Regulat-INGs in tumors and diseases: Focus on ncRNAs

Marjorie Gournay, Mathieu Paineau, Jérôme Archambeau, Remy Pedeux

Abstract

ING family genes (Inhibitor of Growth) are tumor suppressor genes that play a vital role in cell homeostasis. It has been shown that their expression is lost or diminished in many cancers and other diseases. The main mechanisms by which they are regulated in oncogenesis have not yet been fully elucidated. The involvement of non-coding RNAs (ncRNAs) and in particular microRNAs (miRNAs) in post-transcriptional gene regulation is well established. miRNAs are short sequences (18 to 25 nucleotides) that can bind to the 3 'UTR sequence of the targeted messenger RNA (mRNA), leading to its degradation or translational repression. Interactions between the ING family and miRNAs have been described in some cancers but also in other diseases. The involvement of miRNAs in ING family regulation opens up new fields of investigation, particularly for targeted therapies. In this review, we will summarize the regulatory mechanisms at the RNA and protein level of the ING family and focus on the interactions with ncRNAs.

Regulat-INGs in tumors and diseases: focus on ncRNAs

Marjorie Gournay[1, 2], Mathieu Paineau[1, 2], Jérôme Archambeau[1, 2], Rémy Pedeux[1, 2, *]

[1] INSERM U1242, Chemistry Oncogenesis Stress and Signaling, CLCC Eugène Marquis, Rennes, France

[2] Université de Rennes 1, Rennes, France

***Corresponding author :**

Rémy Pedeux

Université Rennes 1

CLCC Eugène Marquis, INSERM U1242-COSS

Rue Bataille Flandres Dunkerque

Bat D, 1er étage

35042 RENNES, FRANCE

Tel : 33 (0)2 23 23 47 02

Fax : 33 (0)2 99 25 31 64

E-mail : remy.pedeux@univ-rennes1.fr

Abstract

ING family genes (Inhibitor of Growth) are tumor suppressor genes that play a vital role in cell homeostasis. It has been shown that their expression is lost or diminished in many cancers and other diseases. The main mechanisms by which they are regulated in oncogenesis have not yet been fully elucidated. The involvement of non-coding RNAs (ncRNAs) and in particular microRNAs (miRNAs) in post-transcriptional gene regulation is well established. miRNAs are short sequences (18 to 25 nucleotides) that can bind to the 3 'UTR sequence of the targeted messenger RNA (mRNA), leading to its degradation or translational repression. Interactions between the ING family and miRNAs have been described in some cancers but also in other diseases. The involvement of miRNAs in ING family regulation opens up new fields of investigation, particularly for targeted therapies. In this review, we will summarize the regulatory mechanisms at the RNA and protein level of the ING family and focus on the interactions with ncRNAs.

Introduction

p33ING1 was discovered in 1996 and identified as a candidate tumor suppressor gene (TSG) (1). The other members of the ING family were identified by homology search, and were then named *ING2-ING5* (2–4). All INGs proteins share a conserved C-term (Carboxyl-terminus) structure that contains a Plant HomeoDomain (PHD), known to interact with the histone 3 trimethylated on lysine 4 (H3K4me3) (5). They also have a Nuclear Localisation Signal (NLS) (6) and therefore, the ING proteins are mainly located in the nucleus. INGs are well-conserved from yeast to humans as suggested by phylogenetic studies (6,7), which implies an important role in biological processes. Indeed, by regulating the expression of genes, they are known to play a role in the cell cycle, senescence, apoptosis (5,8–11) and have therefore been classified as "gatekeepers" Tumor Suppressor Genes (TSG). ING proteins are able to promote apoptosis in a p53 dependent and independent manner (3,4,12). Moreover, *ING1* and *ING2* KO mice spontaneously develop tumors (13,14). More recently, they have also been shown to have "caretakers" properties by participating in DNA repair (15–18) and DNA replication (10,19,20).

Since they are "gatekeeper and "caretaker" TSG, the family of INGs may play a role in many types of cancers such as lung, head and neck cancer, breast, ovarian, melanoma or brain (17,21–27). Indeed, they are usually lost or down-regulated in these types of cancer.

Data summarized from The Cancer Genome Atlas and The Human Protein Atlas (Fig. 1) show that INGs RNA and protein expression vary according to tissue types and cancers. INGs protein are highly expressed in few tissues, and have usually a medium to low expression. RNA sequencing seems to be the most reliable method to compare INGs expression.

The mechanisms that regulate INGs expression are just beginning to be understood. Although some mutations (Fig. 2) and LOH have been found (24,28–31), several recent studies have shown that non coding RNAs (ncRNAs) such as microRNAs (miRNAs) (32,33) can regulate of INGs.

Non coding RNAs were discovered about 23 years ago in *Caenorhabditis elegans* (34). The discovery of several ncRNAs followed: microRNAs (miRNAs), transcribed ultra-conserved regions (T-UCR) (35) and circular RNAs (circRNAs) which are highly conserved, and others which are less conserved such as long ncRNAs (lncRNAs) (36). miRNAs are short, about 18-25 nucleotide-long, and usually modulate the post-transcriptional gene expression by binding to seed sequences in the 3'-untraslated regions (3'-UTR) (37), thus suppressing mRNA translation and reducing mRNA stability. Since their discovery, miRNAs

have been implicated in many signaling pathways and various diseases (38–42) including cancers (43). In fact, some miRNAs can act as cancer enhancers and are usually called oncomiR, on the other hand, other can repress a cancerous phenotype and are classified as tumor suppressor miRNAs (44). For example, the miR-17-92 has been shown to be up-regulated in several solid and hematopoietic cancers (45–48). Indeed, by targeting TSG, such as *PTEN* (49), miR-17-92 cluster containing miR-17-5p, miR-17-3p, miR-18a, miR-19a, miR-20a, miR-19b-1 and miR-92a-1, can promote oncogenesis, is associated with poor survival and thus is considered an oncomiR (46,47,50,51). In contrast, miR-217 is considered as tumor suppressor because its overexpression decreases cancer invasion and migration by targeting Enhancer of Zeste Homolog 2 (*EZH2*) in gastric cancer (52), known to enhance cell cycle or *PTPN14*, which modulates epithelial-to-mesenchymal transition (53).

Recently, some lncRNAs have also been described as deregulated in cancer. In fact, the antisense RNA of the HOX transcript (HOTAIR) is a lncRNA which has been shown to be upregulated in several cancers such as brain, lung, colorectal, breast, ovarian, renal, hepatocellular and hematopoietic (54). Besides, its upregulation would enhance tumor progression (55) and lead to resistance to paclitaxel and doxorubicin in gastric cancer (56) by targeting the miR-217 tumor suppressor (57).

This review describes the mechanisms responsible for the regulation of INGs and in particular the loss of expression of INGs in tumors and other diseases with a particular interest for the role that ncRNAs could play.

I. INGs alteration in cancer and regulation of expression mechanisms

Various causes explaining the loss or down regulation of the INGs protein in cancer such as mutations, Loss of Heterozygosity (LOH), hypermethylations, phosphorylations or SUMOylations have been described. However, those are not sufficient to explain the majority of INGs down regulation. It suggests that post-translational regulation such as ncRNA regulation could have an important impact on INGs regulation.

1. INGs alteration of expression in cancer

INGs expression is lost or decreased in several types of cancer, such as non-small cell lung cancer, breast, ovarian, hepatocellular cancer or osteosarcoma (21,23,58). Some mutations have been reported in the TCGA database, (0,2 %-9,43 % for ING1, 0,10 %-2,45 % for ING2, 0,2%-8,3% for ING3, 0,2-3,21% for ING4 and 0,2-5,85% for ING5), and are

summarized in Figure 1. Interestingly, mutations are more frequent in uterine and colorectal cancers, and no hotspot mutations have been found. Moreover, few silent mutations of ING2 were found (59) and a study found 9.6 % of mutations of ING5 in oral squamous cancer (60). Overall, mutations of ING genes are not frequent in human tumors.

Other mechanisms such as LOH (Loss of Heterozygosity) are involved in the regulation of ING genes in cancer. For instance, ING1 loss of expression occurs mainly at the RNA level, and LOH (between 55,7 % and 61,1%) have also been observed (24,28,29,61). Shen et al. reported that hypermethylation of ING1 promoter in ovarian cancer (28% of the cases) is associated with ING1 down-regulation (62). With respect to ING2, high frequencies of LOH in the chromosomal region 4q32-35.1 in ameloblastoma, sporadic basal cell carcinoma and squamous cell carcinoma of the head and neck (30%, 46.1% and 54.6%, respectively) (24, 30, 64) have been described. Finally, no increased methylation of ING2 promoter have been found in NSCLC (22). Loss of ING3 by LOH was observed in 10,2% of HHNSC (31) and in 68% of ameloblastomas (24). The expression ING4 can also be lost by LOH, which can occur in 5% to 66% of cases depending on the cancer (63,64) , by abnormal transcription (65) or post-transcriptionnal regulation (66). In some cases it has also been reported that ING4 is more expressed in the cytoplasm than in the nucleus, leading to tumorigenesis, but the exact reason of this change of location remains to be explained (67). Various causes have been described to explain the dysregulation of ING5 gene expression in cancer. One of them being the LOH occurring in up to 68 % of cancers (24,68). In addition, it has been shown that the nucleocytoplasmic translocation of ING1 and ING5 may play a role in cancers (69,70). Indeed, ING1 and ING5 overexpression in the cytoplasm rather than in the nucleus prevents it from fulfilling its tumor suppressive roles such as regulating the chromatin or the DNA replication. Cytoplasmic expression of ING5 was positively correlated with tumor size in breast cancers (70).

Thus, mechanisms for explaining loss of expression of ING genes have been described in cancers. However, they are not enough to explain the loss of expression of ING in the vast majority of cases.

2. <u>INGs post-translationnal regulation</u>

Several mechanisms of regulation of INGs proteins have been discovered. For example, SUMOylation of ING1b has been shown to affect the regulation of gene transcription such as *ISG15* (Interferon-Stimulated Gene 15) and *DGCR8* (DiGeorge Syndrome Critical Region 8)

(71). Moreover, Garate et al. showed that p33ING1 phosphorylation would inhibit cyclin B1 activity, and therefore cyclin B1 dependent cell proliferation in melanoma cells (72). It also has been shown that Src tyrosine kinase can phosphorylate ING1 and leads to its nuclear to cytoplasmic relocalization resulting in an inhibition of its tumor suppressive effects (73). In addition, SUMOylation of ING2 enhances its association with Sin3a, leading to gene repression or activation (20). Another study has shown that p53 can repress *ING2* promoter activity and its expression (74). This could be a negative feedback mechanism in response to p53 activation. Indeed, ING2 can interact with the acetylase p300 to enhance p53 acetylation and its action in apoptosis, senescence, and the cell cycle (75). Besides, Jing et al. showed that the degradation of ING2 can be mediated by the Smad 1 ubiquitination regulatory factor 1 (Smurf 1) (76). Smurf1 has been reported to be upregulated in lung and gastric cancer and may promote oncogenesis by regulating cell cycle-related proteins such as Wee1 (77–79). Thus, the strong expression of Smurf1 in cancer could contribute to the degradation and downregulation of ING2. Concerning ING3, one study showed that it can be degraded through the CFSkp2-mediated ubiquitin–proteasome pathway (80). Since Skp2 expression is increased especially in melanoma (81,82), it could contribute to ING3 loss of expression in that type of cancer. Guo et al. showed that ING4 citrullination increases its degradation, disrupts its interaction with p53 (83). ING4 protein degradation occurs through the ubiquitin/proteasome pathway, and no dysregulation of it has been found in cancer (84). ING5 can be phosphorylated by CDK2 although it has a minor effect on cell proliferation (85). ING5 degradation remains to be studied.

II. INGs function and interaction with ncRNAs

1. ING1 and ING2 interactions with miRNAs and ncRNAs

a. Functions of ING1 and ING2

ING1 has a role in cell proliferation by regulating cell cycle arrest, apoptosis or senescence (13) and subsequently is involved in cancer development (1). Moreover, ING1 can regulate chromatin regulation through its interaction with the mSin3a/HDAC1/2 complex (86), and plays a role in DNA repair (87). One report suggests that *ING1* would participate in angiogenesis, but its involvement is less clear (27). Finally, our group showed that ING1 can regulate the hypoxic response by triggering hypoxia inducible factors α (HIF1α) degradation (88).

ING2 is the closest ING1 homolog leading to common properties between ING1 and ING2. In fact, ING2 is involved in cell cycle, senescence and apoptosis regulation (3,89). It also interacts with the mSin3a/HDAC1/2 complex to modulate gene expression (20), and participates in DNA repair through Nucleotide Excision Repair (NER) regulation (90).

b. Regulation of miRNAs by ING1

Interestingly, ING1 can regulate the expression of miRNAs in order to regulate gene expression with two discovered mechanisms. First, ING1 can play a role in miRNAs synthesis. Indeed, it has been shown in osteosarcoma cell lines that ING1 can regulate and increase through chromatin modification, the miR-203 expression (91). mir-203 has notably been described as a tumor suppressor in several cancer type (92–94). It also account for a significant proportion of the inhibitory effects of ING1 on cell proliferation by targeting several common mRNAs such as c-Abl oncogene 1, RB1 (RB transcriptional corepressor 1), or BRCA1 (BRreast CAncer 1) (91). Those genes are known to be part of cancer pathway and their inhibition is consistent with tumor suppressive functions of ING1.

Furthermore, epigenetic is not the only way for ING1 to control miRNAs expression. In fact, a study has shown that DGCR8, a miRNA regulator protein involved in the early stages of the majority of miRNA processing, is negatively controlled by ING1 (95). Since miRNAs are usually deregulated in cancer (43), this could contribute to neoplastic transformation following ING1 dysfunction. Besides, ING1 is involved in apoptosis in a p53 dependent and independent way (12,96,97). Tran et al. demonstrated that ING1 and p53 interact to increase levels of large intergenic long non-coding RNA p21 (lincRNA-p21) involved in apoptosis (98). This could explain in part the p53-independent apoptosis mediated by ING1. Thus, the close relationship between ING1 and miRNAs emphasizes their role in oncogenesis and needs to be further explored.

c. Regulation of ING1 and ING2 by miRNAs

It has been shown that ING1 can be regulated by miRNAs. Indeed, one report described that ING1 is a target of the miR-371-5p in pancreatic cancer, which is associated with tumorigenesis and poor survival (33). However, ING1 regulation by miRNAs remains unclear and would require further investigation.

Only one recent study described ING2 regulation by a miRNA. In fact, Gao et al. demonstrated *in silico* and *in vitro* that ING2 is the first reported putative target of miR-8084 in breast cancer (99). mir-8084 has been found to be upregulated in serum from breast cancer patient (100) and promotes the migration and invasion of breast cancer cells (99). It has been shown that miR-8084 down-regulates ING2, and by thus can suppress the p53 signaling pathway (99). miR-8084 would act as an oncomiR at least by targeting ING2 and inhibiting its tumor suppressive functions.

2. ING3 role and ncRNAs involvement

ING3 differs with other members of ING family in its chromosomal location (which is central and not telomeric) and in fact it is considered as a phylogenetic branch distinct from the other INGs (6). However, *ING3* is also considered as a TSG since it plays a role in cell cycle regulation, senescence and apoptosis (10,101,102). ING3 can modulate chromatin modification and gene expression by interacting with the hNuA4/Tip60 complex (10). Our group has also shown that ING3 can also participate in the DNA damage response signaling (unpublished results).

ING3 overexpression has been shown to inhibit the migration and proliferation of hepatocytes (103,104) and the expression of ING3 is decreased in colorectal cancer or in head and neck squamous cell carcinoma (HNSCC) (31,105). This suggests that ING3 plays a role in the progression of cancer. Indeed, decreased ING3 expression has been shown to be a marker of poor prognosis in several cancers (104,106,107). However, the involvement of ING3 in carcinogenesis has not been completely elucidated yet. Indeed, several studies suggest that ING3 would act as an oncogene in prostate cancer by increasing expression of androgen-regulated genes and is associated with poor prognosis in ERG-negative prostate cancer (108–110).

The interactions between ING3 and miRNAs have been poorly documented. In colorectal cancer (CRC), Zhang et al. observed in CRC tissues that the lncRNA CASC7 (CAncer Susceptibility Candidate 7) expression was low whereas miR-21 expression was high (111). Moreover, they have shown in CRC cell lines that *ING3* is a direct target of miR-21, known to act as an oncomiR in several types of cancer by targeting genes with an important role in cell migration, such as *FZD6*, or in cell proliferation such as *PTEN* (111–114). They demonstrated that CASC7 can indirectly increase ING3 expression and have tumor suppressive effects by sponging miR-21.

One report showed that in periodontitis, a non-oncogenic disease, ING3 would play a role and be targeted by miR-494 and miR-522, however these *in silico* results have not been confirmed *in vitro* (115).

Thus, further studies concerning ING3 regulation by miRNA or ncRNAs would be needed in order to document their interactions in cancer and other diseases.

3. ING4 and miRNAs in cancer and other diseases

Reports show that ING4 has tumor suppressive functions. Indeed, it can regulate cell proliferation (116), chromatin modification since it belongs to the HBO1/JADE complex (117,118) and DNA replication (119). Moreover, ING4 can inhibit both cell migration (120,121) and neoangiogenesis (27,122). Therefore, ING4 is characterized as both a type I « caretaker » and type II « gatekeeper » Tumor Suppressor Gene (TSG).

Several miRNAs have been found to decrease the expression of ING4 in cancers by binding to its mRNA, especially in its 3'-UTR region. ING4 has been characterized as a target of miR-650 which is upregulated in gastric cancer, leukemia, hepatocellular cancer, osteosarcoma cells and lung adenocarcinoma (123–127). In the latter case, it has been demonstrated that miR-650 confers chemoresistance to docetaxel, an anti-cancerous drug (127). miR-650 can also trigger epithelial to mesenchymal transition in breast cancer by targeting ING4 and NDRG2 (128). Furthermore, several other miRNAs are able to inhibit ING4 expression in cancers. It is the case of mir-214 in pancreatic cancers (129,130), mir-761 in NSCLC (131), mir-330 in hepatocellular carcinoma (132) and miR-423-5p in glioblastoma (133).

Beside cancers, studies have shown that miRNAs are involved in many other pathologic processes. For instance, miR-214 which plays a role in the development of pancreatic cancers is also more expressed in cardiac injuries in response to carvedilol, a drug that has protective properties in ischemic injuries. Overexpression of miR-214 decreases the apoptosis of cardiomyocytes by inhibiting ING4 (134). Moreover, one study showed that miR-361-3p, miR-1910-5p, miR-3691-3p could target ING4 in chronic idiopathic urticaria and active hives and could be used as biomarkers (135). There are some limitations to studying the interaction between miRNAs and ING4. In fact, one study showed by a luciferase assay, that ING4 is not a target of miR-2478 despite being characterized as a putative one by *in silico* analysis (135).

4. ING5 regulation by miRNAs

Several studies have shown that ING5 has tumor suppressive functions. Indeed, ING5 is involved in the regulation of cell proliferation (136), chromatin modification since it belongs to the HBO1/JADE or MOZ/MORF complexes (118,137), DNA replication (10) and repair (138) and cell migration (139).

Numerous reports have shown that the overexpression of miRNAs is of key importance in the development of several cancers. In fact, miRNA can bind to the 3'UTR of ING5 to degrade its mRNA and thereby increase cell proliferation. Various miRNAs are involved such as miR-196a in pancreatic cancer (140), miR-1307 in ovarian cancer (32), miR-24 in breast cancer (141) and miR-27-3p in osteosarcoma (142). In addition, two reports have shown that miR-331-3p and miR-181b both of which target the 3'UTR of ING5 are upregulated by the hepatitis B virus protein X (143,144). This overexpression can promote the proliferation of hepatocarcinoma cancer cells. Moreover, it has been shown that miRNAs are involved in chemoresistance to anti-cancerous drugs by degrading ING5 which, on the contrary, promotes chemosensitivity to these drugs. This is the case of miR-193a-3p in bladder cancer (138) and of miR-1307 in ovarian cancer (32).

Nevertheless, the upregulation of miRNAs is not specific to cancers. In fact, a report has demonstrated that miR-193 is overexpressed in response to low-level laser irradiation (LLLI) in multipotent stem cells resulting in ING5 inhibition and thus cell proliferation (145). The LLLI technique could increase the proliferation of stem cells, especially those used in stem cell therapy.

III. Conclusion

The members of the ING family play a critical role in cell homeostasis and their dysregulation can maintain oncogenesis. As a matter of fact, they appear to be down-regulated in several cancer (21), and associated with poor prognosis or chemoresistance (32,106,107,127,146,147). Moreover INGs dysregulation may have a role in other diseases. For instance, ING4 KO mice don't spontaneously develop tumors but regulation of NF-κB–mediated innate immunity is impaired (148). Thus we could hypothesize that ING4 may be involved in inflammatory or immunity diseases. INGs regulation in cancer and diseases has not been totally elucidated yet. We reported that INGs protein can be mutated (28,59–61), have LOH (24,30,31), or be degraded (76,77,80,84), which make them both class I TSG (which are lost due to mutation or deletion), and class II TSG (which are not altered at the DNA level) (149). Nonetheless, those mechanisms are not sufficient to explain the frequent

loss of expression or down-regulation of INGs in cancer. Recently, some reports described INGs regulations by ncRNAs. As a matter of fact, ncRNAs, and more especially miRNAs, have been described to be dysregulated in cancer and other diseases, with pro-oncogenic or tumor suppressor effects (43,44). Of note, some reported miRNA studies need to be taken with caution. Indeed, some studies considered candidate miRNAs based on *in silico* analysis (115,135). However, *in vitro* experiments did not confirm these analyzes. Thus, to characterize INGs as a target of a newly-found miRNAs, *in silico* analysis should systematically be confirmed by *in vitro* experiments.

IV. Hypotheses and perspectives

One intriguing hypothesis would be that ING proteins could be targeted by a same miRNA. miRNAs which measure approximately 20 bases bind preferentially to the 3'UTR sequences of transcripts thanks to a seed sequence that measures at least 6 bases (150). This means that theoretically a miRNA could target different INGs, but that has never been reported yet. When 3' and 5' UTR sequences of INGs are compared with Blast or Ensembl, 3'UTR regions of several INGs share some common sequences of around 10-25 (Table 2) whereas not a single sequence match is observed for the 5'UTR regions. For instance, ING3 and ING5 3'UTRs have 9 small sequences in common. Although the INGs share some small sequences in their 3'UTR, it should be noted that there are no significant homologies when looking at the whole 3'UTRs. In fact, there is a diversity of the 3'UTR sequences even when comparing different isoforms of the same ING gene. For instance, the ING1b 3'UTR sequence is included within the ING1a 3'UTR sequence but the latter is more than ten folds longer than the former. This variability could explain the variable expressions of the different ING isoforms between different tissues. When 3'UTR of ING genes are compared with other sequences in the genome, it is observed that the 3'UTR of ING1 shares approximately a hundred bases with INGX sequence. *INGX* is an *ING1* pseudogene (2) which has never been shown to be translated. Its role has never been described yet. Thus, we could speculate that *INGX* could be involved in ING1 regulation of expression. However, it should be taken into account that *INGX* is much less transcribed than ING1 according to databases like ensembl.

It has been reported that RNA hybridization within the CDS has a qualitatively similar effect than the 3'-UTR sites, and can induce translational repression (151). When comparing coding sequences of the different ING genes transcripts according to their closest homologue

(*ING1/ING2*, *ING4/ING5*, *ING1/ING3* and *ING1/INGX*), homologies are more present within the C-terminal region of the INGs (>70%) (Fig. 3). Interestingly, the NCR (Novel Conserved Region) of ING1b and ING2 transcripts share 56% of homologies, which is consistent with the fact that they both interact with the mSin3a/HDAC complex through this NCR domain. Consequently, some *ING*s CDS could also be targeted by common miRNAs.

Finally, whereas INGs protein can be regulated by miRNA, at least ING1 can interfere with miRNA synthesis (91,95), which raises the question of the other INGs involvement in miRNA regulation.

Recently, therapeutics targeting miRNAs have emerged (152), hence the importance to understand their mechanisms of action. Indeed, since INGs proteins are TSG and are down-regulated in many types of cancer, restoring their functions by inhibiting miRNAs could be a therapeutic possibility. Some studies showed that ING reintroduction mediated by adenovirus suppresses tumor growth, angiogenesis, enhance apoptosis and can have a synergistic effect with radiation therapy (153–155). Moreover, ING4 reintroduction through photothermal combined gene therapy showed *in vitro* and *in vivo* decreased cell viability and tumor growth (156).

Acknowledgements:

M.G is a recipient of a fellowship from the FRM (Fondation pour la Recherche Médicale, DEA20170637832) and R.P. is supported by INSERM (Institut National de la Santé et de la Recherche Médicale). The work was supported by La Ligue Contre le Cancer (Grand Ouest), Association pour la Recherche sur le Cancer (ARC).

Conflicts of interest: none

References

1. Garkavtsev I, Kazarov A, Gudkov A, Riabowol K. Suppression of the novel growth inhibitor p33ING1 promotes neoplastic transformation. Nat Genet. déc 1996;14(4):415‑20.

2. Shimada Y, Saito A, Suzuki M, Takahashi E, Horie M. Cloning of a novel gene (ING1L) homologous to ING1, a candidate tumor suppressor. Cytogenet Cell Genet. 1998;83(3‑4):232‑5.

3. Nagashima M, Shiseki M, Miura K, Hagiwara K, Linke SP, Pedeux R, et al. DNA damage-inducible gene p33ING2 negatively regulates cell proliferation through acetylation of p53. Proc Natl Acad Sci U S A. 14 août 2001;98(17):9671‑6.

4. Shiseki M, Nagashima M, Pedeux RM, Kitahama-Shiseki M, Miura K, Okamura S, et al. p29ING4 and p28ING5 bind to p53 and p300, and enhance p53 activity. Cancer Res. 15 mai 2003;63(10):2373‑8.

5. Shi X, Hong T, Walter KL, Ewalt M, Michishita E, Hung T, et al. ING2 PHD domain links histone H3 lysine 4 methylation to active gene repression. Nature. 6 juill 2006;442(7098):96‑9.

6. He GHY, Helbing CC, Wagner MJ, Sensen CW, Riabowol K. Phylogenetic analysis of the ING family of PHD finger proteins. Mol Biol Evol. janv 2005;22(1):104‑16.

7. Lee WY, Lee D, Chung W-I, Kwon CS. Arabidopsis ING and Alfin1-like protein families localize to the nucleus and bind to H3K4me3/2 via plant homeodomain fingers. Plant J Cell Mol Biol. mai 2009;58(3):511‑24.

8. Campos EI, Chin MY, Kuo WH, Li G. Biological functions of the ING family tumor suppressors. Cell Mol Life Sci CMLS. oct 2004;61(19‑20):2597‑613.

9. COLES AH, JONES SN. The ING Gene Family in the Regulation of Cell Growth and Tumorigenesis. J Cell Physiol. janv 2009;218(1):45‑57.

10. Doyon Y, Cayrou C, Ullah M, Landry A-J, Côté V, Selleck W, et al. ING tumor suppressor proteins are critical regulators of chromatin acetylation required for genome expression and perpetuation. Mol Cell. 6 janv 2006;21(1):51‑64.

11. Russell M, Berardi P, Gong W, Riabowol K. Grow-ING, Age-ING and Die-ING: ING proteins link cancer, senescence and apoptosis. Exp Cell Res. 15 avr 2006;312(7):951‑61.

12. Garkavtsev I, Grigorian IA, Ossovskaya VS, Chernov MV, Chumakov PM, Gudkov AV. The candidate tumour suppressor p33ING1 cooperates with p53 in cell growth control. Nature. 15 janv 1998;391(6664):295‑8.

13. Coles AH, Liang H, Zhu Z, Marfella CGA, Kang J, Imbalzano AN, et al. Deletion of p37Ing1 in mice reveals a p53-independent role for Ing1 in the suppression of cell proliferation, apoptosis, and tumorigenesis. Cancer Res. 1 mars 2007;67(5):2054‑61.

14. Saito M, Kumamoto K, Robles AI, Horikawa I, Furusato B, Okamura S, et al. Targeted disruption of Ing2 results in defective spermatogenesis and development of soft-tissue sarcomas. PloS One. 19 nov 2010;5(11):e15541.

15. Soliman MA, Riabowol K. After a decade of study-ING, a PHD for a versatile family of proteins. Trends Biochem Sci. nov 2007;32(11):509‑19.

16. Li N, Zhao G, Chen T, Xue L, Ma L, Niu J, et al. Nucleolar protein CSIG is required for p33ING1 function in UV-induced apoptosis. Cell Death Dis. 15 mars 2012;3:e283.

17. Wang Y, Li G. ING3 promotes UV-induced apoptosis via Fas/caspase-8 pathway in melanoma cells. J Biol Chem. 28 avr 2006;281(17):11887‑93.

18. Wang J, Chin MY, Li G. The novel tumor suppressor p33ING2 enhances nucleotide excision repair via inducement of histone H4 acetylation and chromatin relaxation. Cancer Res. 15 févr 2006;66(4):1906‑11.

19. Larrieu D, Ythier D, Binet R, Brambilla C, Brambilla E, Sengupta S, et al. ING2 controls the progression of DNA replication forks to maintain genome stability. EMBO Rep. oct 2009;10(10):1168‑74.

20. Ythier D, Larrieu D, Binet R, Binda O, Brambilla C, Gazzeri S, et al. Sumoylation of ING2 regulates the transcription mediated by Sin3A. Oncogene. 4 nov 2010;29(44):5946‑56.

21. Guérillon C, Bigot N, Pedeux R. The ING tumor suppressor genes: status in human tumors. Cancer Lett. 1 avr 2014;345(1):1‑16.

22. Ythier D, Brambilla E, Binet R, Nissou D, Vesin A, de Fraipont F, et al. Expression of candidate tumor suppressor gene ING2 is lost in non-small cell lung carcinoma. Lung Cancer Amst Neth. août 2010;69(2):180‑6.

23. Zhao S, Yang X-F, Gou W-F, Lu H, Li H, Zhu Z-T, et al. Expression profiles of inhibitor of growth protein 2 in normal and cancer tissues: An immunohistochemical screening analysis. Mol Med Rep. févr 2016;13(2):1881‑7.

24. Borkosky SS, Gunduz M, Beder L, Tsujigiwa H, Tamamura R, Gunduz E, et al. Allelic loss of the ING gene family loci is a frequent event in ameloblastoma. Oncol Res. 2010;18(10):509‑18.

25. Zhang F, Zhang X, Meng J, Zhao Y, Liu X, Liu Y, et al. ING5 inhibits cancer aggressiveness via preventing EMT and is a potential prognostic biomarker for lung cancer. Oncotarget. 30 juin 2015;6(18):16239‑52.

26. Zhao Q-Y, Ju F, Wang Z-H, Ma X-Z, Zhao H. ING5 inhibits epithelial-mesenchymal transition in breast cancer by suppressing PI3K/Akt pathway. Int J Clin Exp Med. 2015;8(9):15498‑505.

27. Garkavtsev I, Kozin SV, Chernova O, Xu L, Winkler F, Brown E, et al. The candidate tumour suppressor protein ING4 regulates brain tumour growth and angiogenesis. Nature. 18 mars 2004;428(6980):328‑32.

28. Yu G-Z, Zhu M-H, Zhu Z, Ni C-R, Zheng J-M, Li F-M. Genetic alterations and reduced expression of tumor suppressor p33(ING1b) in human exocrine pancreatic carcinoma. World J Gastroenterol. 15 déc 2004;10(24):3597‑601.

29. Luo Z-G, Tang H, Li B, Zhu Z, Ni C-R, Zhu M-H. Genetic alterations of tumor suppressor ING1 in human non-small cell lung cancer. Oncol Rep. avr 2011;25(4):1073‑81.

30. Sironi E, Cerri A, Tomasini D, Sirchia SM, Porta G, Rossella F, et al. Loss of heterozygosity on chromosome 4q32-35 in sporadic basal cell carcinomas: evidence for the involvement of p33ING2/ING1L and SAP30 genes. J Cutan Pathol. avr 2004;31(4):318‑22.

31. Gunduz M, Ouchida M, Fukushima K, Ito S, Jitsumori Y, Nakashima T, et al. Allelic loss and reduced expression of the ING3, a candidate tumor suppressor gene at 7q31, in human head and neck cancers. Oncogene. 27 juin 2002;21(28):4462‑70.

32. Chen W-T, Yang Y-J, Zhang Z-D, An Q, Li N, Liu W, et al. MiR-1307 promotes ovarian cancer cell chemoresistance by targeting the ING5 expression. J Ovarian Res. 11 janv 2017;10(1):1.

33. He D, Miao H, Xu Y, Xiong L, Wang Y, Xiang H, et al. MiR-371-5p facilitates pancreatic cancer cell proliferation and decreases patient survival. PloS One. 2014;9(11):e112930.

34. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 3 déc 1993;75(5):843‑54.

35. Peng JC, Shen J, Ran ZH. Transcribed ultraconserved region in human cancers. RNA Biol. déc 2013;10(12):1771‑7.

36. Kopp F, Mendell JT. Functional Classification and Experimental Dissection of Long Noncoding RNAs. Cell. 25 janv 2018;172(3):393‑407.

37. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell. 23 janv 2004;116(2):281‑97.

38. Ghahhari NM, Babashah S. Interplay between microRNAs and WNT/β-catenin signalling pathway regulates epithelial-mesenchymal transition in cancer. Eur J Cancer Oxf Engl 1990. août 2015;51(12):1638‑49.

39. Wang Y, Liu J, Liu C, Naji A, Stoffers DA. MicroRNA-7 regulates the mTOR pathway and proliferation in adult pancreatic β-cells. Diabetes. mars 2013;62(3):887‑95.

40. Chen J-J, Zhao B, Zhao J, Li S. Potential Roles of Exosomal MicroRNAs as Diagnostic Biomarkers and Therapeutic Application in Alzheimer's Disease. Neural Plast. 2017;2017:7027380.

41. Yu CX, Sun S. An Emerging Role for Circular RNAs in Osteoarthritis. Yonsei Med J. mai 2018;59(3):349‑55.

42. Kadamkode V, Banerjee G. Micro RNA: an epigenetic regulator of type 2 diabetes. MicroRNA Shariqah United Arab Emir. 2014;3(2):86‑97.

43. Peng Y, Croce CM. The role of MicroRNAs in human cancer. Signal Transduct Target Ther. 28 janv 2016;1:15004.

44. Svoronos AA, Engelman DM, Slack FJ. OncomiR or Tumor Suppressor? The Duplicity of MicroRNAs in Cancer. Cancer Res. 01 2016;76(13):3666‑70.

45. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, et al. A microRNA polycistron as a potential human oncogene. Nature. 9 juin 2005;435(7043):828‑33.

46. Gruszka R, Zakrzewska M. The Oncogenic Relevance of miR-17-92 Cluster and Its Paralogous miR-106b-25 and miR-106a-363 Clusters in Brain Tumors. Int J Mol Sci. 16 mars 2018;19(3).

47. Hayashita Y, Osada H, Tatematsu Y, Yamada H, Yanagisawa K, Tomida S, et al. A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation. Cancer Res. 1 nov 2005;65(21):9628‑32.

48. Mogilyansky E, Rigoutsos I. The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease. Cell Death Differ. déc 2013;20(12):1603‑14.

49. Dou L, Wang S, Huang X, Sun X, Zhang Y, Shen T, et al. MiR-19a mediates gluconeogenesis by targeting PTEN in hepatocytes. Mol Med Rep. mars 2018;17(3):3967‑71.

50. Liu F, Zhang F, Li X, Liu Q, Liu W, Song P, et al. Prognostic role of miR-17-92 family in human cancers: evaluation of multiple prognostic outcomes. Oncotarget. 15 sept 2017;8(40):69125‑38.

51. Xu X, Zhu S, Tao Z, Ye S. High circulating miR-18a, miR-20a, and miR-92a expression correlates with poor prognosis in patients with non-small cell lung cancer. Cancer Med. 21 déc 2017;

52. Chen D, Zhang D, Lu Y, Chen L, Zeng Z, He M, et al. microRNA-217 inhibits tumor progression and metastasis by downregulating EZH2 and predicts favorable prognosis in gastric cancer. Oncotarget. 10 mai 2015;6(13):10868‑79.

53. Liu Y-P, Sun X-H, Cao X-L, Jiang W-W, Wang X-X, Zhang Y-F, et al. MicroRNA-217 suppressed epithelial-to-mesenchymal transition in gastric cancer metastasis through targeting PTPN14. Eur Rev Med Pharmacol Sci. avr 2017;21(8):1759‑67.

54. Tang Q, Hann SS. HOTAIR: An Oncogenic Long Non-Coding RNA in Human Cancer. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol. 24 mai 2018;47(3):893‑913.

55. Wang L-P, Wang J-P, Wang X-P. HOTAIR contributes to the growth of liver cancer via targeting miR-217. Oncol Lett. mai 2018;15(5):7963‑72.

56. Wang H, Qin R, Guan A, Yao Y, Huang Y, Jia H, et al. HOTAIR enhanced paclitaxel and doxorubicin resistance in gastric cancer cells partly through inhibiting miR-217 expression. J Cell Biochem. 1 juin 2018;

57. Yan J, Wu G, Chen J, Xiong L, Chen G, Li P. Downregulated miR-217 expression predicts a poor outcome in acute myeloid leukemia. Cancer Biomark Sect Dis Markers. 2018;22(1):73‑8.

58. Han X-R, Bai X-Z, Sun Y, Yang Y. Nuclear ING2 expression is reduced in osteosarcoma. Oncol Rep. 1 nov 2014;32(5):1967‑72.

59. Okano T, Gemma A, Hosoya Y, Hosomi Y, Nara M, Kokubo Y, et al. Alterations in novel candidate tumor suppressor genes, ING1 and ING2 in human lung cancer. Oncol Rep. mars 2006;15(3):545‑9.

60. Cengiz B, Gunduz E, Gunduz M, Beder LB, Tamamura R, Bagci C, et al. Tumor-specific mutation and downregulation of ING5 detected in oral squamous cell carcinoma. Int J Cancer. 1 nov 2010;127(9):2088‑94.

61. Chen L, Matsubara N, Yoshino T, Nagasaka T, Hoshizima N, Shirakawa Y, et al. Genetic alterations of candidate tumor suppressor ING1 in human esophageal squamous cell cancer. Cancer Res. 1 juin 2001;61(11):4345‑9.

62. Shen D-H, Chan KY-K, Khoo U-S, Ngan HY-S, Xue W-C, Chiu P-M, et al. Epigenetic and genetic alterations of p33ING1b in ovarian cancer. Carcinogenesis. avr 2005;26(4):855‑63.

63. Gunduz M, Nagatsuka H, Demircan K, Gunduz E, Cengiz B, Ouchida M, et al. Frequent deletion and down-regulation of ING4, a candidate tumor suppressor gene at 12p13, in head and neck squamous cell carcinomas. Gene. 15 août 2005;356:109‑17.

64. Stegmaier K, Pendse S, Barker GF, Bray-Ward P, Ward DC, Montgomery KT, et al. Frequent loss of heterozygosity at the TEL gene locus in acute lymphoblastic leukemia of childhood. Blood. 1 juill 1995;86(1):38‑44.

65. Berger PL, Frank SB, Schulz VV, Nollet EA, Edick MJ, Holly B, et al. Transient induction of ING4 by Myc drives prostate epithelial cell differentiation and its disruption drives prostate tumorigenesis. Cancer Res. 15 juin 2014;74(12):3357‑68.

66. Li M, Jin Y, Sun W, Yu Y, Bai J, Tong D, et al. Reduced expression and novel splice variants of ING4 in human gastric adenocarcinoma. J Pathol. sept 2009;219(1):87‑95.

67. Li X, Kikuchi K, Zheng Y, Noguchi A, Takahashi H, Nishida T, et al. Downregulation and translocation of nuclear ING4 is correlated with tumorigenesis and progression of head and neck squamous cell carcinoma. Oral Oncol. mars 2011;47(3):217‑23.

68. Cengiz B, Gunduz M, Nagatsuka H, Beder L, Gunduz E, Tamamura R, et al. Fine deletion mapping of chromosome 2q21-37 shows three preferentially deleted regions in oral cancer. Oral Oncol. mars 2007;43(3):241‑7.

69. Nouman GS, Anderson JJ, Lunec J, Angus B. The role of the tumour suppressor p33 ING1b in human neoplasia. J Clin Pathol. juill 2003;56(7):491‑6.

70. Ding X-Q, Zhao S, Yang L, Zhao X, Zhao G-F, Zhao S-P, et al. The nucleocytoplasmic translocation and up-regulation of ING5 protein in breast cancer: a potential target for gene therapy. Oncotarget. 10 oct 2017;8(47):81953‑66.

71. Satpathy S, Guérillon C, Kim T-S, Bigot N, Thakur S, Bonni S, et al. SUMOylation of the ING1b tumor suppressor regulates gene transcription. Carcinogenesis. oct 2014;35(10):2214‑23.

72. Garate M, Campos EI, Bush JA, Xiao H, Li G. Phosphorylation of the tumor suppressor p33(ING1b) at Ser-126 influences its protein stability and proliferation of melanoma cells. FASEB J Off Publ Fed Am Soc Exp Biol. nov 2007;21(13):3705‑16.

73. Yu L, Thakur S, Leong-Quong RY, Suzuki K, Pang A, Bjorge JD, et al. Src Regulates the Activity of the ING1 Tumor Suppressor. PLOS ONE. avr 2013;8(4):e60943.

74. Kumamoto K, Spillare EA, Fujita K, Horikawa I, Yamashita T, Appella E, et al. Nutlin-3a activates p53 to both down-regulate inhibitor of growth 2 and up-regulate mir-34a, mir-34b, and mir-34c expression, and induce senescence. Cancer Res. 1 mai 2008;68(9):3193‑203.

75. Pedeux R, Sengupta S, Shen JC, Demidov ON, Saito S, Onogi H, et al. ING2 regulates the onset of replicative senescence by induction of p300-dependent p53 acetylation. Mol Cell Biol. août 2005;25(15):6639‑48.

76. Nie J, Liu L, Wu M, Xing G, He S, Yin Y, et al. HECT ubiquitin ligase Smurf1 targets the tumor suppressor ING2 for ubiquitination and degradation. FEBS Lett. 16 juill 2010;584(14):3005‑12.

77. Li H, Xiao N, Wang Y, Wang R, Chen Y, Pan W, et al. Smurf1 regulates lung cancer cell growth and migration through interaction with and ubiquitination of PIPKIγ. Oncogene. 12 2017;36(41):5668‑80.

78. Tao Y, Sun C, Zhang T, Song Y. SMURF1 promotes the proliferation, migration and invasion of gastric cancer cells. Oncol Rep. sept 2017;38(3):1806‑14.

79. Wei R, Guo J, Li M, Yang X, Zhu R, Huang H, et al. Smurf1 controls S phase progression and tumorigenesis through Wee1 degradation. FEBS Lett. 2017;591(8):1150‑8.

80. Chen G, Wang Y, Garate M, Zhou J, Li G. The tumor suppressor ING3 is degraded by SCF(Skp2)-mediated ubiquitin-proteasome system. Oncogene. 11 mars 2010;29(10):1498‑508.

81. Li Q, Murphy M, Ross J, Sheehan C, Carlson JA. Skp2 and p27kip1 expression in melanocytic nevi and melanoma: an inverse relationship. J Cutan Pathol. nov 2004;31(10):633‑42.

82. Woenckhaus C, Maile S, Uffmann S, Bansemir M, Dittberner T, Poetsch M, et al. Expression of Skp2 and p27KIP1 in naevi and malignant melanoma of the skin and its relation to clinical outcome. Histol Histopathol. 2005;20(2):501‑8.

83. Guo Q, Fast W. Citrullination of Inhibitor of Growth 4 (ING4) by Peptidylarginine Deminase 4 (PAD4) Disrupts the Interaction between ING4 and p53. J Biol Chem. 13 mai 2011;286(19):17069‑78.

84. Tsai K-W, Tseng H-C, Lin W-C. Two wobble-splicing events affect ING4 protein subnuclear localization and degradation. Exp Cell Res. 15 oct 2008;314(17):3130‑41.

85. Linzen U, Lilischkis R, Pandithage R, Schilling B, Ullius A, Lüscher-Firzlaff J, et al. ING5 is phosphorylated by CDK2 and controls cell proliferation independently of p53. PloS One. 2015;10(4):e0123736.

86. Skowyra D, Zeremski M, Neznanov N, Li M, Choi Y, Uesugi M, et al. Differential association of products of alternative transcripts of the candidate tumor suppressor ING1 with the mSin3/HDAC1 transcriptional corepressor complex. J Biol Chem. 23 mars 2001;276(12):8734‑9.

87. Ceruti JM, Ogara MF, Menéndez C, Palmero I, Cánepa ET. Inhibitor of growth 1 (ING1) acts at early steps of multiple DNA repair pathways. Mol Cell Biochem. juin 2013;378(1‑2):117‑26.

88. Bigot N, Guérillon C, Loisel S, Bertheuil N, Sensebé L, Tarte K, et al. ING1b negatively regulates HIF1α protein levels in adipose-derived stromal cells by a SUMOylation-dependent mechanism. Cell Death Dis. 22 janv 2015;6:e1612.

89. Guérillon C, Larrieu D, Pedeux R. ING1 and ING2: multifaceted tumor suppressor genes. Cell Mol Life Sci CMLS. oct 2013;70(20):3753‑72.

90. Li J, Wang Y, Wong RPC, Li G. The role of ING tumor suppressors in UV stress response and melanoma progression. Curr Drug Targets. mai 2009;10(5):455‑64.

91. Chen J, Tran UM, Rajarajacholan U, Thalappilly S, Riabowol K. ING1b-inducible microRNA203 inhibits cell proliferation. Br J Cancer. 19 mars 2013;108(5):1143‑8.

92. Chen T, Xu C, Chen J, Ding C, Xu Z, Li C, et al. MicroRNA-203 inhibits cellular proliferation and invasion by targeting Bmi1 in non-small cell lung cancer. Oncol Lett. juin 2015;9(6):2639‑46.

93. Zhao G, Guo Y, Chen Z, Wang Y, Yang C, Dudas A, et al. miR-203 Functions as a Tumor Suppressor by Inhibiting Epithelial to Mesenchymal Transition in Ovarian Cancer. J Cancer Sci Ther. 2015;7(2):34‑43.

94. Xiang J, Bian C, Wang H, Huang S, Wu D. MiR-203 down-regulates Rap1A and suppresses cell proliferation, adhesion and invasion in prostate cancer. J Exp Clin Cancer Res CR. 31 janv 2015;34:8.

95. Gómez-Cabello D, Callejas S, Benguría A, Moreno A, Alonso J, Palmero I. Regulation of the microRNA processor DGCR8 by the tumor suppressor ING1. Cancer Res. 1 mars 2010;70(5):1866‑74.

96. Liu J, Lin Y, Yang H, Deng Q, Chen G, He J. The expression of p33(ING1), p53, and autophagy-related gene Beclin1 in patients with non-small cell lung cancer. Tumour Biol J Int Soc Oncodevelopmental Biol Med. déc 2011;32(6):1113‑21.

97. Tsang FC, Po LS, Leung KM, Lau A, Siu WY, Poon RYC. ING1b decreases cell proliferation through p53-dependent and -independent mechanisms. FEBS Lett. 23 oct 2003;553(3):277‑85.

98. Tran UM, Rajarajacholan U, Soh J, Kim T–., Thalappilly S, Sensen CW, et al. LincRNA-p21 acts as a mediator of ING1b-induced apoptosis. Cell Death Dis. 5 mars 2015;6:e1668.

99. Gao Y, Ma H, Gao C, Lv Y, Chen X, Xu R, et al. Tumor-promoting properties of miR-8084 in breast cancer through enhancing proliferation, suppressing apoptosis and inducing epithelial-mesenchymal transition. J Transl Med. 23 févr 2018;16(1):38.

100. Shimomura A, Shiino S, Kawauchi J, Takizawa S, Sakamoto H, Matsuzaki J, et al. Novel combination of serum microRNA for detecting breast cancer in the early stage. Cancer Sci. mars 2016;107(3):326‑34.

101. Nagashima M, Shiseki M, Pedeux RM, Okamura S, Kitahama-Shiseki M, Miura K, et al. A novel PHD-finger motif protein, p47ING3, modulates p53-mediated transcription, cell cycle control, and apoptosis. Oncogene. 23 janv 2003;22(3):343‑50.

102. Zhao S, Wang L, Zhang C, Deng Y, Zhao B, Ren Y, et al. Inhibitor of growth 3 induces cell death by regulating cell proliferation, apoptosis and cell cycle arrest by blocking the PI3K/AKT pathway. Cancer Gene Ther. 1 juin 2018;

103. Lu M, Chen F, Wang Q, Wang K, Pan Q, Zhang X. Downregulation of inhibitor of growth 3 is correlated with tumorigenesis and progression of hepatocellular carcinoma. Oncol Lett. juill 2012;4(1):47‑52.

104. Yang H-Y, Liu H-L, Tian L-T, Song R-P, Song X, Yin D-L, et al. Expression and prognostic value of ING3 in human primary hepatocellular carcinoma. Exp Biol Med Maywood NJ. avr 2012;237(4):352‑61.

105. Gou W, Sun H, Zhao S, Niu Z, Mao X-Y, Takano Y, et al. Downregulated inhibitor of growth 3 (ING3) expression during colorectal carcinogenesis. Indian J Med Res. avr 2014;139(4):561‑7.

106. Gunduz M, Beder LB, Gunduz E, Nagatsuka H, Fukushima K, Pehlivan D, et al. Downregulation of ING3 mRNA expression predicts poor prognosis in head and neck cancer. Cancer Sci. mars 2008;99(3):531‑8.

107. Wang Y, Dai DL, Martinka M, Li G. Prognostic significance of nuclear ING3 expression in human cutaneous melanoma. Clin Cancer Res Off J Am Assoc Cancer Res. 15 juill 2007;13(14):4111‑6.

108. Almami A, Hegazy SA, Nabbi A, Alshalalfa M, Salman A, Abou-Ouf H, et al. ING3 is associated with increased cell invasion and lethal outcome in ERG-negative prostate cancer patients. Tumour Biol J Int Soc Oncodevelopmental Biol Med. juill 2016;37(7):9731‑8.

109. McClurg UL, Nabbi A, Ricordel C, Korolchuk S, McCracken S, Heer R, et al. Human ex vivo prostate tissue model system identifies ING3 as an oncoprotein. Br J Cancer. 6 mars 2018;118(5):713‑26.

110. Nabbi A, McClurg UL, Thalappilly S, Almami A, Mobahat M, Bismar TA, et al. ING3 promotes prostate cancer growth by activating the androgen receptor. BMC Med. 16 2017;15(1):103.

111. Zhang Z, Fu C, Xu Q, Wei X. Long non-coding RNA CASC7 inhibits the proliferation and migration of colon cancer cells via inhibiting microRNA-21. Biomed Pharmacother Biomedecine Pharmacother. nov 2017;95:1644‑53.

112. Pan X, Wang Z-X, Wang R. MicroRNA-21: a novel therapeutic target in human cancer. Cancer Biol Ther. 15 déc 2010;10(12):1224‑32.

113. Yan J, Liu T, Zhou X, Dang Y, Yin C, Zhang G. FZD6, targeted by miR-21, represses gastric cancer cell proliferation and migration via activating non-canonical wnt pathway. Am J Transl Res. 15 mai 2016;8(5):2354‑64.

114. Yan-nan B, Zhao-yan Y, Li-xi L, jiang Y, Qing-jie X, Yong Z. MicroRNA-21 accelerates hepatocyte proliferation in vitro via PI3K/Akt signaling by targeting PTEN. Biochem Biophys Res Commun. 17 janv 2014;443(3):802‑7.

115. Zhang B, Lin T, He H. Comparative analysis of blood and saliva expression profiles in chronic and refractory periodontitis patients. BMC Oral Health. 24 déc 2015;15:166.

116. Zhang X, Wang K-S, Wang Z-Q, Xu L-S, Wang Q-W, Chen F, et al. Nuclear localization signal of ING4 plays a key role in its binding to p53. Biochem Biophys Res Commun. 17 juin 2005;331(4):1032‑8.

117. Avvakumov N, Lalonde M-E, Saksouk N, Paquet E, Glass KC, Landry A-J, et al. Conserved molecular interactions within the HBO1 acetyltransferase complexes regulate cell proliferation. Mol Cell Biol. févr 2012;32(3):689‑703.

118. Lalonde M-E, Avvakumov N, Glass KC, Joncas F-H, Saksouk N, Holliday M, et al. Exchange of associated factors directs a switch in HBO1 acetyltransferase histone tail specificity. Genes Dev. 15 sept 2013;27(18):2009‑24.

119. Larrieu D, Pedeux R. SharING out the roles in replicatING DNA. Cell Cycle Georget Tex. 15 nov 2009;8(22):3623‑4.

120. Shen J-C, Unoki M, Ythier D, Duperray A, Varticovski L, Kumamoto K, et al. Inhibitor of growth 4 suppresses cell spreading and cell migration by interacting with a novel binding partner, liprin alpha1. Cancer Res. 15 mars 2007;67(6):2552‑8.

121. Kim S, Chin K, Gray JW, Bishop JM. A screen for genes that suppress loss of contact inhibition: identification of ING4 as a candidate tumor suppressor gene in human cancer. Proc Natl Acad Sci U S A. 16 nov 2004;101(46):16251‑6.

122. Chen Y, Huang Y, Hou P, Zhang Z, Zhang Y, Wang W, et al. ING4 suppresses tumor angiogenesis and functions as a prognostic marker in human colorectal cancer. Oncotarget. 29 nov 2016;7(48):79017‑31.

123. Mraz M, Dolezalova D, Plevova K, Stano Kozubik K, Mayerova V, Cerna K, et al. MicroRNA-650 expression is influenced by immunoglobulin gene rearrangement and affects the biology of chronic lymphocytic leukemia. Blood. 1 mars 2012;119(9):2110‑3.

124. Yun JH, Moon S, Lee H-S, Hwang MY, Kim Y-J, Yu H-Y, et al. MicroRNA-650 in a copy number-variable region regulates the production of interleukin 6 in human osteosarcoma cells. Oncol Lett. oct 2015;10(4):2603‑9.

125. Zeng Z-L, Li F-J, Gao F, Sun D-S, Yao L. Upregulation of miR-650 is correlated with down-regulation of ING4 and progression of hepatocellular carcinoma. J Surg Oncol. févr 2013;107(2):105‑10.

126. Zhang X, Zhu W, Zhang J, Huo S, Zhou L, Gu Z, et al. MicroRNA-650 targets ING4 to promote gastric cancer tumorigenicity. Biochem Biophys Res Commun. 30 avr 2010;395(2):275‑80.

127. Huang J-Y, Cui S-Y, Chen Y-T, Song H-Z, Huang G-C, Feng B, et al. MicroRNA-650 was a prognostic factor in human lung adenocarcinoma and confers the docetaxel chemoresistance of lung adenocarcinoma cells via regulating Bcl-2/Bax expression. PloS One. 2013;8(8):e72615.

128. Lango-Chavarría M, Chimal-Ramírez GK, Ruiz-Tachiquín ME, Espinoza-Sánchez NA, Suárez-Arriaga MC, Fuentes-Pananá EM. A 22q11.2 amplification in the region encoding microRNA-650 correlates with the epithelial to mesenchymal transition in breast cancer primary cultures of Mexican patients. Int J Oncol. févr 2017;50(2):432‑40.

129. Kuninty PR, Bojmar L, Tjomsland V, Larsson M, Storm G, Östman A, et al. MicroRNA-199a and -214 as potential therapeutic targets in pancreatic stellate cells in pancreatic tumor. Oncotarget. 24 févr 2016;7(13):16396‑408.

130. Zhang XJ, Ye H, Zeng CW, He B, Zhang H, Chen YQ. Dysregulation of miR-15a and miR-214 in human pancreatic cancer. J Hematol OncolJ Hematol Oncol. 24 nov 2010;3:46.

131. Yan A, Yang C, Chen Z, Li C, Cai L. MiR-761 Promotes Progression and Metastasis of Non-Small Cell Lung Cancer by Targeting ING4 and TIMP2. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol. 2015;37(1):55‑66.

132. Hu X, Feng Y, Sun L, Qu L, Sun C. Roles of microRNA-330 and Its Target Gene ING4 in the Development of Aggressive Phenotype in Hepatocellular Carcinoma Cells. Dig Dis Sci. 2017;62(3):715‑22.

133. Li S, Zeng A, Hu Q, Yan W, Liu Y, You Y. miR-423-5p contributes to a malignant phenotype and temozolomide chemoresistance in glioblastomas. Neuro-Oncol. 2017;19(1):55‑65.

134. Park K-M, Teoh J-P, Wang Y, Broskova Z, Bayoumi AS, Tang Y, et al. Carvedilol-responsive microRNAs, miR-199a-3p and -214 protect cardiomyocytes from simulated ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol. 1 août 2016;311(2):H371-383.

135. Lin C-KE, Kaptein JS, Sheikh J. Differential expression of microRNAs and their possible roles in patients with chronic idiopathic urticaria and active hives. Allergy Rhinol Provid RI. 1 juin 2017;8(2):67‑80.

136. Jafarnejad SM, Li G. Regulation of p53 by ING family members in suppression of tumor initiation and progression. Cancer Metastasis Rev. juin 2012;31(1‑2):55‑73.

137. Avvakumov N, Lalonde M-E, Saksouk N, Paquet E, Glass KC, Landry A-J, et al. Conserved molecular interactions within the HBO1 acetyltransferase complexes regulate cell proliferation. Mol Cell Biol. févr 2012;32(3):689‑703.

138. Li Y, Deng H, Lv L, Zhang C, Qian L, Xiao J, et al. The miR-193a-3p-regulated ING5 gene activates the DNA damage response pathway and inhibits multi-chemoresistance in bladder cancer. Oncotarget. 30 avr 2015;6(12):10195‑206.

139. Gou W, Shen D, Yang X, Zhao S, Liu Y, Sun H, et al. ING5 suppresses proliferation, apoptosis, migration and invasion, and induces autophagy and differentiation of gastric cancer cells: a good marker for carcinogenesis and subsequent progression. Oncotarget. 14 août 2015;6(23):19552‑79.

140. Liu M, Du Y, Gao J, Liu J, Kong X, Gong Y, et al. Aberrant expression miR-196a is associated with abnormal apoptosis, invasion, and proliferation of pancreatic cancer cells. Pancreas. oct 2013;42(7):1169‑81.

141. Cui S, Liao X, Ye C, Yin X, Liu M, Hong Y, et al. ING5 suppresses breast cancer progression and is regulated by miR-24. Mol Cancer. 10 2017;16(1):89.

142. Ye P, Ke X, Zang X, Sun H, Dong Z, Lin J, et al. Up-regulated MiR-27-3p promotes the G1-S phase transition by targeting inhibitor of growth family member 5 in osteosarcoma. Biomed Pharmacother Biomedecine Pharmacother. mai 2018;101:219‑27.

143. Cao Y, Chen J, Wang D, Peng H, Tan X, Xiong D, et al. Upregulated in Hepatitis B virus-associated hepatocellular carcinoma cells, miR-331-3p promotes proliferation of hepatocellular carcinoma cells by targeting ING5. Oncotarget. 10 nov 2015;6(35):38093‑106.

144. Xie X, Xu X, Sun C, Yu Z. Hepatitis B virus X protein promotes proliferation of hepatocellular carcinoma cells by upregulating miR-181b by targeting ING5. Biol Chem. 24 mai 2018;399(6):611‑9.

145. Wang J, Huang W, Wu Y, Hou J, Nie Y, Gu H, et al. MicroRNA-193 pro-proliferation effects for bone mesenchymal stem cells after low-level laser irradiation treatment through inhibitor of growth family, member 5. Stem Cells Dev. 1 sept 2012;21(13):2508‑19.

146. Borkosky SS, Gunduz M, Nagatsuka H, Beder LB, Gunduz E, Ali MALS, et al. Frequent deletion of ING2 locus at 4q35.1 associates with advanced tumor stage in head and neck squamous cell carcinoma. J Cancer Res Clin Oncol. mai 2009;135(5):703‑13.

147. Thakur S, Nabbi A, Klimowicz A, Riabowol K. Stromal ING1 expression induces a secretory phenotype and correlates with breast cancer patient survival. Mol Cancer. 27 août 2015;14:164.

148. Coles AH, Gannon H, Cerny A, Kurt-Jones E, Jones SN. Inhibitor of growth-4 promotes IκB promoter activation to suppress NF-κB signaling and innate immunity. Proc Natl Acad Sci. 22 juin 2010;107(25):11423‑8.

149. Sager R. Expression genetics in cancer: shifting the focus from DNA to RNA. Proc Natl Acad Sci U S A. 4 févr 1997;94(3):952‑5.

150. Ellwanger DC, Büttner FA, Mewes H-W, Stümpflen V. The sufficient minimal set of miRNA seed types. Bioinforma Oxf Engl. 15 mai 2011;27(10):1346‑50.

151. Hausser J, Syed AP, Bilen B, Zavolan M. Analysis of CDS-located miRNA target sites suggests that they can effectively inhibit translation. Genome Res. avr 2013;23(4):604‑15.

152. Hosseinahli N, Aghapour M, Duijf PHG, Baradaran B. Treating cancer with microRNA replacement therapy: A literature review. J Cell Physiol. août 2018;233(8):5574‑88.

153. Zhao Y, Li Z, Sheng W, Miao J, Yang J. Radiosensitivity by ING4-IL-24 bicistronic adenovirus-mediated gene cotransfer on human breast cancer cells. Cancer Gene Ther. janv 2013;20(1):38‑45.

154. Zhao Y, Su C, Zhai H, Tian Y, Sheng W, Miao J, et al. Synergistic antitumor effect of adenovirus-mediated hING4 gene therapy and (125)I radiation therapy on pancreatic cancer. Cancer Lett. 28 mars 2012;316(2):211‑8.

155. Shimada H, Liu T-L, Ochiai T, Shimizu T, Haupt Y, Hamada H, et al. Facilitation of adenoviral wild-type p53-induced apoptotic cell death by overexpression of p33(ING1) in T.Tn human esophageal carcinoma cells. Oncogene. 14 févr 2002;21(8):1208‑16.

156. Meng Y, Wang S, Li C, Qian M, Yan X, Yao S, et al. Photothermal combined gene therapy achieved by polyethyleneimine-grafted oxidized mesoporous carbon nanospheres. Biomaterials. 1 sept 2016;100:134‑42.

Figures legends :

Figure 1. INGs levels of expression in normal tissues and cancers. A) RNA level of expression of INGs in normal tissues and cancers based on RNAseq, according to The Human Protein Atlas (https://www.proteinatlas.org/) database. RNA level is expressed in RPKM (Read Per Kilobase per Million) in the normal tissues graph and in FPKM (number of Fragment Per Kilobase of exon per Million read) in the cancers graph. The size of each colored plot is related to each ING expression. B) Protein level of expression of INGs in normal tissues and cancers based on immunochemistry, according to THPA (normal tissues) and TCGA (cancer tissues) databases. In normal tissues, protein expression is described as 0 (none), 1 (low), 2 (medium) or 3 (high). In cancers, each colored plot represents the percentage of patients with high or medium protein expression. Few antibodies have been validated and are reliable.

Figure 2. ING genes mutation rate. Mutation rate for the different INGs according to TCGA database (https://portal.gdc.cancer.gov/) with tissue location.

Table 1. ncRNAs targeting the INGs. Summary of the ncRNAs targeting the INGs with their functional consequences (oncomiR or tumor suppressor), the analysis used to associate miRNAs with the INGs (*in silico* or *in vitro*), and the tissue or disease studied.

Table 2: INGs' 3' and 5'UTRs blast of small similar sequences. We have reported the length of the INGs' 3' and 5' UTRs, the number of small similar sequences (10-25bp) between the ING transcripts and the homologies (>80%) with other gene sequences (https://blast.ncbi.nlm.nih.gov and http://www.ensembl.org).

Figure 3. Homologies between different INGs transcripts. Homologies between INGs transcripts have been analyzed between ING1/ING2, ING1/ING3, ING1/INGX and ING4/5. The red color indicates an homology superior to 70%, orange an homology between 50% and 70%, and grey an homology inferior to 50%.

	Length	Number of small similar sequences (10-25bp)					BLAST (> 80%)
3'UTR		ING1	ING2	ING3	ING4	ING5	
ING1 (NM_198218)	243		0	0	0	2	5 (INGX included)
ING2 (NM_001564)	144	0		1	0	1	2
ING3 (NM_019071)	2373	0	1		1	9	4
ING4 (NM_016162)	915	0	0	1		2	1
ING5 (NM_032329)	4447	2	1	9	2		100

	Length	Number of small similar sequences (10-25bp)					BLAST (> 80%)
5'UTR		ING1	ING2	ING3	ING4	ING5	
ING1 (NM_198218)	198		0	0	0	0	2
ING2 (NM_001564)	202	0		0	0	0	1
ING3 (NM_019071)	148	0	0		0	0	2
ING4 (NM_016162)	47	0	0	0		0	2
ING5 (NM_032329)	26	0	0	0	0		0

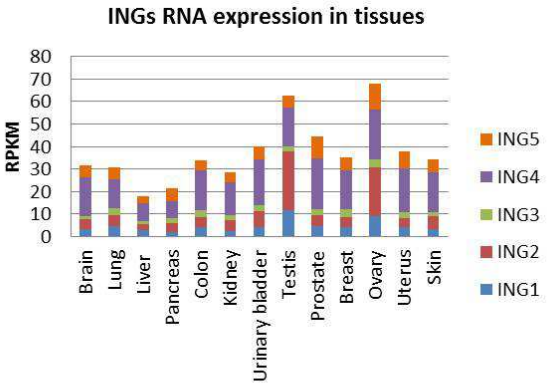
Table 2.

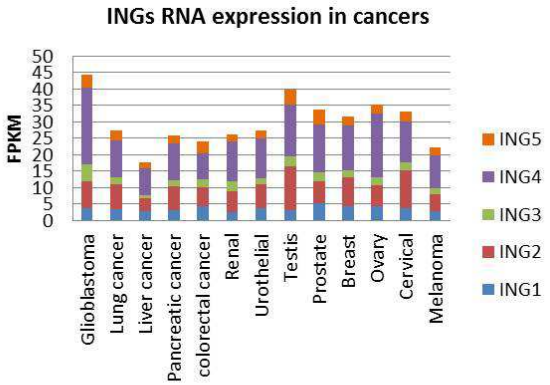
INGs	ncRNAs	Mechanisms of action	In silico analysis	In vitro analysis	Tissue/disease	Refs
ING1	miR-371-5p	oncomiR	Yes	Yes	Pancreas	(33)
ING2	miR-8084	oncomiR	Yes	Yes	Breast	(94)
ING3	miR-21	oncomiR	Yes	Yes	Colon	(106-109)
	miR-494	oncomiR	Yes	No	Saliva	(110)
	miR-522	oncomiR	Yes	No	Saliva	(110)
ING4	miR-650	oncomiR	Yes	Yes	gastric, B cells, lung, liver, bone, breast	(118–123)
	miR-214	oncomiR	Yes	Yes	pancreas (x2), heart	(124, 125, 129)
	miR-761	oncomiR	Yes	Yes	lung	(126)
	miR-330	oncomiR	Yes	Yes	liver	(127)
	miR-423-5p	oncomiR	Yes	Yes	glioma cells	(128)
	miR-2478	Absence of interactions demonstrated by *in vitro* analysis	Yes	Yes	HEK293T cell	(130)
	miR-361-3p	upregulated (could be used as biomarker)	Yes	No	Plasma (chronic idipathic urticarial)	(130)
	miR-1910-5p	upregulated (could be used as biomarker)	Yes	No	Plasma (chronic idipathic urticarial)	(130)
	miR-3691-3p	upregulated (could be used as biomarker)	Yes	No	Plasma (chronic idipathic urticarial)	(130)
ING5	miR-193	Promotes mutipotent stem cells proliferation in response to LLLI	Yes	Yes	Mutipotent Stem Cells	(140)
	miR-193a-3p	oncomiR	Yes	Yes	Bladder	(133)
	miR-196a	oncomiR	Yes	Yes	Pancreas	(135)
	miR-331-3p	oncomiR	Yes	Yes	Liver	(138)
	miR-181b	oncomiR	Yes	Yes	Liver	(139)
	miR-1307	oncomiR	Yes	Yes	Ovary	(32)
	miR-24	oncomiR	Yes	Yes	Breast	(136)
	miR-27-3p	oncomiR	Yes	Yes	Bone	(137)

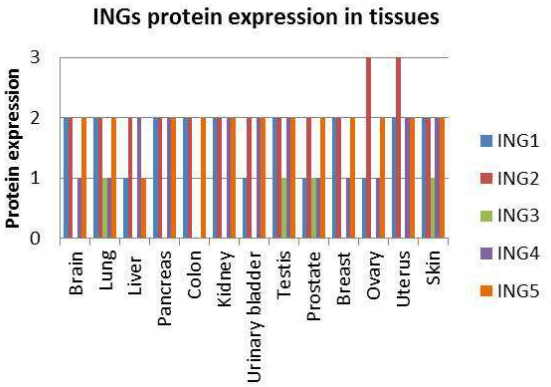
Table 1.

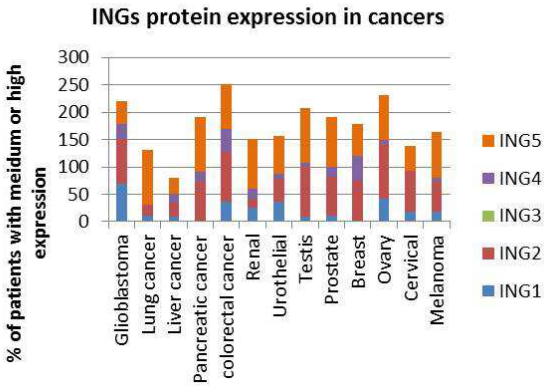
INGs	ncRNAs	Mechanisms of action	In silico analysis	In vitro analysis	Tissue/disease	Refs
ING1	miR-371-5p	oncomiR	Yes	Yes	Pancreas	(33)
ING2	miR-8084	oncomiR	Yes	Yes	Breast	(94)
ING3	miR-21	oncomiR	Yes	Yes	Colon	(106-109)
	miR-494	oncomiR	Yes	No	Saliva	(110)
	miR-522	oncomiR	Yes	No	Saliva	(110)
ING4	miR-650	oncomiR	Yes	Yes	gastric, B cells, lung, liver, bone, breast	(118–123)
	miR-214	oncomiR	Yes	Yes	pancreas (x2), heart	(124, 125, 129)
	miR-761	oncomiR	Yes	Yes	lung	(126)
	miR-330	oncomiR	Yes	Yes	liver	(127)
	miR-423-5p	oncomiR	Yes	Yes	glioma cells	(128)
	miR-2478	Absence of interactions demonstrated by *in vitro* analysis	Yes	Yes	HEK293T cell	(130)
	miR-361-3p	upregulated (could be used as biomarker)	Yes	No	Plasma (chronic idipathic urticarial)	(130)
	miR-1910-5p	upregulated (could be used as biomarker)	Yes	No	Plasma (chronic idipathic urticarial)	(130)
	miR-3691-3p	upregulated (could be used as biomarker)	Yes	No	Plasma (chronic idipathic urticarial)	(130)
ING5	miR-193	Promotes mutipotent stem cells proliferation in response to LLLI	Yes	Yes	Mutipotent Stem Cells	(140)
	miR-193a-3p	oncomiR	Yes	Yes	Bladder	(133)
	miR-196a	oncomiR	Yes	Yes	Pancreas	(135)
	miR-331-3p	oncomiR	Yes	Yes	Liver	(138)
	miR-181b	oncomiR	Yes	Yes	Liver	(139)
	miR-1307	oncomiR	Yes	Yes	Ovary	(32)
	miR-24	oncomiR	Yes	Yes	Breast	(136)
	miR-27-3p	oncomiR	Yes	Yes	Bone	(137)

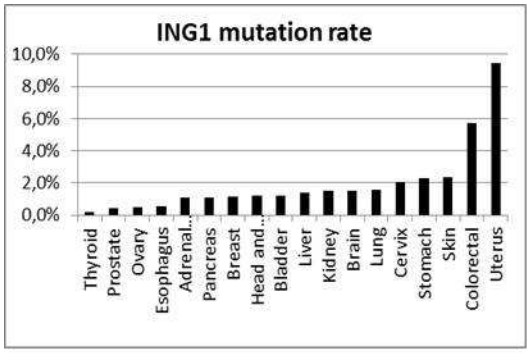
Table 1.

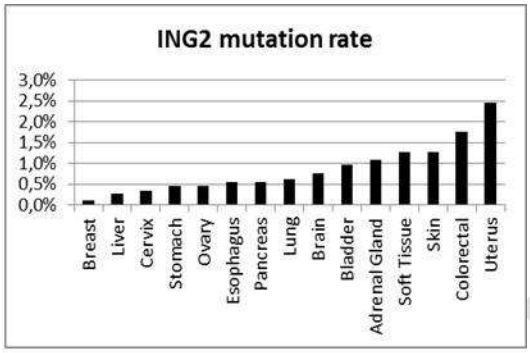


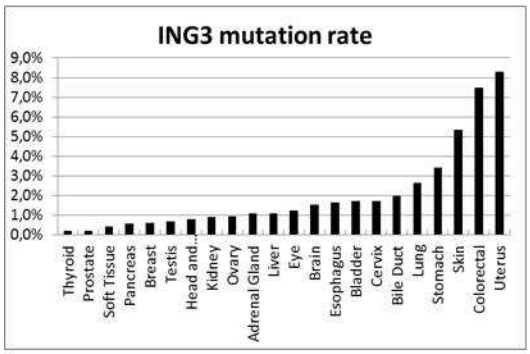


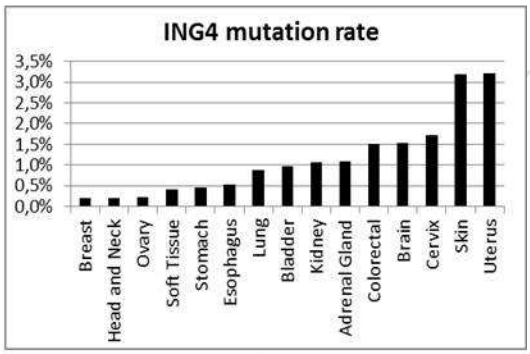


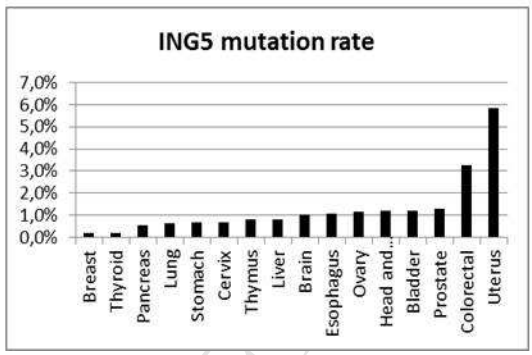












Highlights

- *INGs* are tumor suppressor genes playing a crucial role in cell homeostasis
- Multiple mechanisms may be involved in INGs loss or downregulation
- INGs regulation is still unclear and can involve ncRNAs
- ncRNAs may play an important role in cancer and other disease notably through INGs regulation.