., MIP-1 α) and CCL4 (MIP-1 β) are pro-inflammatory chemokines, that display both pro- and anti-cancer properties. On one hand they cause migration and invasion of cancer cells, angiogenesis and lymphangiogenesis. On the other hand, they have anti-cancer properties by recruiting anti-cancer tumor-infiltrating lymphocytes [54]. Interestingly it was shown that IDE degrades monomeric CCL3 and CCL4, reducing the chemotactic activity of these cytokines [52,53]. Also, IL-6 in HepG2 and C2C12 cells increases IDE expression and activity [124]. A recently described IDE peptidic inhibitor reduces the pro-inflammatory Th17 response against insulin in the NOD mouse model, supposedly by impacting the inflammatory responses of CD4⁺ T-cells toward the insulin beta chain peptide, a major epitope for T-cell activation [125]. These observations create an additional link between the protease and regulation of the tumor environment.

Caravaggio et al reported also that IDE can associate with the cytoplasmic domain of the macrophage scavenger receptor-A (SR-A, CD-204) [126] and studied this in the context of foam cell formation in atherosclerosis. Still, this interaction between SR-A and IDE may be highly relevant in the field of oncology as SR-A-dependent macrophage functions have been reported in the endoplasmic reticulum stress-induced autophagy in macrophages [127], in tumor progression in ovarian and pancreatic cancer [128], as a marker of prognostic in prostate cancer [129], directly involved in tumour infiltration by immune microenvironment and in progression of colorectal cancer [130].

P-glycoprotein (P-gp) or MDR1 (Multidrug resistance protein 1) expressed by cancer cell contribute to drug resistance [131]. In three cancer cell lines, it was shown that IDE interacts with this efflux pump [132]. However, consequences of this interaction are not known, particularly for drug resistance, and need further explorations.

Additionally, IDE displays 13 cysteine residues. Its activity and its oligomerization were shown to be sensitive to oxidation (H_2O_2) and nitrosylation (S-nitrosoglutathione) [30]. The cysteines in IDE act as sensors of reactive oxygen species and reactive nitrogen species. The modification of Cys-819 or Cys-110 leads to the loss of enzymatic activity, while the modification of Cys-178 is protective and prevents both IDE inactivation and oligomerization. The impact of these modifications were also shown to be substrate-dependent [30]. Reactive oxygen and nitrogen species can have many effects including the post-translational modification of many proteins at critical cysteine thiols. This is highly relevant in the context of cancer where both S-oxidation and S-nitrosylation of proteins occur under the tumor environment and impact cancer cell proliferation and even drug-resistance [133,134]. In that context, IDE could be both a target for these events and a sensor for ROS and nitric oxide within cells.

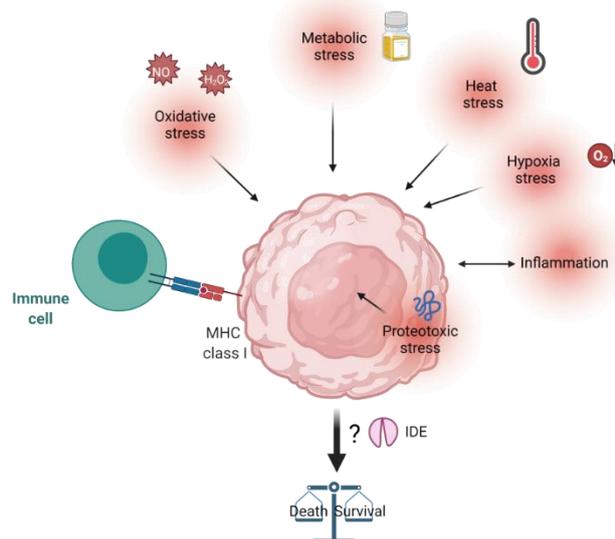


Figure 3. Impact of the environment on cancer cells that could involve IDE modulation as a response. Cancer cells are submitted to various stresses such as oxidative, metabolic, heat, hypoxia, proteotoxic stresses, inflammation and immune recognition that induce a response that can allow cell survival or death. It is known that IDE can modulate -or be modulated by- these different stresses. *Created with BioRender.com*

11. IDE is a druggable target

Importantly, IDE can be considered as a druggable target for the following reasons: i) *in vivo* knockout mice have been described and characterized and allow the comparison of the effect of pharmacological modulators with a wild type environment ii) numerous inhibitors from chemically diverse families have been disclosed; iii) target-engagement

tools have been developed; iv) several crystal structures of IDE with or without ligands are available to rationalize structural impact of ligand binding. Notably, the two different enzymatic activities of IDE, namely the proteolytic activity and the ubiquitin-activating E1-like activity, can be differentially targeted by inhibitors. Indeed Bellia *et al.* reported in 2019 that Copper II inhibits the proteolytic activity of IDE, without compromising the ubiquitin ligase activity [29]. This is consistent with the fact that these activities take place in different subsites of the protein.

Several models of *Ide*^{-/-} mice or tissue selective *Ide*^{-/-} mice have been disclosed and studied especially regarding metabolic or A β degradation phenotypes. These have significantly contributed to explore the causal implication of IDE respectively in type-2 diabetes and Alzheimer's disease. For example, Farris *et al.* reported for the first time that *Ide*^{-/-} mice display hyperinsulinemia and glucose intolerance, evidenced by hyperglycemia after IGTT compared to control mice [97]. This phenotype, including insulin resistance, hyperinsulinemia and glucose intolerance, as well as gain weight, appears to be age-dependent [135]. In *Ide*^{-/-} mice, where expression of neprilysin (the other enzyme responsible for A β clearance) was conserved, the levels of A β are enhanced by 65% [97]. GK rats, which have a loss-of-function IDE mutation, exhibit symptoms of type-2 diabetes and impaired degradation of A β [136].

Recent tissue-selective deletion of *Ide*, in β -pancreatic cells [137], in liver cells [98] or bone marrow [126] in mice have allowed to refine the role(s) of IDE in metabolic phenotypes like β -cell function, insulin resistance, glucose tolerance, insulin clearance or atherosclerosis. All these models could be of high value for the exploration of IDE implication in cancer phenotypes.

Several IDE modulators, mainly inhibitors, have been developed in the past decade and could be used to chemically validate IDE in different phenotypes related to cancer. These compounds display various behaviours regarding substrates and different drug-likeness properties, allowing to explore the various functions of IDE both in cells and *in vivo*.

Both small organic compounds and peptidic and pseudopeptidic compounds have been disclosed. While most inhibitors of IDE are pan-substrate inhibitors (**BDM44768**, **Ii1**) [62,138], some are selective of a single substrate [139] (**6bK**) or behave as activators for some substrates (**BDM43079**) [140,141]. These small-organic or peptidic compounds were most often discovered either by screening of diverse or focused libraries [140,141], DNA-templated libraries (**6bK**) [139], fragments [142] or drugs [143] (**ebsele**) or discovered via a kinetic target-guided synthesis (**BDM44768**) [62]. A few inhibitors were designed by rational design taking inspiration from either insulin (**Ii1**) [138] or a VZV-peptide (compound **ADT21**). A recent beta-hairpin inhibitor of IDE, **B35**, was designed as a constrained mimic of the insulin B chain binding sequence EALYLVCG [144]. [Pt(O,O'-acac)(γ -acac)(DMSO)] was disclosed as a novel inhibitor of IDE [145]. Interestingly, it was evaluated on neuroblastoma cells in which IDE overexpression has been linked to more aggressive tumor and progression, proliferation and viability. This new inhibitor decreased viability of these cells [145].

Fewer activators are known for IDE. Several of them were discovered by screening. Cabrol *et al.* discovered the activators **Ia1-2** [146]. Recently, Kraupner *et al.* reported the ATP binding site activator (**BDM35899**) [140,141]. To our knowledge however, none of the IDE activators has yet been used *in vivo*.

Along with inhibitors, methods to evaluate target engagement by these compounds [147], was developed in HepG2 cancer cells.

Finally, the availability of 3D-structures of IDE obtained via X-Ray diffraction of the apo protein or the liganded protein, or via CryoEM, has helped to understand binding of inhibitors as well as to rationalize their development. Inhibitors were shown to bind either the catalytic site (**BDM44768**, **Ii1**) or the exosite (**6bK**) or both (**BDM43079**). A recent

study using CryoEM has elucidated how various families of inhibitors disturb the disordered IDE catalytic cleft and how their binding impacts the dynamics of the door subdomain of the enzyme thus modify the catalytic activity [19]. Along with the activity of the modulators, these structural data could help rationalize which of the roles of IDE in cancer depend on its catalytic activity or from another function.

12. Conclusions

IDE has been shown to be overexpressed in some cancer. Numerous IDE's substrates are highly relevant in the context of cancer, in particular IGF-II, insulin and CCL3. Aside its proteolytic activity, IDE was shown to interact closely with the ubiquitin proteasome system and to display chaperone or E1-ligase like activities. IDE has been implicated in proliferation and survival of cancer cells. Other studies have highlighted how its expression or activity impacts and is impacted by the tumor microenvironment. There are now body of evidences that IDE is implicated in several hallmarks of cancer (Figure 4) that are worth exploring, in a tissue-dependent and substrate-dependent manner.

Interestingly, thanks to the availability of a large variety of IDE modulators as well as of KO animals, it is relatively straightforward to engage in comprehensive pharmacological studies to understand IDE's role(s) in cancer and generate key data for the qualification of this protease as a target in oncology both *in vitro* and *in vivo*. Indeed several IDE modulators initially evaluated *in vivo* -mostly for their effect on glucose metabolism-, display good animal exposure, suggesting that they can also be used *in vivo* to explore IDE implication in cancer.

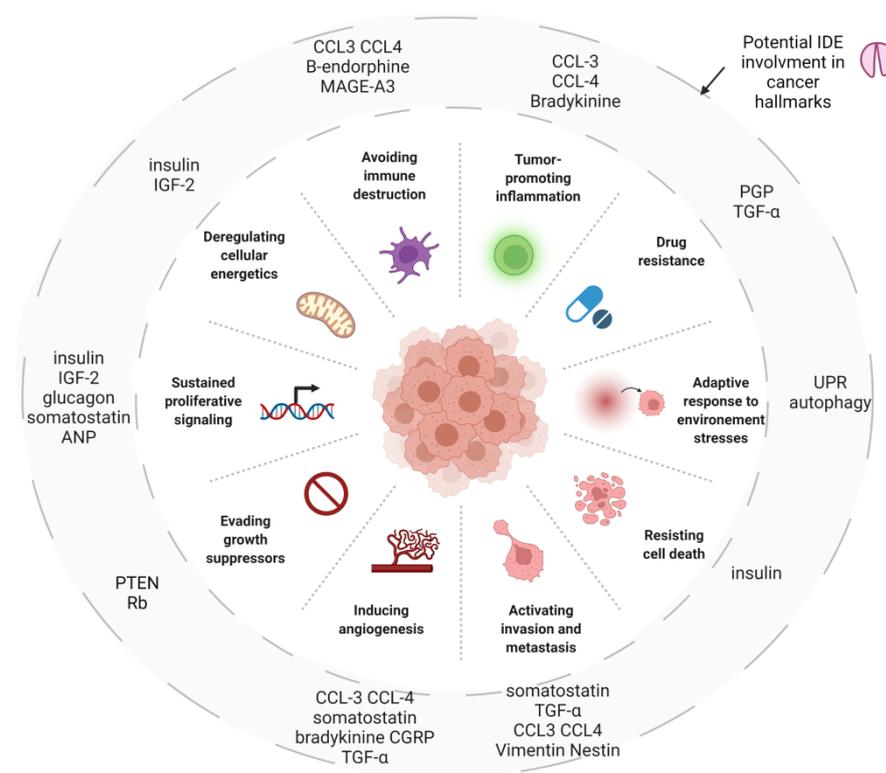


Figure 4. Potential IDE involvement in some cancer hallmarks by its substrates, its protein-protein interactions or by itself with its modulations. The main effect of substrates is reported and can be acts positively or negatively on cancer hallmarks (Table 1). Created with BioRender.com

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