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### ► To cite this version:

Marjorie Gournay, Mathieu Paineau, Jérôme Archambeau, Remy Pedoux. Regulat-INGs in tumors and diseases: Focus on ncRNAs. *Cancer Letters*, 2019, 447, pp.66-74. 10.1016/j.canlet.2019.01.006 . hal-02015576

**HAL Id: hal-02015576**

**<https://hal-univ-rennes1.archives-ouvertes.fr/hal-02015576>**

Submitted on 28 Feb 2019

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**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

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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 ING 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'-untranslated 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 ING proteins and in particular the loss of expression of ING proteins 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 ING proteins 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 ING proteins down regulation. It suggests that post-translational regulation such as ncRNA regulation could have an important impact on ING proteins regulation.

### 1. INGs alteration of expression in cancer

ING proteins 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-transcriptional 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. INGs post-translational regulation

Several mechanisms of regulation of ING 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  $\alpha$  (HIF1 $\alpha$ ) 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 ING's dysregulation may have a role in other diseases. For instance, ING4 KO mice don't spontaneously develop tumors but regulation of NF- $\kappa$ B-mediated innate immunity is impaired (148). Thus we could hypothesize that ING4 may be involved in inflammatory or immunity diseases. ING's regulation in cancer and diseases has not been totally elucidated yet. We reported that ING's 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 ING proteins in cancer. Recently, some reports described ING protein 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 analyses. Thus, to characterize ING proteins 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 ING proteins, but that has never been reported yet. When 3' and 5' UTR sequences of ING proteins are compared with Blast or Ensembl, 3'UTR regions of several ING proteins 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 ING proteins 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 protein 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 protein 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 protein 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 *INGs* 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

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**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%.

| 3'UTR            | Length | Number of small similar sequences (10-25bp) |      |      |      |      | BLAST (> 80%)     |
|------------------|--------|---|------|------|------|------|-------------------|
|                  |        | 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               |

| 5'UTR            | Length | Number of small similar sequences (10-25bp) |      |      |      |      | BLAST (> 80%) |
|------------------|--------|---|------|------|------|------|---------------|
|                  |        | 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             |

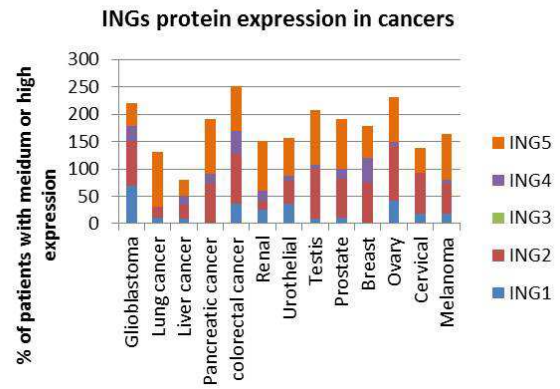
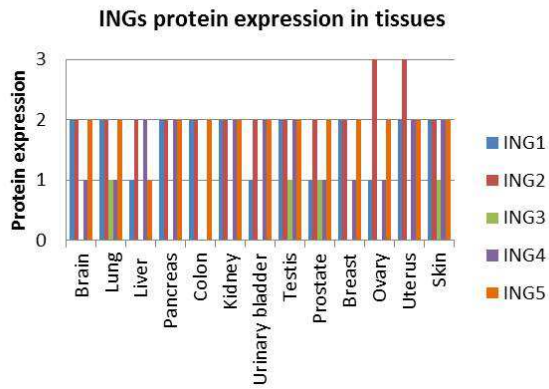
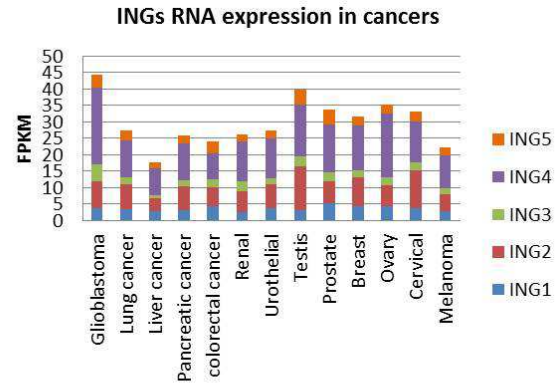
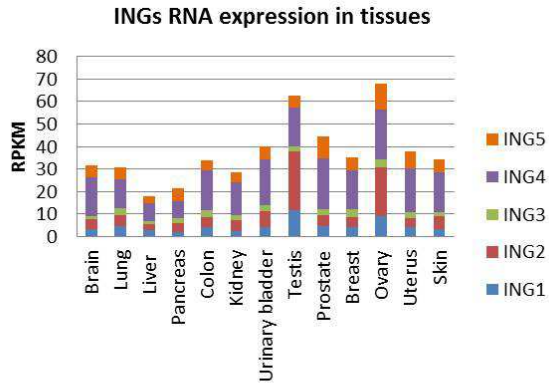
Table 2.

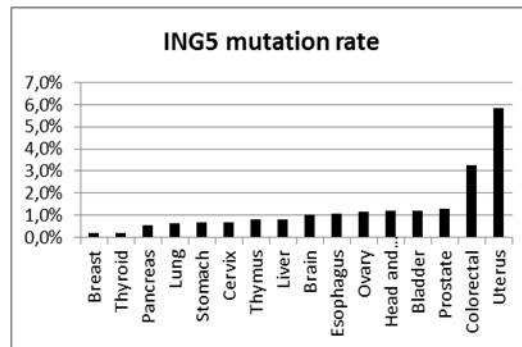
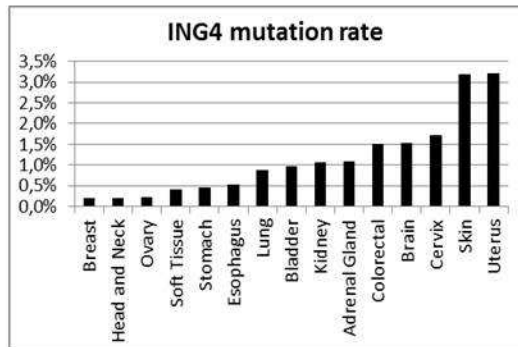
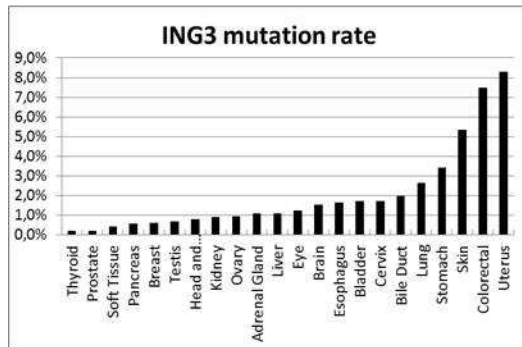
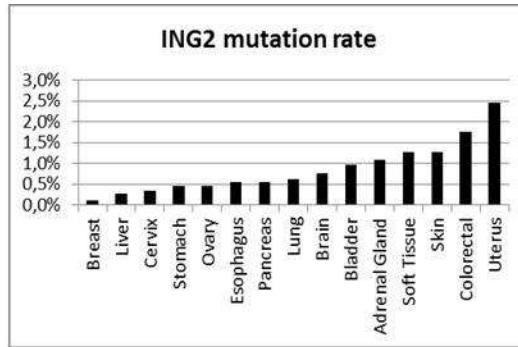
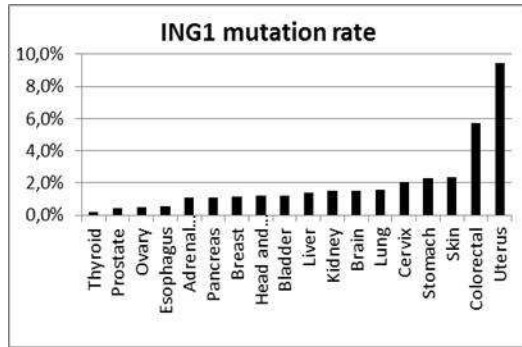
| INGs        | ncRNAs      | Mechanisms of action   | In silico analysis   | In vitro analysis | Tissue/disease                              | Refs                   |
|-------------|-------------|--|--|-------------------|---|------------------------|
| ING1        | miR-371-5p  | oncomiR  | Yes  | 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 <i>in vitro</i> analysis | Yes  | Yes               | HEK293T cell                                | (130)                  |
|             | miR-361-3p  | upregulated (could be used as biomarker)                         | Yes  | No                | Plasma (chronic idiopathic urticarial)      | (130)                  |
|             | miR-1910-5p | upregulated (could be used as biomarker)                         | Yes  | No                | Plasma (chronic idiopathic urticarial)      | (130)                  |
|             | miR-3691-3p | upregulated (could be used as biomarker)                         | Yes  | No                | Plasma (chronic idiopathic urticarial)      | (130)                  |
|             | ING5        | miR-193  | Promotes multipotent stem cells proliferation in response to LLI | Yes               | Yes   | Multipotent Stem Cells |
| 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 <i>in vitro</i> analysis | Yes  | Yes               | HEK293T cell                                | (130)                  |
|             | miR-361-3p  | upregulated (could be used as biomarker)                         | Yes  | No                | Plasma (chronic idiopathic urticarial)      | (130)                  |
|             | miR-1910-5p | upregulated (could be used as biomarker)                         | Yes  | No                | Plasma (chronic idiopathic urticarial)      | (130)                  |
|             | miR-3691-3p | upregulated (could be used as biomarker)                         | Yes  | No                | Plasma (chronic idiopathic urticarial)      | (130)                  |
|             | ING5        | miR-193  | Promotes multipotent stem cells proliferation in response to LLI | Yes               | Yes   | Multipotent Stem Cells |
| 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.







ACCEPTED MANUSCRIPT



**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.