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# Newly identified tumor suppressor functions of ING proteins

Léane Heliez<sup>1</sup>, Charles Ricordel<sup>1,2</sup>, Philippe Becuwe<sup>1,3</sup> and Rémy Pedoux<sup>1</sup>

## Abstract

The INhibitor of Growth (ING) proteins (ING1, ING2, ING3, ING4 and ING5) are a family of epigenetic regulators. Their decreased expression in numerous cancers led to identifying the ING proteins as gatekeeper tumor suppressors as they regulate cell cycle progression, apoptosis and senescence. Subsequently, they were also described as caretaker tumor suppressors through their involvement in DNA replication and the DNA damage response (DDR). Recent studies have identified new interactions of the ING proteins with proteins or pathways implicated in cell proliferation, the maintenance of stem cells pluripotency or the DDR. Furthermore, the ING proteins have been identified as regulators of ribosomal RNA synthesis and of mRNA stability and as regulators of mitochondrial DNA transcription resulting in the regulation of metabolism. These new findings highlight new antitumorigenic activities of the ING proteins that are potential targets for cancer treatment.

## Addresses

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## Background

The ING (INhibitor of Growth) protein family is composed of 5 members, from ING1 to ING5. From the identification of ING1 in 1996 [1], ING2 to ING5 were discovered by sequence homology. Genes encoding ING

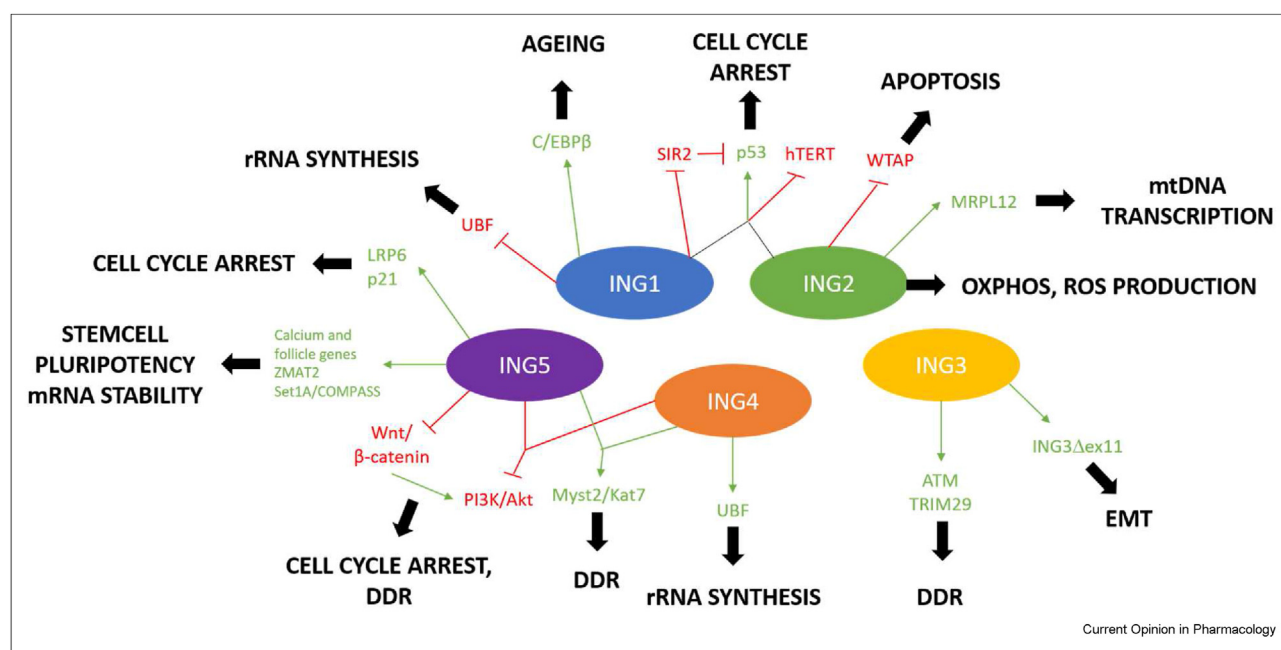
proteins are highly conserved from yeast to human, testifying to their importance in cellular functions [2,3]. ING proteins are mainly located in the nucleus thanks to an NLS (Nuclear Localization Sequence) [4]. INGs are well described for their role as epigenetic regulators, via their PHD (Plant HomeoDomain), which has a high affinity for H3K4me3 [5]. ING proteins have the ability to modify the state of chromatin compaction and thus the expression of genes, thanks to their association with acetylation/deacetylation complexes. ING1 and ING2 associate with Sin3A/HDAC1/2 deacetylation complexes [6]. ING3 associates with the TIP60/NuA4 acetylation complex (HAT), ING4 and ING5 with the HBO1 acetylation complex, and ING5 with the MOZ/MORF complex. Furthermore, all ING proteins can interact with the acetylase p300 [4].

Although oncogenic activity has been reported for ING3 in various cancers [7,8], ING proteins are mainly involved in suppressing tumor growth and invasiveness, making them promising therapeutic targets in cancer therapy. In the following review, we will focus on recent findings that reveal a role for ING proteins in cell proliferation, stem cell differentiation, the DNA damage response, regulation of ribosomal RNA synthesis, mRNA stability, but also in mitochondrial DNA transcription and metabolism (Figure 1).

## Cell proliferation, stem cell differentiation and the DNA damage response

Numerous studies have reported a decrease in the expression of ING family members in various cancers, suggesting ING genes may have tumor suppressor roles. INGs were initially described as gatekeeper tumor suppressors through their involvement in cell cycle arrest and induction of apoptosis. Through their interactions with acetylation complexes, INGs promote acetylation of the transcription factor p53, which plays a role in cell cycle arrest and apoptosis [4]. Recently, P33ING1b, the main isoform of ING1, has been shown to facilitate p53 acetylation by inhibiting SIR2 (Silent Information Regulator 2), a protein belonging to a deacetylation complex targeting p53 [9]. Similarly, ING2 promotes p53 acetylation, particularly in response to hyperglycemic stimulation [10]. On the other hand,

Figure 1



Recently identified pathways and functions implicating the ING proteins.

INGs also play a role in the control of proliferation and apoptosis by acting as epigenetic factors on the expression of specific genes. This is the case of ING1 and ING2, which act on the repression of the gene encoding hTERT (human Telomerase Reverse Transcriptase), in prostate cancer cells, in conjunction with the androgen receptor [11]. A recent study also suggests a role for ING3 in promoting cell growth and regulating Epithelial to Mesenchymal Transition (EMT) via activation of the androgen receptor [8]. Finally, ING4 and ING5 inhibit the phosphorylation of the serine kinase Akt [12,13], thus regulating the PI3K/Akt (Phosphoinositide 3-kinase/Protein kinase B) signaling pathway which is involved in both proliferation and the migratory and invasive capabilities of tumor cells [4,14–17]. Furthermore, overexpression of ING5 in lung tumor cells inhibits the Wnt/β-catenin pathway by increasing β-catenin phosphorylation, leading to a decrease in both cell proliferation and invasiveness [18].

Recently, a role for ING5 in stem cells has begun to emerge. In brain tumor initiating cells ING5 expression promoted maintenance of stem cell characteristics, enhancing PI3K/AKT and MEK/ERK activity by affecting pathways for FSH (follicular stimulating hormone) and calcium metabolism [19]. This function is dependent on ING5 activity as an epigenetic regulator. Then, a synthetic lethal screen conducted with the Set1A/COMPASS complex, an epigenetic regulator involved in embryonic stem cell differentiation, suggested that

ING5 may also play a role in mouse embryonic stem cells survival and differentiation [20].

Multiple studies have identified ING proteins as caretaker tumor suppressors through their role in the DNA damage response (DDR). They are mainly involved in the repair of UV-induced damage or DNA double strand breaks, but also in the induction of apoptosis following DNA damage in order to avoid genomic instability. This role is enabled by their interaction with the PCNA (Proliferating Cell Nuclear Antigen) protein and the ATM/ATR (Ataxia Telangiectasia Mutated/Ataxia Telangiectasia and Rad3 Related kinase) pathway, which have a major role in the activation of DDR [4]. Recently, ING3 has been identified as a key factor in DNA repair by homologous recombination (HR) and non-homologous end joining (NHEJ). In response to DNA damage induced by irradiation or exposure to an anti-cancer agent such as doxorubicin, ING3 is recruited to double strand breaks and facilitates the recruitment of various proteins involved in repair, particularly 53BP1, BRCA1 and TIP60, allowing the activation of ATM, which is required for the initiation of DDR [21]. ATM phosphorylates NBS1 thus increasing the recruitment of DDR mediators. Through TIP60, ING3 interacts with the TRIM29 protein, which is responsible for the assembly of all DDR proteins on chromatin and their activation [22]. ING4 and ING5, may also be involved in the regulation of DDR, through their interaction with the acetyltransferase complex MYST2/Kat7 (HBO1).

Myst2 is encoded by the Myst gene family involved in the control of transcription, replication and DDR. This ING4/ING5/Myst2/Kat7 pathway is inhibited by MEAF6 (Myst/Es1 Associated Factor 6), involved in cell proliferation [23].

### Involvement of ING proteins in rRNA synthesis

Ribosomal rRNAs are synthesized in the nucleolus of cells. ING proteins possess a nucleolar localization signal sequence in their structure, identified in their NLS. Recently, ING1 and ING4 have been shown to play a role in the regulation of rRNA synthesis. ING1 represses rRNA-encoding DNA transcription by recruiting the deacetylation complex HDAC1 and by associating with a nucleolar chromatin remodeling complex (NoRC) [24]. Indeed, ING1 promotes the deacetylation of histones H3K9 and H3K27, which are generally associated with increased rRNA transcription. In addition, ING1, by recruiting the HDAC1 complex, causes deacetylation of an rRNA transcription factor, Upstream Binding Factor (UBF), and inhibits its activity [24]. This inhibition of UBF by ING1 is also responsible for a decrease in both nucleolar localization and activation of mTOR (mammalian Target Of Rapamycin). The latter, by interacting with UBF, is known to play a role in protein synthesis by promoting the synthesis of rRNAs that constitute the structure of ribosomes, which are essential for the translation of mRNAs [24]. It is through this activity that mTOR is described as a stimulator of tumor growth. In contrast, ING4 promotes rRNA synthesis, by interacting with nucleolar proteins, such as NOLC1 (Nucleolar And Coiled-Body Phosphoprotein 1), NGB1 (Nucleolar GTP-Binding Protein 1), nucleolin (NCL), GNL2 (Guanine Nucleotide-Binding Protein-Like 2), and GNL3 (Guanine Nucleotide-Binding Protein-Like 2), but also by increasing the acetylation of histones H3K9 and H4 [25]. The nucleolar proteins NOLC1, NGB1 and NCL are known to play an active role in rRNA transcription and its regulation, while GNL2 and GNL3 are involved in rRNA assembly and ribosome export from the nucleus. This suggests that ING4 plays a role in these different steps of ribosome formation and thus represents a major player in protein synthesis [25]. Over-expression of ING1 or a deficit in ING4 expression leads in both cases to an observable alteration of the nucleolus structure [24,25].

### Involvement of ING2 and ING5 in mRNA stability

A recent study revealed that ING2 may be involved with mRNAs stability by regulating their splicing. This activity of ING2 would depend on it inhibiting the expression of the Wilms Tumor1 Associated Protein (WTAP) [26]. The latter is a pre-splicing regulator of mRNAs belonging to a complex called “m6A writer”,

responsible for their epigenetic modifications of the N6-methyladenosine (m6A) type which increases their stability. Within this complex, WTAP recruits the methyltransferases METTL3 and METTL14 which modulate m6A levels on transcripts [27]. Through its effects on mRNA methylation, WTAP plays a role in cancer development, by inhibiting cell cycle arrest and maintaining the genomic stability of tumor cells, thereby promoting their proliferation. Therefore, its inhibition by ING2 is responsible for inhibiting tumor cell proliferation.

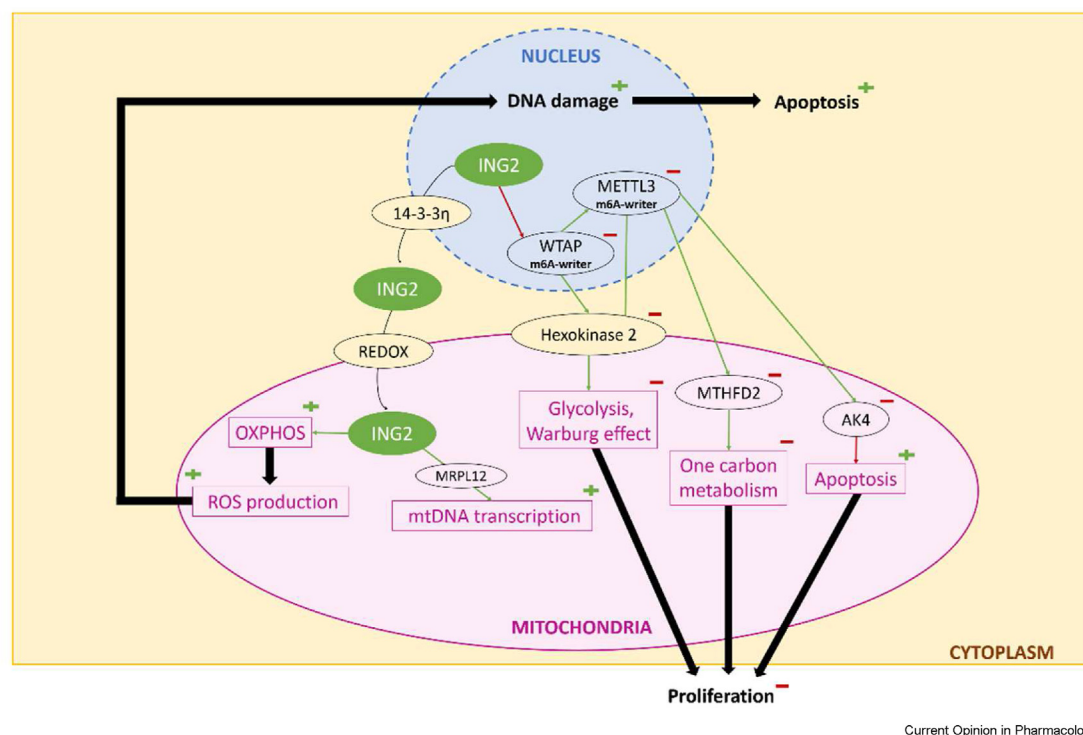
ING5 has also been identified as a regulator of mRNA stability by associating with ZMAT2 (Zinc finger Matrin-Type 2), a protein involved in mRNA splicing. This interaction between ZMAT2 and ING5 plays a role in maintaining epidermal stem cells in an undifferentiated state, by modulating the splicing and thus the stability of mRNAs responsible for cell differentiation of normal and cancer stem cells [28].

### Involvement of ING2 in mitochondrial DNA (mtDNA) transcription and metabolism (see Figure 2)

The ING2 protein is known to be present mainly in the nucleus. However, a recent study has reported that ING2 also localizes to the inner mitochondrial compartment without possessing a mitochondrial import sequence [29]. From the nucleus, ING2 is exported to the cytoplasm via the 14-3-3 $\eta$  protein, then translocated into the mitochondria in a redox-dependent manner. Once in the organelle, ING2 associates with TFAM (Mitochondrial Transcription Factor A), involved in the regulation of mtDNA transcription, demonstrating a potential involvement of ING2 in this activity. ING2 is described as a positive regulator of oxidative phosphorylation. Indeed, the inhibition of its expression leads to a strong decrease in ATP production and consequently the release of reactive oxygen species (ROS). These ROS are known to be responsible for DNA damage that can trigger apoptosis. This partly explains the importance of ING2 in maintaining the integrity of mitochondrial ultrastructure and further expand the tumor suppressor role of this protein [29]. Another study demonstrated the ability of ING2 to regulate the transcription of mitochondrial genes involved in oxidative phosphorylation by opposing the degradation of a protein called MRPL12 (Mitochondrial Ribosomal Protein L12). This protein belongs to the complexes involved in mtDNA transcription [30]. ING2 prevents the degradation of MRPL12 both by participating in its acetylation and by decreasing its ubiquitination rate [31].

The role of ING2 on mitochondrial metabolism also depends on its negative influence on WTAP expression [26]. Indeed, WTAP, by recruiting METTL3 methyltransferases that modulate m6A levels on transcripts

Figure 2



Current Opinion in Pharmacology

Involvement of ING2 in mRNA stability, mitochondrial DNA (mtDNA) transcription and metabolism.

[27], promotes glycolysis in tumor cells by inducing the expression of the enzyme hexokinase 2 and promotes the Warburg effect [32]. This effect, observed in tumor cells, consists in a transition of their metabolism towards an increase in glucose consumption and lactate production in order to optimize their proliferation. Similarly, METTL3 also induces moncarbon metabolism, involved in tumor proliferation, via MTHFD2 (MethyleneTetrahydroFolate Dehydrogenase/Cyclohydrolase) and inhibits apoptosis via the adenylate kinase AK4. Thus, ING2, by inhibiting WTAP, opposes the Warburg effect, moncarbon metabolism and tumor proliferation [31].

### Conclusion and perspectives

The tumor suppressive functions of ING proteins through the inhibition of cell proliferation and participation in the DDR are now well described. They involve interactions with target proteins belonging to signaling pathways such as p53/p21/hTERT, PI3K/Akt, Wnt/ $\beta$ -catenin, Myst2/Kat7 and TIP60/TRIM29. In addition, the most recent findings on the role of ING proteins in the regulation of ribosomal RNA synthesis and mRNA stability, implicate them in the control of normal and cancer stem cell differentiation. These data also report that one member of this family, ING2, has a key role in

mitochondrial metabolism, associated with its positive influence on mitochondrial gene transcription. These studies have reinforced the interest of ING proteins for the development of new anti-cancer therapeutic strategies aiming either to restore their expression in tumors, to target proteins interacting with them, or to modulate their activity. It should be noted that INGs are also involved in the prevention of other pathologies than cancer, such as obesity, by intervening in the metabolism of fatty acids [33]. It is therefore of crucial interest to continue to deepen our knowledge of their biological functions.

### Author contributions

**Léane Heliez:** Writing - Original Draft, Visualization  
**Charles Ricordel:** Writing - Review & Editing  
**Philippe Becuwe:** Writing - Original Draft, Writing - Review & Editing  
**Rémy Pedoux:** Writing - Review & Editing, Supervision, Funding acquisition.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



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