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REVIEW

The ING family tumor suppressors: from structure to function

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Abstract The INhibitor of Growth (ING) proteins belong to a well-conserved family which presents in diverse organisms with several structural and functional domains for each protein. The ING family members are found in association with many cellular processes. Thus, the ING family proteins are involved in regulation of gene transcription, DNA repair, tumorigenesis, apoptosis, cellular senescence and cell cycle arrest. The ING proteins have multiple domains that are potentially capable of binding to many partners. It is conceivable, therefore, that such proteins could function similarly within protein complexes. In this case, within this family, each function could be attributed to a specific domain. However, the role of ING domains is not definitively clear. In this review, we summarize recent advances in structure–function relationships in ING proteins. For each domain, we describe the known biological functions and the approaches utilized to identify the functions associated with ING proteins.

Keywords ING · Tumor suppressor · Protein domain · PHD · NLS

Introduction

The first member of INhibitor of Growth (ING) family was found in 1996 by a strategy based on subtractive hybridization between cDNAs from a normal mammary cell line and seven breast cancer cell lines followed by a subsequent in vivo selection for cDNA fragments capable of promoting neoplastic transformation [1]. This gene is called *ING1* which encodes a 33-kDa protein (p33ING1b). Fluorescent in situ hybridization and radiation hybrid mapping linked *ING1* to the cytogenetic marker SHGC-5819 at 13q34 [2, 3]. The *ING1* gene has three exons and can be alternatively spliced to generate p47ING1a, p33ING1b, p27ING1d, and p24ING1c; the last of these results from an internal initiation at the first ATG within exon 2 [4–8]. Since this discovery, four additional *ING* genes (ING2-5) encoding proteins and several splicing isoforms of ING2 [9] and ING4 [10] have been identified. By homology search of p33ING1b complementary cDNA sequence, the *ING2* (known as *ING1L*) gene was cloned [11]. In 2003, ING3 encoding a 46.8-kDa protein (p47ING3) with a C-terminal plant homeodomain (PHD) finger motif was subsequently identified through a computational domain search [12]. The same year, the two newest members of the ING family, ING4 and ING5 were identified through a computational sequence homology search for expressed sequence tag clones with a PHD finger motif [13].

ING family and biological functions

The ING family proteins regulate a wide variety of cellular processes. The inhibition of ING1 using antisense expression constructs promotes cell transformation in cell lines and tumor formation in vivo, and blocks cells in the G1 phase of the cell cycle when expressed ectopically [1]. Also, studies have indicated that ING proteins are involved in cell cycle checkpoints and cell cycle progression [14, 15].

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ING1 expression is significantly repressed in 44% of human primary breast cancers and 100% of established breast cancer cell lines [16]. Decreased ING1 expression has been found in many other forms of solid and blood tumors [17–26]. Similarly, the expression of ING2, ING3 and ING4 is reduced in human melanoma [27–29]. All ING family proteins have been shown to cooperate with p53 to induce apoptosis and cellular senescence [12, 13, 30–33], and accordingly the notion that the ING family proteins act as class II tumor suppressors has emerged. In addition, suppression of ING proteins has been shown to increase cell migration and to relieve contact inhibition [10, 34, 35].

In addition, many studies using different model systems have implicated the ING family proteins in promotion of apoptosis [30, 31, 36, 37], DNA damage repair [38–40], control of cellular aging [41], negative regulation of cell proliferation [1, 42], chromatin remodeling [43, 44], hormone responses [45, 46] and regulation of tumor growth via NF-κB [47] and hypoxia inducible factor pathways [48, 49]. Several types of tumors have been found to have either altered ING protein subcellular localization, *ING* mutations, or deletions [28, 50–53]. Various studies have suggested that most of the ING proteins are required for proper p53 function [14, 15], although more recent mouse model experiments indicate otherwise [54].

ING family proteins in chromatin remodeling and gene transcription

The ING proteins have been found in chromatin remodeling complexes [55], indicating that ING proteins may act in the nucleus to regulate transcription [56, 57]. The chromatin structure is very dynamic and is affected by multiple modifications of chromatin-associated proteins, including, but not limited to, histones and remodeling cofactors within particular chromatin regions. Indeed, chromosomal DNA and its associated proteins undergo dramatic alterations in structure during normal cellular processes such as DNA synthesis, transcription and repair [58, 59]. Conversely, it is known that DNA damage leads to changes in gene expression [60–62], and it is now clear that mechanisms that affect directly upon higher-order chromatin structure regulate cellular metabolic processes such as transcription, DNA replication and DNA repair.

Chromatin structure is increasingly being attributed to modification of the basic histones, the subunits of nucleosomes. Histones are positively charged, low molecular weight DNA scaffolding proteins that are subject to numerous posttranslational modifications including acetylation, methylation, phosphorylation, SUMOylation and ubiquitination [63, 64]. These modifications play diverse roles in modulating chromatin structure and have been linked to the regulation of gene transcription [65]. Histone acetylation neutralizes the charge of basic (positively charged) lysine residues within histone proteins. Consequently, there is destabilization of the binding of histones to the negatively charged DNA so that other enzymes/protein complexes are capable of unwinding the chromatin, accessing the DNA at selective sites and transcribing target genes. In other words, the dynamic modification of histones through the enzymatic actions of histone acetyltransferase (HAT) and histone deacetylase (HDAC) protein complexes modifies nucleosome structure, altering the degree of DNA relaxation and subsequently modifying the accessibility of regions of DNA to transcription factors [66].

Not surprisingly, HAT and HDAC protein complex activity must be tightly regulated in order to maintain the appropriate level of histone acetylation in a given cellular environment. In fact, deacetylation of histone residues by HDAC can tighten a DNA strand because of the electric charge change of the histone tails; positively charged histone tails, which have high affinity for negatively charged DNA, can be neutralized by acetylation, causing DNA relaxation. Several HAT/HDAC coactivators and corepressors have been identified. The ING family proteins are involved in chromatin remodeling, and bind to and affect the activity of both HAT and HDAC protein complexes. In fact, ING1 induces histone acetylation, promotes DNA repair and interacts with proliferating cell nuclear antigen (PCNA) [39, 67]. ING2 is also implicated in the initial DNA damage sensing and chromatin remodeling in the nucleotide excision repair (NER) process [38, 68], and recently a new function of ING2 in the control of DNA replication has been found [69].

The functional domains of ING family proteins

ING proteins are a well-conserved family which are present throughout eukaryotic proteomes [70]. Phylogenetic analyses have identified new ING family members in diverse organisms, including rats, frogs, fish, mosquitoes, fruit flies, worms, fungi and plants [70]. All *ING* genes with the exception of *ING3* are found near the ends of chromosomes, and the function and expression of *ING5* could be affected by telomere erosion [70]. ING1 has four protein isoforms with identical C-terminus parts containing a conserved PHD finger motif [14]. *p33ING2* shares 60% identity with *p33ING1b* and encodes a 33-kDa protein [11]. Compared to ING1b, ING2 contains an extra and unique leucine zipper domain which is thought to mediate hydrophobic protein–protein interactions [56]. p29ING4 and p28ING5 are highly homologous with 72.8% identity [13].

Various studies have suggested that ING family proteins exert their biological functions through their associations

with specific molecular partners (Table 1). These associations are possible through various structural and functional domains present in proteins. Thus, they allow the assembly and regulate the subnuclear localization of distinct complexes consisting of different combinations of proteins and interactors. In fact, the ING family members share a highly conserved PHD at their C-termini, a conserved central region containing the nuclear localization signal (NLS) and a variable N-terminal region. Thus, within ING proteins there are a number of distinct domains including PCNA-interacting protein (PIP) box, partial bromodomain (PBD), leucine zipper-like (LZL) domain, novel conserved region/lamin interaction domain (NCR/LID), NLS, PHD, and polybasic region (PBR) (Fig. 1).

The N-terminus of ING family proteins

The N-termini of ING proteins are more variable and mediate the majority of reported protein–protein interactions and functions as a protein-binding domain that targets distinct nuclear components and chromatin-remodeling complexes [14]. It contains a LZL domain and a NCR [71]. Also, a functionally defined domain, called SAID (SAP30-interacting domain) has been reported for ING1b at the N-terminus [44]. This domain, which was defined as the region of ING1b that directly interacts with SAP30 (the sin3-associated protein 30), is also suspected to be present on ING2, since both of these proteins directly interact with SAP30 [44, 72]. This interaction is thought to bridge ING1 and ING2 to SAP30-containing HDAC1/2 complexes.

ING1 also has in its N-terminus a PIP box through which it binds PCNA in a DNA damage-inducible manner [67]. Since PCNA is an essential factor for DNA replication and repair, ING1 may act to couple these processes to chromatin remodeling. The interaction of this domain is specifically induced upon UV damage [67] and has been hypothesized to switch PCNA activity away from DNA replication towards DNA repair. Among ING members, the PIP box is unique to ING1b. Bioinformatics analysis has revealed a second domain present only in ING1b and called PBD (partial bromodomain because of its sequence homology to bromodomains). The PBD binds SAP30 of mSin3A-HDAC1 which might target HDAC, and possibly HAT activity for some ING proteins [44].

The LZL domain is found in the N-terminus of all ING proteins, except ING1. This domain consists of four to five conserved leucine or isoleucine residues spanning every seven amino acids (forming a hydrophobic patch near the N-terminus) with a similar leucine distribution for ING3 to ING5 [15, 70]. However, little is known about the function of LZL and it been has reported that the LZL domain of

Table 1 Protein or complex reported to bind to ING family protein domain

Protein	Domain	Protein/complex involved	Reference
ING1	PHD	ARF	[119]
	PHD	Brg1, BAF47/53/60/155/170/250	[44]
	PHD	DMAP-1	[120]
	N/A	GADD45	[40]
	PHD	H3K4me2/3	[103, 105, 121]
	PHD	HDAC1	[122]
	N/A	HMT activity	[123]
	N/A	hSir2	[124]
	NLS	Karyopherin α,β	[78]
	LID	Lamin A	[74]
	PHD	mSin3, HDAC1/2, SAP30, RbAp46/48	[44, 125]
	N/A	p15 (PAF)	[126]
	N/A	p42, p35	[125]
	N/A	p53	[127]
	PHD	p300	[122]
	PIP	PCNA	[67]
	N/A	RBP1	[125]
	N/A	SIRT1	[128]
	N/A	TRRAP, PCAF, CBP	[122]
	N/A	14-3-3	[129]
ING2	PHD	H3K4me2/3	[103, 105]
	N/A	BAF47/53a/155/170	[55]
	N/A	HMT activity	[123]
	PHD	mSin3A, HDAC1/2, RbAp46/48	[55]
	PHD	p300, p300/p53	[32, 73]
	PHD	PtdIns5P	[33]
	PHD	SNON	[130]
	NCR	PCNA	[69]
	N/A	RBP1/RBP1-like	[55]
	N/A	SAP30, SAP130, SDS3, BRMS1/BRMS1-like	[131]
	N/A	SIRT1	[128]
ING3	N/A	AcK5-H4, AcK8-H4, AcK12-H4	[55]
	N/A	DMAP1, RUVBL1/2, MRG15, hEaf6, BAF53a	[55]
	N/A	GAS41	[55]
	PHD	H3K4me2/3	[103, 105]
	PHD	TIP60, p400, TRRAP, Brd8, EPC1/2	[55]
ING4	N/A	AcK5-H4, AcK8-H4, AcK12-H4	[55]
	N/A	G3BP2a	[10, 35]
	PHD	H3K4me1/2/3	[103, 105]
	PHD	HBO1	[55]
	N/A	hEaf6	[55]
	N/A	HPH-2	[48]
	N/A	JADE1/2/3	[55]
	NCR	Liprin alpha 1	[10, 35]
	N/A	NF-κB p65	[47, 132]
	PHD	p53	[13, 77]
	PHD	p300	[13]

Table 1 continued

Protein	Domain	Protein/complex involved	Reference
ING5	N/A	AcK5-H4, AcK8-H4, AcK12-H4, AcK14-H4	[55]
	N/A	BRPF1/2/3	[55]
	PHD	H3K4me1/2/3	[103, 105, 133]
	PHD	HBO1	[55]
	N/A	JADE1/2/3	[55]
	N/A	MCM2/4/6	[55]
	PHD	MOZ/MORF	[55]
	PHD	p53	[13]
	PHD	p300	[13]

N/A not available

ING2 is required for the induction of apoptosis and NER [73]. Truncated ING2 mutants lacking the LZL domain do not display elevated apoptosis following UV exposure [73], suggesting that this domain is required for ING2-mediated apoptosis. RNAi-mediated knockdown of ING2 has also been found to abrogate the NER capacity of melanoma cells [38]. Interestingly, the NER ability of ING2 has been found to require the LZL domain [73]. In 2005, He et al. [70] proposed that this region is responsible for homo- and hetero-oligomerization between the members of the family.

The NCR is found in all ING proteins [70]. It was identified by sequence analyses and constitutes the second most highly conserved domain in the ING family proteins. The NCR domain is now known as LID. This N-terminal region of ING1 has been found to interact directly with lamin A [74]. The NCR/LID domain is found only in ING proteins, through which they bind to and colocalize with lamin A [74], suggesting that the association with nuclear lamina is a common feature of this family. The NCR/LID domain has been speculated to be another region of ING proteins to which HAT and HDAC complexes, including the SAP30 protein, bind by its KIQI or KVQL sequence [15].

The central nuclear localization signal

All ING family proteins contain an NLS with an additional NLS for ING4 and ING5. Recently, many studies have been conducted for ING1 to understand the role of NLS [37, 75], and have shown that NLS deletion results in cytoplasmic accumulation of the protein. The nuclear localization of ING proteins appear critical for their functions, as is evident by the observation of loss of nuclear ING1 staining in a number of cancers [76], and that deleting the entire NLS of ING4 results in a protein that can no longer bind to p53 in cotransfection experiments [77]. Also, the NLS of ING1 contains two copies of a putative nucleolar translocation signal which interacts with the proteins karyopherin-α and -β for nuclear import [78]. The nucleolar translocation of ING1 after exposure to UV light appears to be required for ING-associated apoptosis [37].

The C-terminus plant homeodomain

Among ING family proteins, the greatest homology occurs within the PHD motif [70]. This highly conserved motif is found throughout eukaryotic proteomes, predominantly on chromatin-associated proteins [79]. Structurally, the PHD motif is close to RING (Really Interesting New Gene) and LIM (Lin-11/Isl-1/Mec-3) domains, which contain a zinc-binding domains that ligate two zinc ions [80]. The PHD motif which has been associated with SUMOylation is found in more than 400 eukaryotic proteins and has recently emerged as a chromatin recognition motif that

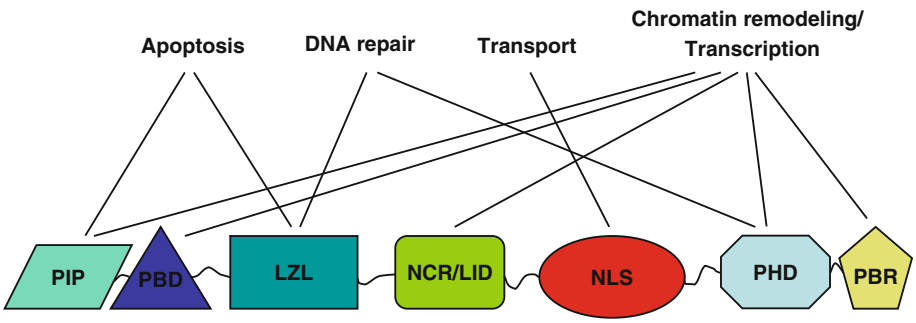

Fig. 1 The ING family protein domains and their functions. The PIP box binds to PCNA and promotes ING1-mediated apoptosis. The PBD and NCR/LID binds to SAP30, HDAC and HAT, and regulates their activities. The LZL domain of ING2 is required for DNA repair and induction of apoptosis. The NLS binds to the karyopherin-α and β transporter proteins for targeting ING proteins to their functional site, the nucleus and/or the nucleolus for ING1. It has also been reported to mediate interaction with p53 [77]. The PHD motif plays a role in HAT and/or HDAC activity, which can then regulate transcription at specific loci. Both PHD and PBR bind to PtdInsPs, suggesting that PBR may also be involved in chromatin remodeling and transcription regulation

reads the methylation state of histones. The PHD motif comprises approximately 60 amino acids with a C4HC3 signature and belongs to the treble class of zinc-binding domains, containing two zinc ions bound in a cross-braced topology [81–83]. Zinc coordination by PHD fingers is achieved via ligation of zinc atoms to alternating pairs of residues from the consensus Cys4-His-Cys3 sequence distribution: zinc one is bound by Cys1, Cys2, His and Cys6, whereas zinc two is bound by Cys3, Cys4, Cys7 and Cys8 [82, 84–86]. Beyond the conservation of zinc-coordinating residues, approximately 150 distinct PHD-bearing proteins have been predicted to occur in humans [81]. PHD fingers display substantial diversity in their sequences, particularly between Cys6 and Cys7, suggesting that the biological activity of PHD fingers might similarly be diverse [85].

There is much evidence that PHD fingers mediate important physiological functions [81]. Mutations within the PHD fingers of numerous proteins have been implicated in tumorigenesis, as well as the pathogenesis of immunodeficiency syndromes, autoimmune syndromes, and several other genetic disorders [82, 87–89]. Many of these mutations occur at zinc-coordinating residues, indicating that zinc ligation and hence integrity of the PHD finger fold are critical for the function of PHD finger-containing proteins. A second class of disease-linked PHD finger mutations do not disrupt zinc coordination but rather are located between the sixth and seventh zinc-coordinating residues, a segment which, based on known PHD finger structures and structural modeling, is thought to be at or near the surface of the domain. Some have postulated that this surface forms a molecular interaction interface and that mutations within this region might disrupt this activity and in doing so manifest the disease phenotype [85, 90]. In fact, substitution of the basic residues between the sixth and seventh zinc-coordinating residues into alanines disrupts binding of the PHD fingers of ING1, ING2, ATP-dependent chromatin remodeling factor, and recombination activating gene 2 (RAG2) to phosphatidylinositol phosphates (PtdInsPs) [89]. Further, such mutations render ING2 and RAG2 largely inactive [33, 89]. The PHD motif closely resembles a canonical RING domain but lacks the RING E2 ubiquitin ligase activity [83]. Insight into the biological function of PHD fingers comes in part from studies of the structurally related FYVE and RING finger modules [82–84, 86, 91, 92]. The FYVE finger is a well-characterized PtdInsP-binding module, and RING fingers function as components of E3 ubiquitin ligase enzymes [93, 94]. Both of these functions have been reported for PHD fingers from different proteins [33, 95–98], though recent analyses argue that putative PHD fingers with E3-ubiquitin ligase activity are more likely to be RING finger variants rather than true PHD fingers [99, 100].

The phosphoinositide signaling pathways regulate a diverse array of cellular processes including actin polymerization, cell migration, and vesicular trafficking. These phosphoinositide-dependent processes are modulated by the tightly regulated synthesis and metabolism of mono- and polyphosphorylated phosphoinosotide species at discrete subcellular sites [101]. A nuclear phosphoinositide signaling was reported in 2003 by Gozani et al. [33] who identified a physiologically important interaction between PtdIns5P and ING2 mediated by the ING2 PHD motif. In addition, PHD fingers have also been reported to be involved in other protein–protein interactions [91, 102] and to interact with nucleosomes by a direct link to methylated histones (Table 2), specifically H3K4me2 and H3K4me3 [103, 104], supporting a functional role for the PHD motif.

In fact, the PHD motif, which is the most conserved region within the ING family showing sequence homology greater than 78%, has been found in all human ING proteins to preferentially bind di- and trimethylated H3K4 and repress gene transcription [103, 105, 106]. Mutations in the PHD motif of p33ING1b and a region found to interact with SAP30 (Sin3A Associated Protein 30), a component of Sin3A corepressor complexes [107], abrogate the enhancement of p33ING1b in DNA repair in host cell reactivation assays and radioimmunoassays [50, 108]. Furthermore, the p33ING1b variant is not recruited to UV-induced DNA lesions, but enhances NER in XPC-proficient cells possibly due to its ability to bind XPA [39]. Since XPC/hHR23B acts as the first step of the NER pathway by recognizing helix-distorting DNA lesions and XPA acts to stabilize the resulting open DNA structure [109], p33ING1b may play an essential role in the early steps of the NER pathway, possibly by facilitating access of the NER machinery to chromatin.

Additionally, two p33ING1b PHD mutations (R102L and N260S) were detected in 20% of 46 tested melanomas [50], and either of these alterations proved to be as detrimental as deletion of the entire PHD motif for the enhancement of NER mediated by p33ING1b in host-cell-reactivation assays and radioimmunoassays. Furthermore, those patients bearing an ING1 codon 102 or 260 mutation had a reduced 5-year survival rate (50 vs. 82%) [50]. These findings highlight the importance of the PHD motif in ING1 function and tumor suppression, as loss of NER activity would likely facilitate tumorigenesis by increasing genomic instability. In agreement with this proposal, other reports have indicated the presence of *ING1* mutations in the coding region for the PHD motif or the NLS in melanoma, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, breast cancer, pancreatic cancer, and in colon cancer [14], supporting a role for ING PHD motif in epigenetic regulation of gene expression.

Table 2 Common function of the PHD of ING proteins in histone H3 tail modification. The ING1–5 PHD domain, known to bind H3K4me2/3, contains conserved Cys and His residues required for the coordination of two zinc ions, residues that make up the aromatic cage and residues that form specific hydrogen bond contacts to the H3K4me3 peptide. In column three, the chromatin remodeling complexes associated with ING proteins that recognize H3K4me are listed. Column four indicates the method used to analyze the interaction between the ING PHD domain and H3K4me peptide

Protein	H3K4 modification	Associated complex	Method	Reference
ING1	H3K4me2/3	CBP/p300 HATS	Fluorescence	[105]
	H3K4me3	mSin3/HDAC1/2	Fluorescence	[121]
ING2	H3K4me2/3	p300 HAT	Fluorescence	[105]
	H3K4me3	mSin3/HDAC1/2	IP	[103]
ING3	H3K4me2/3	TIP60 HAT	Fluorescence	[105]
ING4	H3K4me2/3	HBO1 HAT	Fluorescence	[105, 134]
	H3K4me3	N/A	Fluorescence	[135]
	H3K4me3	N/A	NMR	[114]
	H3K4me3	N/A	NMR	[136]
ING5	H3K4me2/3	MOZ/MORF HAT	Fluorescence	[105]
	H3K4me3	HBO1 HAT	Fluorescence	[133, 134]

N/A not available

The polybasic region

ING1 and ING2, which are evolutionarily and functionally close [55, 70, 110], contain a short region called the PBR in their C-terminus part, adjacent to the PHD motif. Although the biological functions of this region are not well understood, it has been reported that PtdIns5P bind to the PHD motif of ING2 [33, 111]. Later, it was found that PtdIns3P and PtdIns4P can bind to the PBR [112]. These authors showed that when exchanged between different PHD motif, the PBR is a strong determinant of the binding specificity of PtdInsPs [112]. These findings establish the PBR as a phosphoinositide-binding module and suggest that the PHD domains function downstream of phosphoinositide signaling triggered by the interaction between PBRs and phosphoinositides.

Conclusion

Numerous studies have been done to elucidate the functional mechanisms of ING family proteins. To date, two mechanisms have been clearly identified in ING family proteins that regulate the major biological processes. These are the interaction of the ING PHD domain with methylated histone tails [103, 105, 113, 114], and the binding of ING (ING1-2) proteins to bioactive signaling phospholipids [33, 112, 115] to function as nuclear PtdIns receptors [101, 116, 117]. PtdIns have an important role in mediating a variety of biological processes, including the response to stress, and because they regulate essential cellular functions, PtdIns metabolism is tightly regulated at the subcellular level [118]. Therefore, it is possible that the ING proteins transduce stress signals by binding phospholipids, targeting to chromatin, and reading the local histone code, which subsequently contributes to epigenetic regulation. However, these mechanisms cannot by themselves explain all the events in which ING proteins are involved. This is reinforced by the existence within this family of various functional domains, first among the proteins, then among the isoforms of some proteins. Thus, for a better understanding of the precise function of each domain, it would be necessary to pursue a motif–function relationship study for each member and each isoform of ING family proteins. A systematic functional analysis of different domains to understand their inactivation mechanism and the role in tumor suppression should help to define the functional differences between members of the ING family proteins.

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