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Visions & Reflections (Minireview)

(de)MYSTification and INGenuity of tumor suppressors

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Chromosomal DNA in the eukaryotic nucleus is packaged into a compact structure called chromatin in which DNA is wrapped around histones to form nucleosomes. Extensive studies in recent years have shown that the structure of chromatin plays a critical and dynamic role in genome expression and perpetuation. The various specific post-translational modifications (such as acetylation, methylation, phosphorylation, sumoylation etc.) on the tails of histones form the so-called histone code [1]. They create docking sites for factors which alter chromatin structure and play a critical role in signaling for specific nuclear processes. Here we focus on the MYST family of histone acetyltransferases (HATs) and on the INhibitor of Growth (ING) family of proteins. We describe their collaborative functions in many diverse nuclear processes and discuss the mechanisms by which these interactions facilitate the various roles that ING proteins play as cell cycle regulators and tumor suppressors.

The founding member of the ING family of type II tumor suppressors, human ING1, has been studied extensively since it was cloned [2]. Overexpression of ING1 arrests cell growth in the G1 phase of the cell cycle, while its downregulation activates cell transformation and dramatically increases the replicative life of normal fibroblasts. These observations suggested a role for this protein in cell senescence and tumor formation *in vivo* [2]. Interestingly, ING1 mediates growth inhibition by modulating p53-dependent transcription [3–5]. Four additional human homologous genes (ING2–5) have since been identified through sequence homology with ING1 and have also been implicated in cancer [6], while ING homologs have been found in most eukaryotes. Homology is highest at the carboxyl termini of the proteins within a Plant HomeoDomain (PHD) finger, a motif common to many chromatin-regulatory proteins [7, 8]. Four recent reports in *Nature* identified the PHD finger as an important effector domain that binds to the trimethylated lysine 4 residue of histone H3 (H3K4me3), and significantly, all PHD domains of the ING family members were shown to bind preferentially to this histone modification [9–12]. Several studies have implicated ING proteins in the control of cellular aging, senescence, apoptosis, regulation of the cell cycle, negative regulation of cell proliferation, hormone signaling pathways, regulation of brain tumor growth and angiogenesis, transcription regulation, chromatin remodeling and genome integrity (reviewed in [13]).

Recently, the multi-subunit protein complexes containing the human ING family members were purified and characterized [7]. Remarkably, all these complexes function in the regulation of chromatin structure via histone acetylation or deacetylation. The ING complexes harboring histone acetyltransferase activ-

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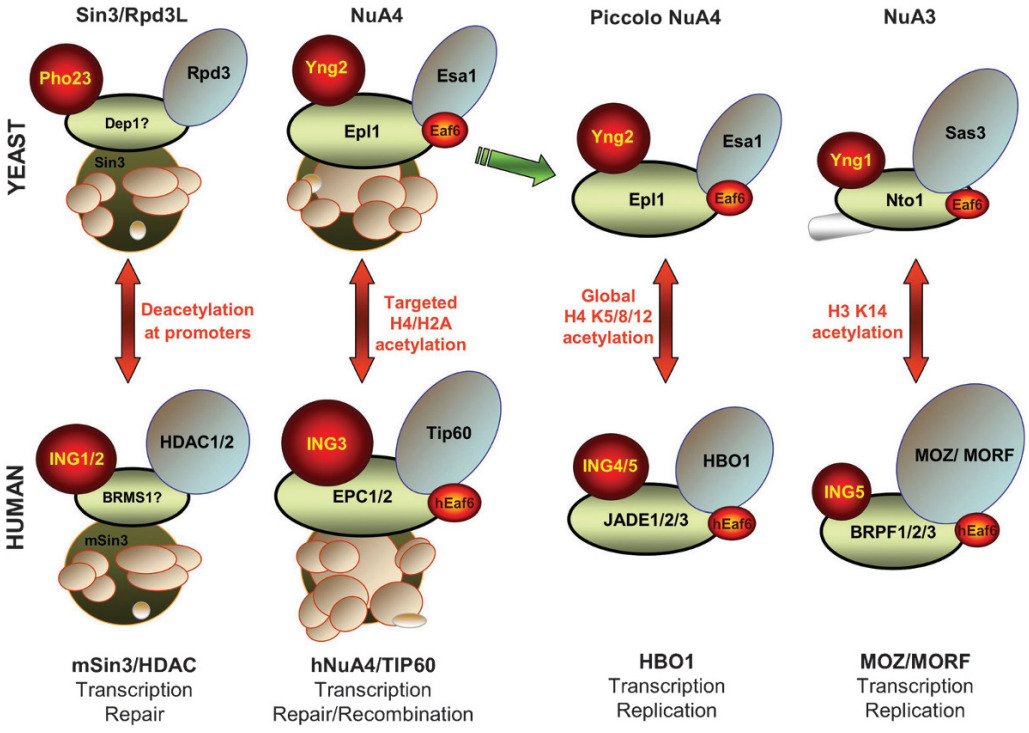

Figure 1. Structural and functional conservation of ING-containing chromatin-modifying complexes in eukaryotes.

ity each contain an enzyme of the MYST family (reviewed in [14]). This family of HATs plays a crucial role in DNA repair and transcription regulation, and is involved in human pathogenesis and disease (reviewed in [15]). Protein complexes associated with the five human ING family members (ING1–5) show structural and functional similarity to the ones purified with the three ING homologs in *Saccharomyces cerevisiae* (Yng1, Yng2 and Pho32), which have been the most studied (Figs. 1, 2) [7, 16–20].

In yeast, the ING protein Yng2 is a stable, stoichiometric component of the 1.3 MDa NuA4 HAT complex, which plays crucial roles in gene regulation and DNA repair [21, 22]. The catalytic subunit of NuA4 is Esa1, the only essential HAT in *S. cerevisiae* and a member of the MYST family of HATs. A sub-complex of NuA4 named piccolo NuA4 is responsible for global acetylation of lysines 5, 8 and 12 of histone H4, in contrast to NuA4, which is thought to function in a more restricted manner, catalyzing locus-specific acetylation (reviewed in [21]). Interestingly, the presence of Yng2 in these complexes is specifically required for histone H4 acetylation in the chromatin context [19]. Yng2 mutants are synthetically lethal with DNA replication mutants and are specifically sensitized to DNA damage in S phase, suggesting a function in the link between replication and DNA repair [23].

MYST protein Sas3 is the catalytic HAT component of the NuA3 complex which also contains Yng1 – another ING family member. NuA3 plays several roles in transcription through acetylation of histone H3 [16, 24, 25]. Recently, a study has shown that interaction between the Yng1 PHD finger and H3K4me stabilizes retention of the NuA3 complex on chromatin [17]. On the other hand, deletion of the Set1 methylase responsible for all H3K4 methylation in yeast has no effect on global binding to chromatin by the NuA3 or NuA4 HAT complexes ([17]; J. Côté, unpublished data). In parallel, deletion of Set2, which catalyzes H3K36 methylation, significantly reduces chromatin binding by NuA3 but not NuA4. When both Set1 and Set2 are deleted, binding of NuA3 to chromatin is very weak, but this double mutant has limited effect on NuA4 ([17]; J. Côté, unpublished data). These results indicate that H3K4 methylation alone has very limited effect on the recruitment *per se* of Yng1 or Yng2-associated HAT complexes to chromatin (reviewed in [26]).

The third ING family member in yeast, Pho23, is associated with the large Rpd3L/Sin3 histone deacetylase (HDAC) complex, whose recruitment to promoters represses transcription initiation [18, 20, 27]. In contrast, the chromodomain protein Eaf3, a subunit of NuA4 and the smaller Rpd3S/Sin3 HDAC complex, binds to nucleosomes methylated by Set2 on histone H3K36, leading to acetylation at promoters and deacetylation of transcribed regions during elongation [28–31] (N. Lacoste et al., unpublished data).

Interestingly, it was also demonstrated that ING proteins exert opposing effects on transcription by p53 ectopically expressed in *S. cerevisiae*. Depletion of Pho23 or Yng1 leads to increased p53-dependent transcription *in vivo*, while loss of Yng2 abrogates it [20].

In human cells, the five ING proteins have been implicated in p53 function, control of cell growth/proliferation and tumor suppression [32]. Following sequence comparison and characterization of all ING complexes, it became apparent that human INGs could be divided into three groups, ING1/2, ING3 and ING4/5, based on association with three distinct types of protein complexes [7].

The first group comprises human ING1 and ING2, which are purified as stable components of mSin3-HDAC1/2 complexes, like yeast Pho23. The structure and function of the ING1 gene has been the most thoroughly studied (see above for references). Interestingly, the ING1/2-mSin3-HDAC1/2 subunit BRMS1 suppresses metastasis of multiple human and murine cancer cells [33]. ING1 has been shown to activate p53 and induce apoptosis when expressed ectopically in mammalian cell lines [5]. ING2 has also been shown to negatively regulate cell proliferation through modulation of p53 acetylation in response to DNA damage [34]. The proposed model suggests that it stabilizes p53 by blocking MDM2-mediated ubiquitination. The PHD finger region of ING2 was implicated in this process as a nuclear receptor for phospholipid signaling [35, 36]. Interestingly, BRMS1 function in metastasis suppression was also linked to phosphoinositide signaling [37]. It appears that the PHD finger region of ING2 has two distinct functional interactions, binding to specific types of phospholipids and methylated chromatin. This dual specificity seems a common trend among PHD fingers. While binding to H3K4me3-containing chromatin resides in the core of the PHD finger structure, a polybasic region just downstream of the last cystein residue is responsible for interaction with phospholipids [35, 38]. It is thought that nuclear phospholipid signaling can modulate localization of chromatin-modifying complexes through the polybasic region of PHD fingers, which in turn leads to interaction with specific methylated state of local chromatin [39].

Generally, H3K4me3-containing chromatin is preferentially detected at active genes, but work in the Gozani lab demonstrated that the interaction between the PHD finger of ING2 and H3K4me3 leads to a decrease of transcriptional activity and potentially tumor suppression [11]. The authors demonstrated that, in response to DNA damage, the PHD domain of ING2 binds with high affinity to H3K4me3 and H3K4me2. This stabilizes the binding of the mSin3-HDAC1/2 complex at the promoter of genes that stimulate proliferation, resulting in spreading of histone deacetylation and hence acute repression of the active genes. In addition, overexpressing wild-type ING2 induced apoptosis, while this effect was impaired in ING2 mutants. Several PHD-finger mutations which seem to be implicated in H3K4me3 binding are prominently mutated in cancer cells, which means that this interaction might be essential in tumor suppressors.

The second group comprises ING3 as a stable stoichiometric component of the human NuA4/Tip60 HAT complex which specifically acetylates histone H4 and H2A [40]. ING3 is also implicated in p53 function in transcription, cell cycle control and apoptosis, and is found mutated in cancer cells [32, 41]. In addition, Tip60 (ortholog of yeast Esa1) and its associated proteins are important cofactors for p53-, NF-κB-, Myc-, E2F1- and nuclear-receptor-dependent transcription activation, cell response to DNA damage, apoptosis and metastasis suppression [15, 21, 42–44]. Tip60 directly acetylates p53 to induce apoptosis, is recruited to DNA double-stranded breaks *in vivo* to stimulate DNA repair and was recently identified as a haplo-insufficient tumor suppressor required for oncogene-induced DNA damage response ([45–48]; N. Avvakumov and J. Côté, unpublished data). *In vitro*, Tip60 alone fails to acetylate chromatin (similar to Esa1), as it requires association with EPC1 and ING3 to target nucleosomes [40]. This raises an interesting question of whether a piccolo NuA4-like complex (Tip60, EPC1/2, ING3 and hEaf6) exists in mammals [49].

The third group comprises ING4 and ING5. ING4 was purified with a relatively simple four-subunit complex containing HBO1 as the main source of histone H4 acetylation *in vivo*, reminiscent of yeast piccolo NuA4 function. ING5 was found in two distinct complexes, one targeting histone H4 through HBO1 and the other targeting H3 through the MOZ/MORF proto-oncogenes [7]. Phylogenic analysis of the MYST HAT family indicates that yeast Sas3 is evolutionarily linked to HBO1 and MOZ/MORF, and the presence of a post-MYST C-terminal acidic region in both Sas3 and MOZ/MORF supports this model [50] (see Fig. 2). Accordingly, the simple subunit structure of ING4 and ING5 complexes is reminiscent of the yeast NuA3 complex (see Figs. 1, 2). Based on the similar H3 lysine specificity of the human MOZ/MORF-ING5 and yeast NuA3 HAT complexes, we suggest that these are functional homologs [7, 16, 25, 51]. Both ING4 and ING5 have been reported to enhance transcriptional activity of p53 [52], while, interestingly, a leukemogenic fusion of MOZ was shown to inhibit it [53].

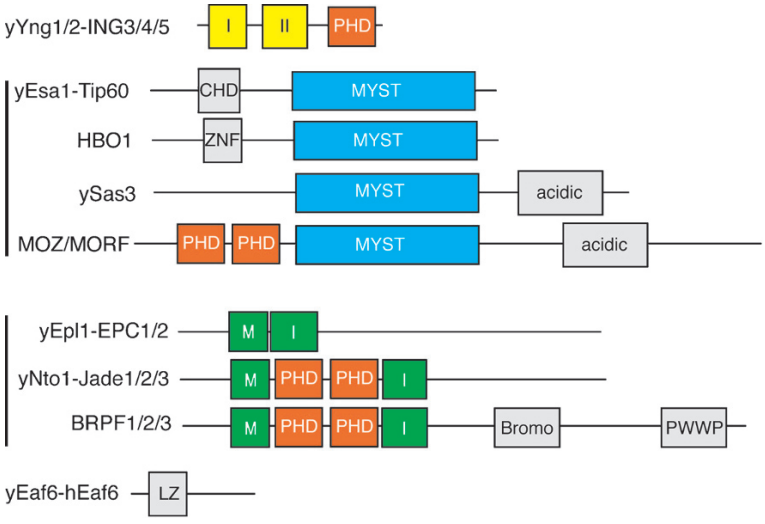

Figure 2. Protein domains present in MYST-ING histone acetyltransferase complexes. The related four core subunits of the yeast and human MYST-ING HAT complexes are depicted. Important protein domains are shown as boxes of different colors. Protein domains indicated but not discussed in the text include I and II of ING proteins, implicated in association with respective complexes (II) and activity on nucleosome substrate (I) [7] (N. Saksouk and J. Côté, in preparation); CHD, chromodomain; ZNF, zinc finger; I and M, implicated in bridging MYST and ING proteins together through independent interactions with EPC/JADE/BRPF subunits [7] (N. Saksouk and J. Côté, in preparation); Bromo, bromodomain, thought to recognize acetylated lysine residues; PWWP, domain related to chromo, tudor and MBT domains, thought to recognize methylated lysine residues; LZ, leucine zipper.

Yeast two-hybrid screens identified interactions between MCM2, ORC1 and HBO1 [54,55]. In addition, Iizuka and colleagues found that HBO1 is a positive regulator of pre-replicative complex assembly and is required for MCM proteins to associate with chromatin [56]. Interestingly, our work showed that ING5 HAT complexes associate with the MCM helicases in vivo and are essential for DNA replication in human cells [7]. These results demonstrate a crucial role of chromatin acetylation during initiation and elongation of DNA synthesis in eukaryotes. Histone H4 and H3 acetylation has been shown to regulate the time of replication origin firing in yeast, *Drosophila* and mouse [57–59]. Recruitment of ING5 HAT complexes associated with MCM helicases is an attractive model that could explain local hyperacetylation at origins of replication. Our data suggest two distinct roles for ING4- and ING5-HBO1 HAT complexes. While ING5-HBO1 is important for DNA replication, ING4-HBO1 plays alternative roles, as depicted by a defect in G2/M passage [7]. The ING4-HBO1 acetyltransferase complex is poised to be further studied to elucidate its mechanistic role in tumor suppression. Subunits ING4 and JADE have been independently linked to regulation of tumor progression and angiogenesis through a repressor role on NFκB- and HIF1-dependent transcription [60–63]. Finally, characterization of the ING4/5 complexes indicates the presence of multiple PHD finger domains in a single protein complex. JADE, BRPF and MOZ/MORF proteins each contain two PHD fingers, bringing the total to five PHDs in the single MOZ/MORF-ING5 HAT complex [7] (Fig. 2). Interestingly, it is now clear that PHD fingers exist with different specificities toward histone H3 N-terminal tail and the methylation state of K4 [64–68]. Current studies in our lab reveal a surprising relationship between ING PHDs and other PHDs present in the same complex in regulating association to chromatin (N. Saksouk and J. Côté, unpublished data).

In conclusion, members of the ING protein family are critical regulators of chromatin acetylation in all eukaryotes. They serve mechanistic roles in permitting various enzymatic activities to modify chromatin substrates. Through their PHD finger regions they also participate in nuclear phospholipid signaling, reading the histone epigenetic signature and modifying it in a combinatorial manner. Such primary roles in chromatin biology put these proteins and their associated complexes at the center of nuclear functions, playing key roles in gene regulation, DNA repair/recombination and DNA replication. Unfortunately, there is a lot of confusion in the literature about the functions and associations of the ING proteins in higher eukaryotes (for a recent review, see [69]). This confusion is due in part to multiple splice variants produced by these genes, strong reluctance to correlate human and yeast studies on ING proteins, but mostly because of reports relying on transient transfection/overexpression in mammalian cell cultures. We have shown that doing so creates artefacts by allowing association of all ING proteins with the same set of factors (HATs and HDACs) [7]. Only near physiological *in vivo* expression and specific RNA interference-type mediated knockdowns can efficiently address the specific associations/functions of each ING family member. It is now clear that each yeast and human ING protein is exclusively associated with a specific, stoichiometric and stable histone-modifying complex (Fig. 1). Functional but transient interactions with other proteins (e.g. p53, Myc, ATM, MCM, PCNA, etc.) are involved in the recruitment to specific loci in order to regulate transcription, repair/recombination and replication. The (de)MYSTifica-

tion and INGenuity of these tumor suppressors in genome expression, maintenance and duplication emphasize their importance in the molecular events leading to cancer, metastasis and angiogenesis.

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