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Molecules in focus

Proliferating cell unclear antigen-associated factor (PAF15): A novel oncogene

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ABSTRACT

*P*roliferating cell nuclear antigen (PCNA)-*A*ssociated *F*actor (PAF15) is a small protein containing a PCNA interacting motif and sequences for association with ubiquitin enzymes. In interaction with PCNA, PAF15 plays a key role in recruiting DNA replicative polymerase by double monoubiquitination at Lys^{15} and Lys^{24}. Under DNA damage conditions, PAF15 regulates the switch from DNA replicative polymerase to translesion synthesis polymerase in order to bypass the replication-blocking lesions. Overexpression of PAF15 promotes the repair of ultraviolet-induced DNA damage and prevents cell death, whereas attenuation of PAF15 decreases DNA replication and cell survival. Ectopic expression of PAF15 in mouse fibroblasts increases colony formation and tumourigenicity. PAF15 is aberrantly increased in various human malignancies with poor prognosis. Collectively, PAF15 may contribute to carcinogenesis and represents one of the potential therapeutic targets in the treatment of cancer.

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Molecule facts

- A 15 kDa protein containing a PCNA interacting motif and sequences for association with ubiquitin enzymes.
- Ubiquitination at Lys^{15} and Lys^{24} plays a key role in regulating interactions between PCNA and DNA replicative or translesion synthesis polymerase.
- Promotes DNA repair and prevents cell death. Ectopic expression in mouse fibroblasts increases colony formation and tumourigenicity.
- Up-regulated by ATF3, NF-κB and NS5A, and down-regulated by $p53/p21^{WAF1}$ pathway. Targeted by APC/C^{Cdh1} for degradation.
- Aberrantly increased in various types of human malignancies with poor clinical outcomes.

1. Introduction

The full length cDNA of *KIAA0101* was cloned by screening a size-fractionated immature myeloid leukaemia cell line-derived cDNA library (Nagase et al., 1995). The gene product of *KIAA0101* was identified to be associated with proliferating cell nuclear antigen (PCNA) *via* a yeast two-hybrid using PCNA as the bait (Yu et al., 2001). The association was further confirmed by transient transfection of *KIAA0101* and co-immunoprecipitation with PCNA (Yu et al., 2001). This 15 kDa protein was subsequently named as *P*CNA-*A*ssociated *F*actor (PAF15) (Povlsen et al., 2012). *KIAA0101* has also been annotated as L5 (dysregulated in non-small-cell lung cancer) (Petroziello et al., 2004), overexpressed in anaplastic thyroid carcinoma-1 (OEATC-1) (Mizutani et al., 2005) and non-structural protein 5A (NS5A)-transactivated protein 9 (NS5ATP9) (Shi et al., 2007). Herein, PAF15 will be used throughout this review.

As one of the interacting proteins of PCNA, the role of PAF15 is closely related to the function of PCNA. PCNA is an auxiliary

Abbreviations: APC/C, anaphase-promoting complex/cyclosome; ATF3, transcription factor 3; Bax, B cell lymphoma-associated X; Cdh1, Fizzy/Cell Division Cycle 20 Related 1; CDK, cyclin-dependent kinase; CDT2, chromatin licensing and DNA replication factor 2; CRL4, cytokine receptor-like 4; D-box, destruction box; DUBs, deubiquitination enzymes; E2, ubiquitin-conjugating enzyme; E2F, elongation 2 transcription factor; E3, ubiquitin ligase; ER, endoplasmic reticulum; KEN-box, the amino acid sequence $KEN(X)_nP$; NF-κB, nuclear factor of kappa B; NIH3T3, primary mouse embryonic fibroblast; NS5A, non-structural protein 5A; NS5ATP9, NS5A-transactivated protein 9; OEATC-1, overexpressed in anaplastic thyroid carcinoma-1; PIDD, p53-induced protein with death domain; PIP-box, PCNA interacting protein-motif; PIP20, a 20 amino-acid peptide corresponding to the PIP-box; $p33^{ING1b}$, inhibitor of growth protein 1 isoform 2; $p21^{WAF1}$, cyclin-dependent kinase inhibitor 1; RAD18, post-replication repair protein RAD18; Rb, retinoblastoma; REV1, DNA repair protein; S, synthesis phase; TLS, translesion DNA synthesis; USP1, ubiquitin specific peptidase 1; UV, ultraviolet.

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factor for DNA replication by tethering polymerases onto the DNA template (Maga and Hubscher, 2003; Mailand et al., 2013). In addition, PCNA provides a scaffold for recruiting components of the DNA damage response (Mailand et al., 2013). As a safety measure, higher eukaryotic cells contain modulating factors that regulate the interaction between PCNA and associated proteins. PAF15 is one of such factors and regulates the binding of DNA polymerase to PCNA (Mailand et al., 2013; Povlsen et al., 2012). PAF15 expression is positively correlated to tumour progression and predicts poor prognosis in a broad range of human cancers (Kais et al., 2011; Kato et al., 2012; Yu et al., 2001; Yuan et al., 2007; Zhu et al., 2013). At cellular level, PAF15 promotes DNA repair (Povlsen et al., 2012), cell survival (Kais et al., 2011), cell growth (Mizutani et al., 2005) and invasion (Jain et al., 2011). Hence, PAF15 is potentially an oncogenic protein.

2. Structure

The *PAF15* gene maps to human chromosome 15q22.1 (Mizutani et al., 2005; Nagase et al., 1995). The promoter region contains typical TATA (+34 ~ +38 bp) and CAAT (−1009 ~ −1006 bp) boxes, a nuclear factor of kappa B (NF-κB p50) binding site (−5 ~ −161 bp), a NS5A binding site (−1868 ~ −1006 bp) and three E2F binding sites (−94 ~ −87, −29 ~ −22, +17 ~ +25 bp) (Chang et al., 2013; Li et al., 2010, 2008; Shi et al., 2007). A minimal promoter region was defined within nucleotides −161 to +50 bp of the transcription initiation site by stepwise deletion in a luciferase reporter assay (Shi et al., 2007). There are seven transcript variants through alternative splicing (Ensembl: ENSG000001668037). Most studies included in this review focused on variant 1 (1508 bp) and 2 (1345 bp) (Liu et al., 2012).

The PAF15 protein contains 111 amino acids, including a conserved PCNA interacting protein motif (PIP-box), a KEN-box, a destruction-box (D-box), and an ubiquitin enzyme E2 initiation motif (Fig. 1). The PIP-box (Gln^{62}-XX-Ile^{65}-XX$Phe^{68}Phe^{69}$) mediates the interaction with PCNA (Emanuele et al., 2011; Povlsen et al., 2012; Yu et al., 2001). The hydrophobic Phe allows PAF15 to bind PCNA with high affinity. Mutation of Ile^{65} to Ala or Phe^{68} to Ala results in disruption of the PCNA–PAF15 interaction (Yu et al., 2001). Anaphase-promoting complex/cyclosome (APC/C) is an E3 ligase, targeting protein for ubiquitin-mediated proteolysis (Williamson et al., 2011). The KEN-box (78–80 aa) mediates association with APC/C, and is recognised by APC/C co-activator Cdh1 (Emanuele et al., 2011). The D-box (23–34 aa) further mediates the interaction with APC/C, and also acts as a recognition signal for degradation *via* the ubiquitin–proteasome. The initiation motif (85–97 aa) is required for the ubiquitin E2 enzyme to initiate ubiquitin chain formation *via* the APC/C, serving to fine-tune the timing of PAF15 proteolysis (Emanuele et al., 2011; Williamson et al., 2011; Yu et al., 2001).

PAF15 contains one Lys-acetylation site (Lys^{95}), one monomethylation site (Lys^{15}), three ubiquitination sites ($Lys^{15,24,63}$) (PhosphositePlus: PAF); one N-glycosylation site (Asn^{34}) (NetNGlyc: PAF15_HUMAN), 11 phosphorylation sites for protein kinase-C ($Ser^{8,12,28,29,31,37,39,40,89}$ and $Thr^{30,31}$), 10 for casein kinase ($Ser^{8,28,31,35,37,39,76,88}$ and $Thr^{36,106}$), and two for tyrosine kinase ($Tyr^{13,47}$) (GPS: Q15004). Notably, Ser^{72} residue was identified in a mass spectrometry-based screen for mitotic phosphoproteins, which lies in SP motif (Ser^{72} Pro^{73}; the minimum targeting sequence by cyclin-dependent kinase, CDKs). Hence, PAF15 may also be a CDK and other mitotic kinase substrate (Emanuele et al., 2011).

3. Expression and turnover

PAF15 is localised primarily in the nucleus and mitochondria, but upon DNA damage its expression is co-localised with centrosomes in the perinuclear region (Simpson et al., 2006; Yu et al., 2001). The expression levels of PAF15 fluctuate throughout cell cycle. PAF15 appears and peaks during S/G_2 phases and diminishes after the initiation of mitosis (Chang et al., 2013; Kais et al., 2011). PCNA is present in the nucleus during the G_1 phase (Mathews et al., 1984), increasing during S phase and subsequently decreasing during the G_2 and M phases (Mailand et al., 2013). Thus, both PAF15 and PCNA peak in S phase, consistent with the notion that both contribute to DNA replication. Under normal conditions, the level of co-localisation of PAF15 and PCNA is low except in highly proliferating cells, such as the skin, hair follicle and colonic crypts (Simpson et al., 2006). UV irradiation up-regulates PAF15 expression and PAF15–PCNA complex formation (Simpson et al., 2006). The turnover of PAF15 is *via* APC/C^{Cdh1}-mediated polyubiquitination and proteasomal degradation during the M/G_1 cell-cycle phases.

The presence of E2F binding sites at the *PAF15* promoter suggests that *PAF15* gene expression may be regulated by Rb/E2F (Li et al., 2010; Shi et al., 2007; Simpson et al., 2006). Phosphorylation of Rb during G_1/S transition, which increases the bioavailable E2F1, may explain the accumulation of PAF15 protein in S phase (Chang et al., 2013; Li et al., 2008). Conversely, E2F4 and E2F6 (transcriptional repressors) have recently been found to bind to the E2F sites in the *PAF15* promoter region and suppress *PAF15* gene transcription (Chang et al., 2013).

Transcription factor 3 (ATF3) (Turchi et al., 2009), NF-κB (p50) (Li et al., 2008) and NS5A (Shi et al., 2007) up-regulate *PAF15* transcription by direct binding to the *PAF15* promoter region. p53 has been found to negatively regulate PAF15 at both mRNA and protein levels through $p21^{WAF1}$ in response to DNA damage (Hosokawa et al., 2007). NS5A may also regulate *PAF15* indirectly through activation of NF-κB, *e.g.*, NS5A increases NF-κB transactivation upon ER stress (Li et al., 2008). NS5A can also suppress $p21^{WAF1}$ gene expression by physical association with p53 (Li et al., 2008; Maga and Hubscher, 2003). Moreover, NF-κB pathway is responsible for ATF3 induction in a p53-dependent or -independent manner (Turchi et al., 2009). Intriguingly, *PAF15* is also an oestrogen-regulated gene (Miller and Larionov, 2010).

4. Biological function

PCNA provides a central platform for DNA synthesis by interacting with both DNA and binding proteins at replication fork. By forming a sliding homotrimeric clamp PCNA encircles double stranded DNA (Fig. 2). PCNA recruits polymerase and other interacting proteins to the DNA template *via* PIP box (Mailand et al., 2013). In association with PCNA, different PIP box-containing proteins influence and regulate DNA replication and repair differently; yet they all bind to the same region of PCNA in a mutually exclusive and competitive manner. Hence, if PCNA is considered as a conductor of DNA replication-linked processes, the absolute and relative levels of PAF15 to other PIP box-containing proteins can affect the harmony of the DNA replication process (Emanuele et al., 2011; Hosokawa et al., 2007; Jain et al., 2011; Kais et al., 2011; Kato et al., 2012; Mizutani et al., 2005; Povlsen et al., 2012; Simpson et al., 2006; Yu et al., 2001).

4.1. DNA replication

During unperturbed S phase, PAF15 is associated with PCNA at DNA replication forks (Emanuele et al., 2011; Povlsen et al.,

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