



NIBAN1, Exploring its Roles in Cell Survival Under Stress Context

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Cell survival must quickly activate specific mechanisms that enable to detect changes in the cellular microenvironment. The impact of these cell alteration has direct consequences on cellular homeostasis. Cellular stress, as well as its regulation and implication, has been studied in different pathologies. In this sense, the alteration in *NIBAN1* expression seems to act in response to different cellular disturbances. Over the years, the knowledge of *NIBAN1* functions has improved, demonstrating its important cell roles, favoring the cell survival under stress context. In response to the disturbances, *NIBAN1* seems to be involved in the decision-making process between cell survival and death. The increase in *NIBAN1* expression has been related to cellular mechanisms that seek to minimize the damage caused to cellular homeostasis. In this review, the main biological insights attributed to the *NIBAN1* gene in different cellular contexts and its role as a mediator of cellular stress are discussed.

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INTRODUCTION

Cellular machinery uses numerous molecular mechanisms to adapt to microenvironment, providing evolutionary success and cell survival. Biological processes associated with stress responses play significant roles in normal development and homeostasis. These biological mechanisms of stress adaptation contribute to formidable cellular resilience. However, these same biological events can also contribute to cellular degeneration over time, invariably culminating in aging and/or disease (Fuchs and Steller, 2015). Among the types of cellular disturbances, we can mention: DNA damage agents, which activate specific repair pathways (Chang et al., 2017; Galluzzi et al., 2018), heat shock or toxin-causing agents, which activate the unfolded protein response (UPR) in the endoplasmic reticulum (ER) and mitochondria (Galluzzi et al., 2018; Hetz and Papa, 2018), hypoxia, respiratory poisons and xenobiotics, which cause mitochondrial stress (Galluzzi et al., 2018; Suomalainen and Battersby, 2018), nutrient deprivation, which activates autophagy (Galluzzi et al., 2017; Galluzzi et al., 2018), and infectious agents, leading to multiples stress responses (Cao, 2016; Galluzzi et al., 2018). To combat these adverse conditions, cells activate fast and transient programs that adjust both RNA and protein synthesis, cytoskeletal and membrane integrity, as well as cell homeostasis (Richter et al., 2010; Vihervaara et al., 2018). In each cell, organelles employ autonomous signaling strategies, which detect and communicate dangerous conditions to both cytosol and nucleus, inducing specific and global transcriptional responses (Walter and Ron, 2011; Vihervaara et al., 2018). This communication is achieved by multiple mechanisms, including (but not limited to) changes in the shape of stressed cells and their connections with the microenvironment, the exposure of specific molecules on its surface, and the active or passive release of bioactive factors, such as ions, small metabolites, intracellular proteins, cytokines, or microvesicles (Galluzzi et al., 2018). Multiple potentially harmful perturbations of the intracellular or extracellular microenvironment can be

successfully managed by mammalian cells after activating stress responses that preserve cellular functions and repair macromolecular damage (Galluzzi et al., 2018).

Understanding the molecular mechanism as well as the change in the gene expression profile, in response to cellular stress, had been an important issue for the Oncology (Chen and Cubillos-Ruiz, 2021). In this cellular context, the analysis of the gene expression, in response to stress, has been one of the methodological strategies. Many genes have been studied as biomarkers for various diseases and cancer. *NIBAN1* is one of these gene, whose expression is unregulated in many cancer and diseases, such as renal cancer (Majima et al., 2000; Adachi et al., 2004; Hino, 2004; Sun et al., 2007; Feng et al., 2019), lung cancer (Ji et al., 2012; Zhang N. et al., 2019), head and neck carcinoma (Ito et al., 2010), thyroid cancer (Cerutti et al., 2004; Maciel et al., 2005; Cerutti et al., 2006; Matsumoto et al., 2006; Cerutti, 2011; Patel et al., 2011; Carvalheira et al., 2013; Carvalheira et al., 2015; Nozima et al., 2019), gynecologic cancers (Yuki et al., 2015; Evstafieva et al., 2018; Salgado-Albarrán et al., 2019; Wang et al., 2020; Chen et al., 2021), prostate cancer (Shaw et al., 2016; Thomas et al., 2016; Pällmann et al., 2019), brain cancer (Miller et al., 2011; Qaisiya et al., 2017), bladder cancer (Zhu et al., 2018; Jiang et al., 2020) and colorectal cancer (Tan et al., 2021; Wang et al., 2021). The *NIBAN1* expression has also been observed in some diseases such as, renal interstitial fibrosis (Liu et al., 2014; Tang et al., 2019; Tang et al., 2021), in asthmatic patients treated with glucocorticoids (Yick et al., 2013; Yick et al., 2014), arterial diseases (Chen et al., 2019), vasomotor dysfunction (Luo et al., 2017; Yim et al., 2020), liver diseases (Kannangai et al., 2005), and pancreatic diseases (Zhang K. et al., 2019). This review analyzes the-state-of-the-art regarding to *NIBAN1* gene and its biological role in response to cell stress.

THE NIBAN APOPTOSIS REGULATOR 1 (*NIBAN1*)

The *NIBAN1* gene encodes a protein that belongs to the FAM129 family (family with sequence similarity 129). This protein family is encoded by three genes: *NIBAN1*, located at 1q25.3 (aliases: *C1orf24*; *FAM129A*; *NIBAN*; *GIG39*); *NIBAN2*, located at 9q34.11 (aliases: *OC58*; *MEG-3*; *C9orf88*; *FAM129B*; *MINERVA*; *bA356B19.6*), and *NIBAN3*, located at 19p13.11 (aliases: *BCNPI*; *FAM129C*). These genes share a pleckstrin homology (PH) domain (PH) in their N-terminal region. The PH domain seems to be involved in signaling, cytoskeleton organization, membrane trafficking, and phospholipid processing (Lenoir et al., 2015). Amino acids sequence analysis of the FAM129 family members revealed that they share a common PH domain on their N-terminal region with high sequence similarity of 57% between *NIBAN1* and *NIBAN2*, and 27% between *NIBAN2* and *NIBAN3* (Old et al., 2009).

These genes have significant cellular functions for many diseases and carcinogenic processes. As mentioned before, the *NIBAN1* protein is highly expressed in several diseases and cancer cells, and may play an important role in cell maintenance, such as

cell stress (Adachi et al., 2004; Sun et al., 2007; Ji et al., 2012; Qaisiya et al., 2017; Nozima et al., 2019; Pällmann et al., 2019; Yim et al., 2020), autophagy (Qaisiya et al., 2017; Nozima et al., 2019), and others survival biological processes (**Table 1**). *NIBAN2* gene seems to be involved in ERK pathway, at least, in human melanoma cells (Chen et al., 2011). On the other hand, *NIBAN3* encodes the membrane protein detected in B lymphocytes from chronic lymphocytic leukemia patients that seems to be involved in regulates B-cell receptor (BCR) signaling and B-cell apoptosis (Boyd et al., 2003).

The *NIBAN1* gene was described in 2000 by Majima et al. (2000) in renal carcinoma, both in murine and human cell lines. This gene was called “Niban” (“second” in Japanese), as it is the second gene found by Majima group, after *Erc* (expressed in renal carcinoma). According to the Gene Nomenclature Committee, from 2019, an official nomenclature for this gene was established and would be *NIBAN1* (Braschi et al., 2019).

The *NIBAN1* messenger RNA (mRNA) identified by Majima et al. (2000) presented expression in normal brain, lung, spleen, and skeletal muscle from Wistar rats. In normal human tissues, strong *NIBAN1* expression was found in heart, skeletal muscle, pancreas, white blood cells, and prostate, whereas it presented moderate expression in colon and spleen. They also demonstrated that *NIBAN1* expression was dramatically increased in the early stage of renal carcinogenesis and that *NIBAN1* had a conserved structure between humans and rats. The absence of expression in normal rat/human kidneys and strong expression in tumor suggests an inverse relationship between *NIBAN1* expression and progression of renal carcinogenesis (Majima et al., 2000). Although the expression of *NIBAN1* has been described more than 20 years ago, its functions are not elucidated yet.

NIBAN1: STRUCTURE AND EXPRESSION

The structure of *NIBAN1* gene is located at reverse strand (antisense) of the 1q25.3 region, and has 184,784 kb, according to the coordinates 184.790.724–184.974.508 (GRCh38.p13, **Figure 1**). This gene has a predicted promoter region containing 9,797 bp, 16 exons, and presents five transcriptional variants (Genome Browser, GRChHg38.p13). Using gene expression data obtained from the Atlas of Human Proteins database (HPA, version: 20.1), under basal conditions, it is observed that smooth muscle, urinary bladder, and salivary gland have high transcriptional levels of *NIBAN1*, while protein levels are high in breast, bronchus, endometrium, Fallopian tube, liver, pancreas, and tonsil (Uhlén et al., 2005; Uhlén et al., 2015; Uhlen et al., 2017).

In humans, the *NIBAN1* protein (ENSP00000356481.3, **Figure 1**) has 928 amino acids, and its location seems to be in some cellular compartments, such as cytoplasmic (Adachi et al., 2004; Cerutti et al., 2006; Matsumoto et al., 2006; Ito et al., 2010; Zhang N. et al., 2019), membranous (Uhlén et al., 2005; Uhlén et al., 2015; Uhlen et al., 2017), associated with both ER and plasma membrane, at least in prostate cancer (Pällmann et al., 2019), and nucleus (Adachi et al., 2004; Uhlen et al., 2017). It has

TABLE 1 | The biological effects of *NIBAN1* upregulation in human cancer.

Biological effect	Cancer type	Genomic and molecular context	References
Cell stress	Kidney cancer	Mutations Tsc1/Tsc2; mTOR pathway; endoplasmic reticulum stress; translation process; knockout of NIBAN1; knockdown of NIBAN1	Majima et al. (2000) Adachi et al. (2004) Sun et al. (2007)
	Thyroid cancer	Altered mitochondrial functions; cell stress; knockdown by miR-106b	Matsumoto et al. (2006) Carvalho et al. (2013) Carvalho et al. (2015)
	Prostate cancer	Regulation by AR; regulation by ATF4; eIF2 α phosphorylation via PERK; endoplasmic reticulum stress; translation process	Shaw et al. (2016) Thomas et al. (2016) Pällmann et al. (2019)
	Colon cancer	Regulation by ATF4	Evstafieva et al. (2018)
Cell migration and proliferation	Thyroid cancer	Knockdown by miR-106b	Carvalho et al. (2015)
	Colon cancer	Overexpression of zinc-finger protein 777	Yuki et al. (2015)
	Kidney cancer	Knockdown by miR-4521; TIMP-1/MMP2/MMP9	Feng et al. (2019)
	Lung cancer	FAK signaling pathway	Zhang N. et al. (2019)
Cell apoptosis	Lung cancer	Interaction with NPM, MDM2 and p53 degradation	Ji et al. (2012)
	Thyroid cancer	Knockdown by miR-106b	Carvalho et al. (2015)
	Kidney cancer	MDM2/p53/Bcl2/Bax pathway	Feng et al. (2019)
Cell autophagy	Nerve cells cancer	Unconjugated bilirubin neurotoxicity, oxidative stress	Qaisiya et al. (2017)
	Thyroid cancer	Oncogene-dependent; mutation RET/PTC1; AKT/mTOR/p70S6K	Nozima et al. (2019)
Immune microenvironment	Colon cancer	CCDC69, CLMP, FAM110B, GUCY1B3, PALLD, PLEKHO1, STY11; tumor mutational burden	Wang et al. (2020)
	Colorectal cancer	Overexpression BCL2, PMAIP1 and RPS6; immune infiltration	Tan et al. (2021)

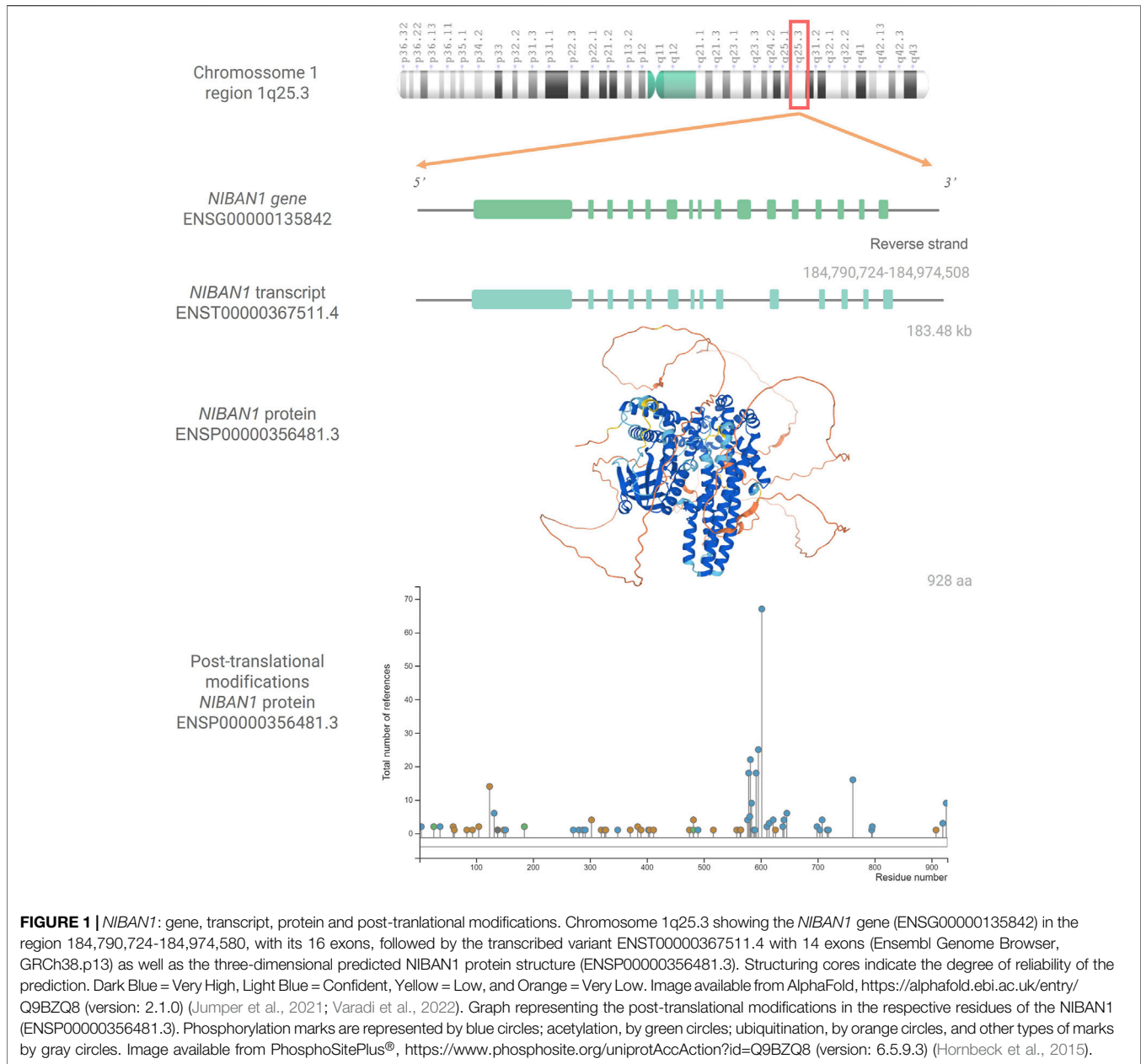
been shown that under homeostasis conditions, the NIBAN1 protein has a 130 kDa molecular weight. However, under stress conditions, such as heat shock, oxidative stress, hypertonic stress, and endotoxin (lipopolysaccharide) administration, NIBAN1 could be observed in two sizes, 70 kDa and 130 kDa (Adachi et al., 2004). Note that, NIBAN1 isoform had been predicted, containing around 100 aa (ENSP00000414039.1, GRCh38.p13). However, this isoform did not have yet been described *in vivo* associated with NIBAN1 expression. Under stressful conditions it is suggested that the NIBAN1 moves from the cytoplasm to the nucleus. It is important to address that NIBAN1 has a dnaJ domain in its polypeptide sequence. This domain is found in members of the heat shock protein family, up-regulated under stress conditions (Adachi et al., 2004). Thus, possibly the presence of 70 kDa NIBAN1 may be a consequence of the cellular stress.

It has been described that NIBAN1 protein can undergo several post-translational modifications, being the phosphorylations marker the most common one (Figure 1) (Sun et al., 2007; Ji et al., 2012; Luo et al., 2017; Yim et al., 2020). Ji et al. (2012) suggested that AKT seems to be responsible for the NIBAN1 phosphorylation. According to predictions from the PhosphoSitePlus database (version: 6.5.9.3), NIBAN1 phosphorylation seems to occur at different serine, tyrosine, and threonine residues. On the other hand, acetylation and

ubiquitination can occur in lysine residues (Hornbeck et al., 2015).

As mentioned above, *NIBAN1* expression occurs in different types of tumors (Majima et al., 2000; Adachi et al., 2004; Cerutti et al., 2004; Sun et al., 2007; Ji et al., 2012; Shaw et al., 2016; Qaisiya et al., 2017; Evstafieva et al., 2018; Zhu et al., 2018; Feng et al., 2019; Wang et al., 2021). Data from The Cancer Genome Atlas (TCGA) integrated into the Pathology Atlas (The Pathology Atlas, version: 20.1) (Uhlén et al., 2005; Uhlén et al., 2015; Uhlen et al., 2017) have shown increased expression of *NIBAN1* in several types of cancer, many has been described in both early carcinogenesis process (Adachi et al., 2004; Matsumoto et al., 2006; Ito et al., 2010) and associated with stress response (Adachi et al., 2004; Sun et al., 2007; Ji et al., 2012; Luo et al., 2017; Qaisiya et al., 2017; Nozima et al., 2019; Pällmann et al., 2019; Yim et al., 2020). Under stress conditions, *NIBAN1* seems to play an important role in the regulation of apoptosis, preventing cell death and allowing tumor progression (Sun et al., 2007; Ji et al., 2012; Nozima et al., 2019; Pällmann et al., 2019). However, the molecular mechanisms underlining *NIBAN1* expression as well as its biological role in carcinogenesis are not elucidated yet.

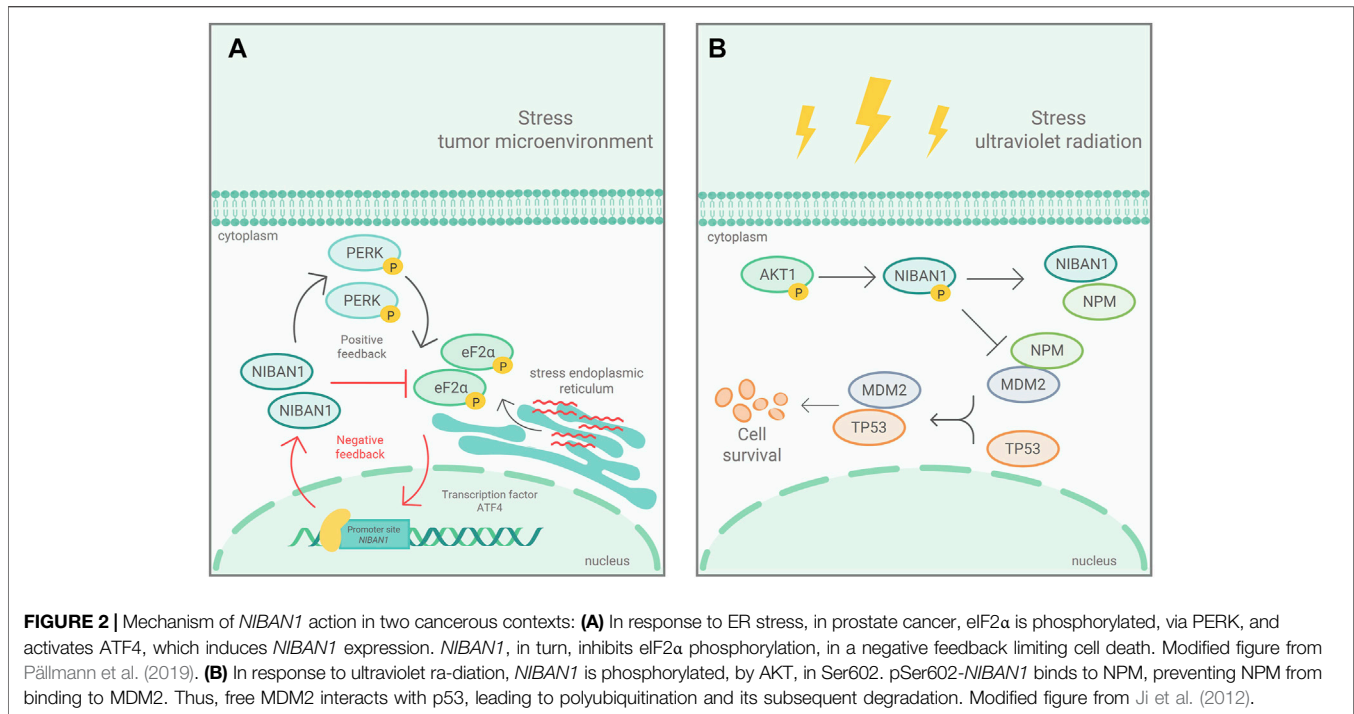
As stated earlier, the *NIBAN1* was overexpressed in early renal carcinogenesis in human and rats (Majima et al., 2000). The dysregulated expression of *NIBAN1* has also been described in



head and neck squamous cell carcinomas (HNSCCs), as well as in squamous dysplasia of the mucosa of the head and neck (Ito et al., 2010). In these lesions, the *NIBAN1* expression has been observed in mild dysplasia, gradually increasing during carcinogenesis. This data suggests that *NIBAN1* overexpression may be an important process in HNSCCs initiating carcinogenesis and maintenance of this tumor progression (Ito et al., 2010). In thyroid cancer, increased *NIBAN1* expression has been described in different tumors subtypes: microcarcinomas; papillary carcinomas; follicular carcinomas; metastases, and tumors with oxyphilic cytoplasm, such as Hürthle cell carcinoma, and some oxyphilic cells, originating from Hashimoto's Thyroiditis (Cerutti et al., 2004; Maciel et al., 2005; Cerutti et al., 2006; Matsumoto et al., 2006; Cerutti,

2011; Patel et al., 2011; Carvalho et al., 2013; Carvalho et al., 2015; Nozima et al., 2019). Due to the presence of *NIBAN1* in many histological thyroid tumors, it has been suggested that this gene may be overexpressed from the early stage of carcinogenesis and remain expressed during neoplastic progression (Matsumoto et al., 2006). Also, in lung cancer, *NIBAN1* overexpression was associated with advanced staging, lymph node metastasis, and poor survival rates (Zhang N. et al., 2019). Corroborating these data, in ovarian cancer, *NIBAN1* overexpression was related to poor prognosis, chemoresistance, and metastasis (Salgado-Albarrán et al., 2019).

As aforementioned, *NIBAN1* expression has been detected in Hashimoto's thyroiditis. In this type of lesions, thyrocytes are under both chronic inflammation and stress condition, due to



oxidative damage, presenting many modified mitochondria with oxyphilic cytoplasm (Ralli et al., 2020). As a result of the cellular characteristics of these neoplasia, it has been suggested that *NIBAN1* may be closely associated with altered mitochondrial functions in pre-neoplastic conditions and in oxyphilic tumors (Matsumoto et al., 2006). In prostate cancer, *NIBAN1* expression is regulated by androgen receptor (AR) (Shaw et al., 2016). It had been demonstrated the existence of a strong AR transcription factor binding site at the *NIBAN1* locus. These data suggest that *NIBAN1* may be regulated by androgens, and its expression may increase in hormone-sensitive tissues (Thomas et al., 2016). CBFβ and RUNX2 are others transcription factors that activate *NIBAN1* expression in colon cancer (Wang et al., 2021). On the other hand, in ovarian cancer, it had been observed that the BORIS (Brother of the Regulator of Imprinted Sites) transcription factor downregulates both *AR* and *NIBAN1* expression (Salgado-Albarrán et al., 2019). All these data together suggest that *NIBAN1* may be a biomarker or even a therapeutic target (Adachi et al., 2004; Cerutti et al., 2004; Cerutti et al., 2006; Matsumoto et al., 2006; Ito et al., 2010; Carvalho et al., 2013; Zhang N. et al., 2019).

NIBAN1 FUNCTIONS

Cell Stress

As mentioned earlier, *NIBAN1* overexpression was found in early renal carcinogenesis in human and Eker rats (Majima et al., 2000), as well as in many neoplastic lesions. These findings suggest that its expression is commonly induced in the early stage of carcinogenesis, regardless of its genetic context. To confirm that *NIBAN1* expression was associated with the

genetic context, it was demonstrated in Eker rats, which have mutations in the *Tsc1* and *Tsc2* genes, that the expression of *NIBAN1* seems to act independently of the mTOR pathway (Majima et al., 2000; Adachi et al., 2004). The group also demonstrated that *NIBAN1* presented itself with 130 and 70 KDa, in response to different stressors (heat shock, oxidative stress, hypertonic stress, and endotoxin), suggesting that this protein could undergo post-translational modifications (Adachi et al., 2004). On the other hand, Sun et al. (2007) demonstrated that *NIBAN1* expression seems to be induced by ER stress. They also observed that, in knockout mouse for *NIBAN1*, the phosphorylation in both p70 ribosomal kinase S6 subunit (S6K) and eukaryotic initiation translation factor 4E (4E-BP) was reduced. These findings suggest that *NIBAN1* may be involved with phosphorylation of S6K and 4E-BP in response to ER stress, which are significant components of the translation process. Moreover, they have also shown that reduced phosphorylation of these proteins modulated cell death signaling (Sun et al., 2007).

Ji et al. (2012) demonstrated that *NIBAN1* is phosphorylated by AKT in response to ultraviolet stress, in human glioblastoma and lung cancer cell lines, which inhibits cell apoptosis. The suppression of cell death in response to stressful condition has been also associated to *NIBAN1* expression (Ye et al., 2011; Cevik et al., 2020). In prostate cancer, *NIBAN1* is rapidly activated in response to ER stress by ATF4, either by stimulating eIF2α phosphorylation, via PERK, or by inhibiting eIF2α phosphorylation directly, via *NIBAN1* (Figure 2A). These positive and negative feedbacks, in response to ER stress, demonstrate that *NIBAN1* contributes to ATF4 pro-survival role by suppressing senescence and apoptosis, depending on environmental issues and/or cell type (Pällmann et al., 2019).

The results are supported by the findings of Cevik et al. (2020) and suggest that *NIBAN1* may be involved in the decision-making process between cell survival and death in response to stressful conditions. In osteoclasts, the *GBF1* knockdown, responsible for activation of the ARFs family and vesicular transport at the endoplasmic reticulum-Golgi interface, led to increased *NIBAN1*, BiP, p-PERK, and p-EIF2 α expression (Wen et al., 2021). These genes are considered biomarkers of reticulum stress and their up-regulation seems to promote the autophagic axis of Beclin1, Atg7, p62, and LC3 (Wen et al., 2021).

Cell Migration and Proliferation

Feng et al. (2019) demonstrated that *NIBAN1* interacts with the TIMP-1/MMP2/MMP9 pathway, interfering with the processes of cell migration, invasion and proliferation, in clear cell renal carcinoma (ccRCC), the most aggressive subtype of renal cancer, contributing to tumor progression. Zhang N. et al. (2019) demonstrated that *NIBAN1* seems to up-regulate MMP2 and Cyclin D1, inducing cell proliferation and invasion, in the development and progression of non-small cell lung cancer. These findings have been corroborated in both colon cancer and thyroid carcinoma cell lines, whose results showed that decreased *NIBAN1* expression inhibits cell proliferation and migration (Carvalho et al., 2015; Yuki et al., 2015).

Cell Apoptosis

As aforementioned, *NIBAN1* is strictly related to cell death and survival. In fact, pSer602-*NIBAN1* by AKT, in response to ultraviolet stress (Figure 2B) showed that phosphorylated *NIBAN1* binds to NPM, preventing NPM from binding to MDM2. The resulting free MDM2 interacts with p53, leading to p53 degradation, which in turn inhibits UV-irradiation induced cell apoptosis (Ji et al., 2012). The results indicate that pSer602-*NIBAN1* is sufficient to lead to p53 degradation, regulating cell apoptosis (Ji et al., 2012). On the other hand, in head and neck tumors it was observed that the loss of transcriptional activity of p53 was inversely proportional to the expression of *NIBAN1* (Van der Vorst et al., 2012). These findings suggest that *NIBAN1*, in some cancers, may favor cell survival in relation to other stress-dependent manners, regulating apoptosis via p53-independent pathways (Ji et al., 2012). Feng et al. (2019) demonstrated that *NIBAN1* seems to play an important role in down-regulation of apoptosis due to its interaction with the MDM2/p53/Bcl2/Bax pathway. *NIBAN1* overexpression induced an increase in MDM2 and Bcl2 while decreasing p53 and Bax, responsible for cell death. It had been demonstrated that *NIBAN1* silencing leads to increased apoptotic levels in follicular and papillary thyroid carcinomas cell lines (Carvalho et al., 2015). These findings suggest that *NIBAN1* may indeed be involved in apoptosis.

Although the comprehension about the role of *NIBAN1* in other pathologies concerning the apoptosis pathway is scarce, it had been shown its participation in tissue damage recovery (Luo et al., 2017; Yim et al., 2020). Vascular injury leads to cell membrane rupture, ATP release, and endothelial dysfunction (Yim et al., 2020). In saphenous vein grafts used for revascularization procedures, the injuries caused during the

collection and preparation of the graft lead to failures in the regeneration process, increasing the rates of apoptosis in the implanted vein (Conte et al., 2006). In vascular lesions, the p38/MAPK/AKT pathway inhibits apoptosis through *NIBAN1* phosphorylation at serine 602 (Luo et al., 2017; Yim et al., 2020). These findings corroborate with the fact that *NIBAN1* may represent an endogenous regulator of p38 MAPK activation, inhibiting apoptosis in vascular lesions.

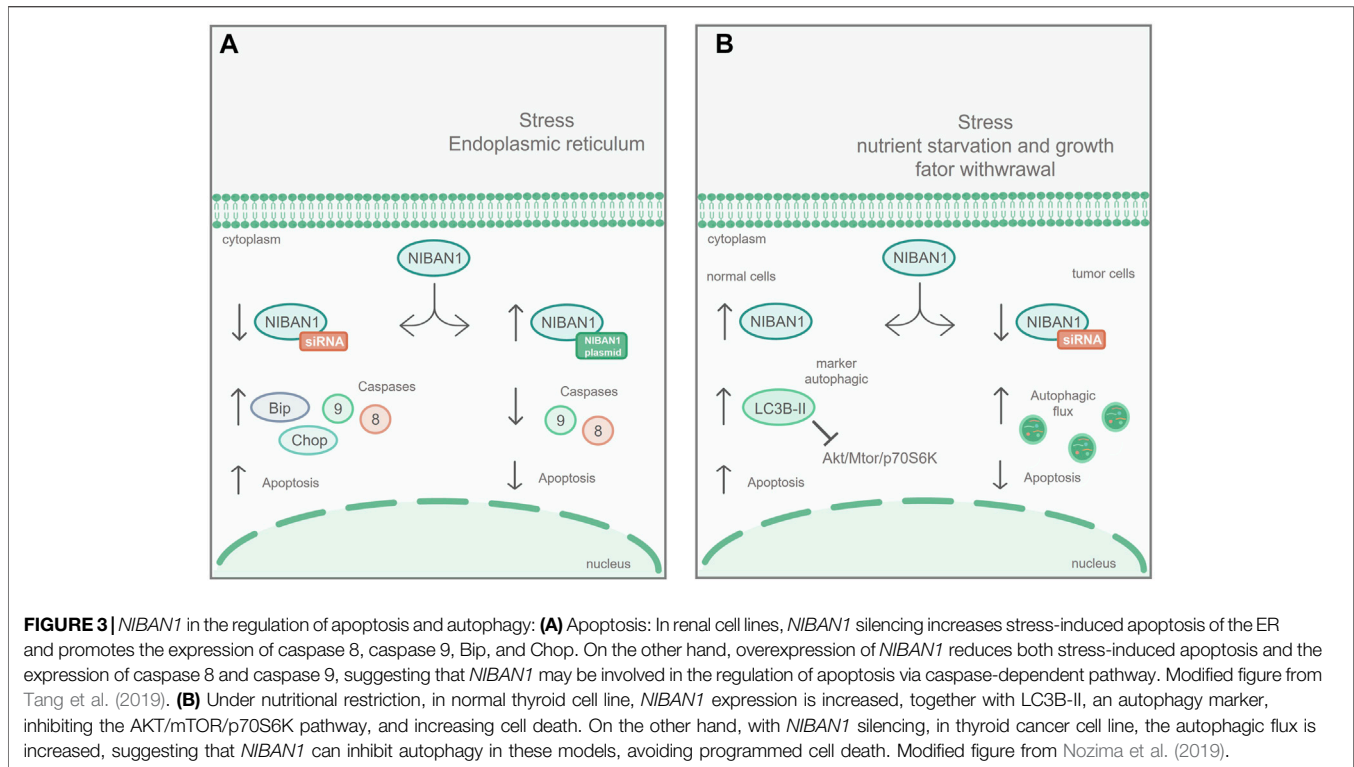
It has also been described that *NIBAN1* plays an important role in renal interstitial fibrosis, regulating the apoptosis of renal tubular epithelial cells (HK-2) *in vitro* (Tang et al., 2019). Using the unilateral ureteral obstruction (UO) model, in C57BL/6 mice, it was demonstrated that, during the obstruction development, *NIBAN1* expression gradually decreases while apoptosis rates increase (Tang et al., 2019). Furthermore, *NIBAN1* silencing, in the HK-2 lineage, increased stress-induced apoptosis, promoting caspases 8 and 9 expression, as markers of apoptosis process, as well as increased the stress biomarkers BIP and CHOP, in ER (Figure 3A). On the other hand, overexpression of *NIBAN1* reduced apoptosis and expression of caspases 8 and 9, as a result of ER stress (Tang et al., 2019). These data suggest that *NIBAN1* seems to be involved in the apoptosis regulation, via a caspase-dependent pathway.

Cell Autophagy

Nozima et al. (2019), using normal thyroid cell lines derived from human and rat, demonstrated that *NIBAN1* expression was induced along with proteins related to autophagy suppression (Figure 3B) under stress conditions, through AKT/mTOR/p70S6K inhibition pathway. On the other hand, in thyroid cancer cell lines, *NIBAN1* silencing increased autophagic flux, suggesting that *NIBAN1* inhibits autophagy during the thyroid carcinogenic process. These data suggest that *NIBAN1* may play a dual role in the autophagy regulation: 1) It can increase baseline autophagy in normal thyroid cells in response to nutrient and growth factors depletion, and 2) can inhibit autophagy in thyroid carcinomas in the presence of activating mutations in oncogenes (Nozima et al., 2019). These findings are supported by studies with neuronal cell lines in response to treatment with unconjugated bilirubin (UCB), which triggers oxidative stress, through calcium signaling and stress in the ER (Qaisiya et al., 2017). In these cells, treatment with UCB changed the expression of *NIBAN1* along with other proteins related to autophagy (Qaisiya et al., 2017). All these functional studies suggest that *NIBAN1* can be activated early in response to cellular stress, promoting the autophagic process.

Immune Microenvironment

NIBAN1 also seems to play important roles in the immune mechanism (Wang et al., 2020; Zhang et al., 2020; Chen et al., 2021; Tan et al., 2021). In colorectal cancer, four-gene signature (*NIBAN1*, *BCL2*, *PMAIP1*, and *RPS6*) have been detected, correlating with immune infiltration (Tan et al., 2021). Zhang et al. (2020) evaluated the transcriptomic heterogeneity of regulatory T cells (Treg) in different tissues: spleen (s-Treg), lymph nodes (LN-Treg), intestine (int-Treg) and visceral adipose tissue (VAT-Treg). They emphasize how the biological context of



the tissue is associated with transcriptomic remodeling of Treg cells. They characterized Treg heterogeneity by examining gene signature and demonstrated that elevated levels of 11 genes were present in these tissues, being *NIBAN1* one of them. These results suggest that these genes may play major roles in immune environments (Zhang et al., 2020). The relationship between *NIBAN1* and tumor immune microenvironment may help to understand the molecular mechanisms by which immune escapes are originated. These biological events are crucial processes in tumorigenesis as well as may involve both recruitment of immunosuppressive cells, such as T reg cells, and/or the response to pathogens (Togashi et al., 2019).

CONCLUSION

Considering the cell molecular machinery, we emphasize the importance to expand knowledge about the gene functional status in different types of cellular contexts, including diseases and tumorigenesis. The study of gene functions is essential to understand the molecular mechanisms involved in the cellular microenvironment. In this sense, the comprehension of the *NIBAN1* function, in many diseases and cancer progression, is fundamental for the management of cell stability as well as both diseases and cancer treatments.

The increased *NIBAN1* expression in early tumorigenesis, highlights the significance of this gene in cellular survival. This high expression seems to be associated with stress response in different biological conditions (Sun et al., 2007; Ji et al., 2012; Nozima et al., 2019; Pällmann et al., 2019). In these stressful

environments, *NIBAN1* downregulates apoptosis to allow the cell survival (Ji et al., 2012; Carvalho et al., 2015; Feng et al., 2019; Yim et al., 2020). Furthermore, *NIBAN1* plays an ambiguous role in relation to apoptosis and autophagy, and the cellular microenvironment is crucial for its performance in these functions (Qaisiya et al., 2017; Nozima et al., 2019). It had been demonstrated that *NIBAN1* may be involved with protein translation processes to alleviate the ER stress (Sun et al., 2007; Pällmann et al., 2019). *NIBAN1* expression also seems to be associated with the immune microenvironment (Wang et al., 2020; Zhang et al., 2020; Chen et al., 2021; Tan et al., 2021). It is known that the immune microenvironment of the tumor greatly determines the therapeutic effectiveness of immunological cancer treatments (Tang et al., 2021). The *NIBAN1* is part of gene signatures, such as immune infiltration (Tan et al., 2021) and in Treg cells (Zhang et al., 2020). Evidence has demonstrated the importance of tumor infiltration in immune cells, such as tumor-associated macrophages and dendritic cells, T helper and cytotoxic T, in tumor progression, therapeutic responses and prognosis (Liu et al., 2020). The overexpression of *NIBAN1* in regulatory T cells also has an important correlation, this cell type mainly migrates to inflammatory sites and suppresses several types of effector lymphocytes (Togashi et al., 2019). In fact, in the cancer context, T reg cells are often detected in inflamed tumors. Cancers exploit different immune escape mechanisms that are sometimes dependent on certain intrinsic tumor factors, such as mutations in the driver genes. Thus, the signals provided by these mutations may allow tumor cells to recruit T reg cells, mainly by changing the local environment of chemokines and the metabolic environment. Therefore, alterations in the driver genes may play

crucial roles in promoting not only tumor growth but also in evading anti-tumor immunity. Thus, understanding the genetic context and how it influences *NIBAN1* expression and the immune environment will yield important results for the understanding of this gene functions (Togashi et al., 2019). Additionally, some studies describe the association of *NIBAN1* with cell proliferation and migration (Carvalho et al., 2015; Yuki et al., 2015; Feng et al., 2019; Zhang N. et al., 2019). All these data demonstrate the *NIBAN1* roles in cell survival, and consequently, its biological functions associated with tumor progression. Furthermore, post-translational modifications in *NIBAN1* protein—especially serine 602 phosphorylation—seem to be crucial for its functional activity in apoptosis regulation (Ji et al., 2012; Yim et al., 2020).

Although *NIBAN1* has been described more than 20 years ago, its roles in cancer and other cellular contexts still need to be elucidated. The robust study gathered here demonstrates the importance of *NIBAN1* for cell stability and survival. However, there is much to understand about its broad functionality as well as its role in diagnosis (Adachi et al., 2004; Cerutti et al., 2004; Maciel et al., 2005; Cerutti et al., 2006; Matsumoto et al., 2006; Sun et al., 2007; Ito et al., 2010; Cerutti 2011; Patel et al., 2011; Carvalho et al., 2013) and therapeutic use (Luo et al., 2017; Yim et al., 2020).

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AUTHOR CONTRIBUTIONS

PD and GC wrote the main manuscript text. PD completed the tables and relevant figures. GC conducted the manuscript revision. All authors reviewed and approved the final manuscript.

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