Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

FEN1 (flap structure-specific endonuclease 1)

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Identity

Other names: FEN-1; hFEN-1; MF1; RAD2

HGNC (Hugo): FEN1

Location: 11q12.2

DNA/RNA

Description

Spans 4561 bp; two exons; one intron (Figure 1).

Transcription

Spliced transcript is 2265 bp in length. First exon is 1-351 bp and the second exon comprises 352 to 2265 bps of the spliced mRNA. The open reading frame spans 1142 base pairs (bp 373-1515).

Protein

Description

Human FEN1 is a metallonuclease comprised of 380 amino acid residues (Nazarkina et al., 2008). The protein has a nuclease core domain composed of the N, I, and C regions and an extended C-terminus (Figure 2A) (Shen et al., 1998). The extended C-terminus is dispensable for nuclease activity, but is important for protein-protein interaction with partners like PCNA and WRN (Brosh et al., 2001; Brosh et al., 2002; Zheng et al., 2005; Zheng et al., 2007; Guo et al., 2008; Nazarkina et al., 2008; Karanja and Livingston, 2009) and contains a bipartite nuclear localization signal (Qiu et al., 2001). Structural studies show that the nuclease core domain of FEN1 has a SAM-like or PIN-like fold with a mixed beta-sheet buttressed on both sides by alpha-helical structure and spanned by an arch-like structure (Figure 2B and C) (Horton, 2008). Moreover, the N and C regions form the saddle-like structure of the protein that binds dsDNA and provide the amino acid residues that bind the requisite divalent ions (Figure 2D). hFEN1 binds two divalent metal ions (Sakurai et al., 2005) and is thought to achieve phosphodiesterase activity using a 'two-metal-ion' mechanism (Yang et al., 2006; Syson et al., 2008). The C-region contains an H3tH motif and binds the downstream dsDNA of the substrate (Figure 3E). The N-region interacts with the upstream dsDNA. Notably, a hydrophobic wedge stacks on the terminal base pair of the upstream duplex closest to the active site and a cleft or pocket binds to a 3'-extrahelical nucleotide. The N and C regions are interrupted by the I-region, which forms an arch that spans the beta-sheet and the active site residues. The arch likely interacts with the 5'-ssDNA flap (Chapados et al., 2004; Liu et al., 2006; Devos et al., 2007; Nazarkina et al., 2008).

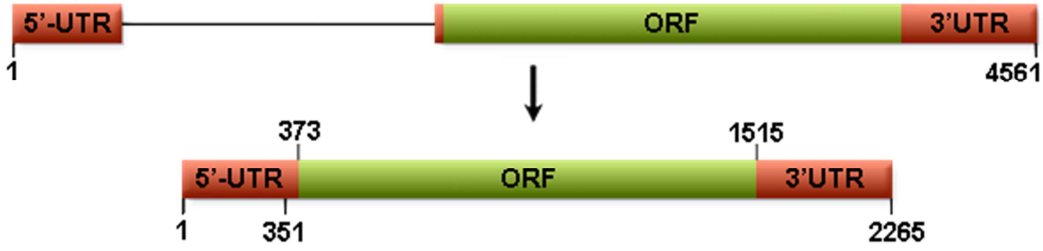

Figure 1.

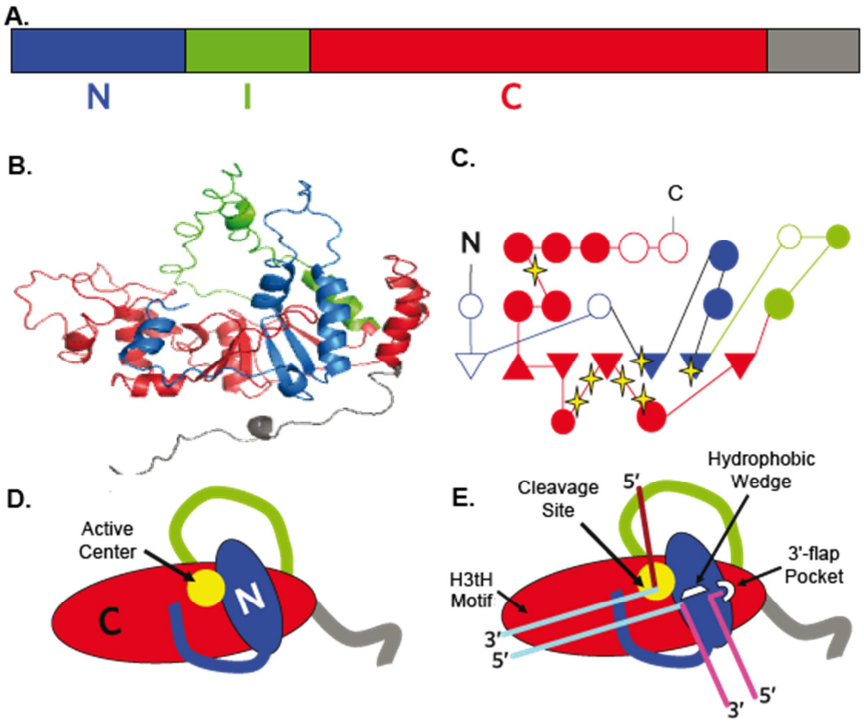

Figure 2. Structure of human FEN1.
A. Schematic of hFEN1 organization as determined by primary sequence analysis (Shen et al., 1998). The protein is divided into the N-terminal (N), Intermediate (I), C-terminal (C), and extended C-terminal regions colored in blue, green, red, and grey, respectively. **B.** Structure of hFEN1 (1UL1) colored according to region. Note: electron density for portions of the I-region and the extended C-terminus were not observed (Sakurai et al., 2005). **C.** Topology diagram of hFEN1 (Horton, 2008) colored according to region. Filled triangles and circles indicate structural elements that are conserved in all known FEN1s, whereas open circles and triangles indicate structural elements that vary between phage and archaeal/eukaryotic FEN1s. Yellow stars indicate the relative positions of the active site carboxylate residues that bind the requisite divalent metal ions. **D.** Two-dimensional schematic of the hFEN1 structure (Grasby J, U. Sheffield, personal communication). Note: the amino terminus of hFEN1 (true for other archaeal and eukaryotic FEN1s as well) is structured and resides near the active site. **E.** Schematic illustration of hFEN1 and its interaction with a double-flap substrate. The duplex DNA 3' of the cleavage site is denoted as the downstream duplex (cyan). The upstream duplex dsDNA (magenta) is 5' to the cleavage site. The 5'-ssDNA flap (brown) likely interacts with the helical arch formed by the I-region (Chapados et al., 2004; Liu et al., 2006; Devos et al., 2007; Nazarkina et al., 2008).

Human FEN1 is subject to post-translational modifications, which are thought to regulate hFEN1 activities in vivo (Nazarkina et al., 2008). The extended C-terminal domain can be acetylated in vitro by p300 at four lysine residues (Friedrich-Heineken et al., 2003). A mass spec analysis identified K267 and K375 of hFEN1 as in vivo sites of acetylation (Choudhary et al., 2009). Amino acid residue S187 can be phosphorylated in vitro and in vivo by CDK1-Cyclin A, which regulates the S to G2 transition. S187 phosphorylation has been shown to decrease FEN1 activity in vitro, which is consistent with the role of CDK1-Cyclin A in cell cycle regulation (Henneke et al., 2003).

Expression

FEN1 is detectable in all proliferative tissues, but barely detectable in non-proliferative tissues (Warbrick et al., 1998; Kim et al., 2000). FEN1 is often overexpressed in tumor tissues (LaTulippe et al., 2002; Freedland et al., 2003; Iacobuzio-Donahue et al., 2003; Sato et al., 2003; Kim et al., 2005; Krause et al., 2005; Lam et al., 2006; Singh et al., 2008; Nikolova et al., 2009). Furthermore, cancer tissues have been reported to exhibit FEN1 promoter hypomethylation (Singh et al., 2008).

Localisation

The localization of FEN1 in human cells is predominantly nuclear (Warbrick et al., 1998; Kim et al., 2000), but is also found in mitochondria (Liu et al., 2008; Szczesny et al., 2008; Kalifa et al., 2009).

Function

General biochemistry: Human FEN1 can cleave a wide variety of substrates with a 5' to 3' polarity exo- and endo-nucleolytically, albeit with widely varying levels of efficiency (Shen et al., 2005; Nazarkina et al., 2008). Regardless of substrate and cleavage efficiency, FEN1 phosphodiesterase activity results in 5'-phosphate monoester and 3'-hydroxyl products (Pickering et al., 1999; Yang et al., 2006). Consistent with its in vivo roles, hFEN1 preferentially cleaves substrates bearing a single nucleotide 3'-flap and a 5'-flap of varying length (i.e., double-flaps) (Friedrich-Heineken and Hubscher, 2004).

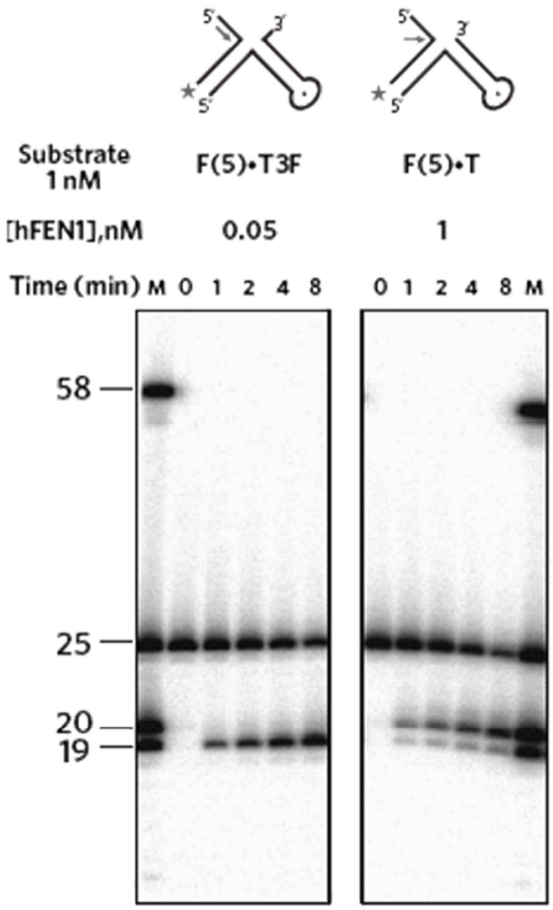

Figure 3. The 3'-flap directs cleavage site specificity. Using double- and single-flap synthetic substrates labeled at the 3'-terminus (indicated by the gray star), the predominant cleavage site is observed to change from the dsDNA-ssDNA junction (single flap - F(5)•T) to one nucleotide into the downstream duplex (double flap - F(5)•T3F). Single-flap substrates have a secondary cleavage site one nucleotide into the duplex that is equivalent to the cleavage site on the double flap substrate. Note: similar studies with 5'-radiolabelling show that a six-nucleotide product is formed with F(5)•T3F, whereas a 5- and 6-nucleotide product are formed with F(5)•T.

The 3'-flap stabilizes the enzyme-substrate complex and increases subsequent first-order rates of reaction to augment "enzyme commitment" to the forward reaction (Finger et al., 2009).

Furthermore, the presence of a 3'-flap on the substrate increases the cleavage site specificity, such that the enzyme cleaves exclusively at the nucleotide that lies one nucleotide into the downstream duplex (Figure 3 and 4A). With a substrate lacking a 3'-flap, the cleavage on the 5'-flap predominantly occurs at the dsDNA-ssDNA flap junction and to a lesser extent one nucleotide into the downstream duplex (Figure 3 and 4B) (Friedrich-Heineken and Hubscher, 2004; Finger et al., 2009).

Okazaki fragment maturation: Cleaves 5'-flap bifurcated nucleic acid flap structures generated by lagging-strand DNA synthesis during Okazaki fragment maturation in the nucleus (Liu et al., 2004; Garg and Burgers, 2005; Shen et al., 2005; Rossi et al., 2006; Nazarkina et al., 2008). Deletion of the FEN1 gene in mammals is embryonically lethal (Larsen et al., 2003), but deletion of its homolog in Saccharomyces cerevisiae, RAD27, is tolerated (Reagan et al., 1995). Studies in haploid yeast have shown that the deletion of RAD27 increases rates of nuclear mitotic recombination, point mutation, reversion, microsatellite instability, and frameshifts (Johnson et al., 1995; Sommers et al., 1995; Tishkoff et al., 1997; Kokoska et al., 1998; Callahan et al., 2003; Navarro et al., 2007). In a similar manner, direct-repeat recombination, chromosome loss, and interhomolog recombination were increased in rad27Δ/rad27Δ diploids (Navarro et al., 2007). In contrast to nuclear DNA, rad27Δ causes a decrease in mitochondrial direct-repeat mediated deletion and mitochondrial microsatellite instability (Kalifa et al., 2009); however, the origins of these decreases are not understood.

Long-patch base excision repair: FEN1 cleaves 5'-flap bifurcated nucleic acid structures generated during nuclear (Nazarkina et al., 2008; Robertson et al., 2009) and mitochondrial long-patch base excision repair (Liu et al., 2008; Kalifa et al., 2009; Robertson et al., 2009). Consistent with the role of FEN1 in mitochondrial long-patch base excision repair in yeast, rad27Δ mutants accumulate point mutations in mitochondrial DNA (Kalifa et al., 2009).

Telomere maintenance: FEN1 has been shown to be important for telomere stability in yeast and mammalian cells by ensuring efficient telomere replication (Parenteau and Wellinger, 1999; Parenteau and Wellinger, 2002; Saharia et al., 2008) and is essential for telomere stability in ALT-positive cells (Saharia and Stewart, 2009). Furthermore, FEN1 forms a complex with telomerase (Sampathi et al., 2009).

Homology

Member of the Rad2 nuclease family (i.e., close cousin to XPG, EXO1, and GEN1) (Lieber, 1997).

Mutations

Note

Two FEN1 polymorphisms have been reported to be associated with an increased risk of lung cancer. The first polymorphism is c.69G>A (rs174538:G>A) and resides in the FEN1 promoter region. The second is c.4150G>T (rs4246215:G>T) and resides in the 3'-UTR of the transcript (Figure 1). Both polymorphisms are associated with decreased FEN1 expression levels (Yang et al., 2009).

DNA sequencing of DNA from tumors and tumor-derived cell lines has revealed mutations in the FEN1 gene that affect nuclease activity (Zheng et al., 2007). Furthermore, studies have shown that mice from two genetic backgrounds that are homozygous for an active site mutation known to alter enzymatic activity in vitro show an increased incidence of cancer (Zheng et al., 2007; Larsen et al., 2008).

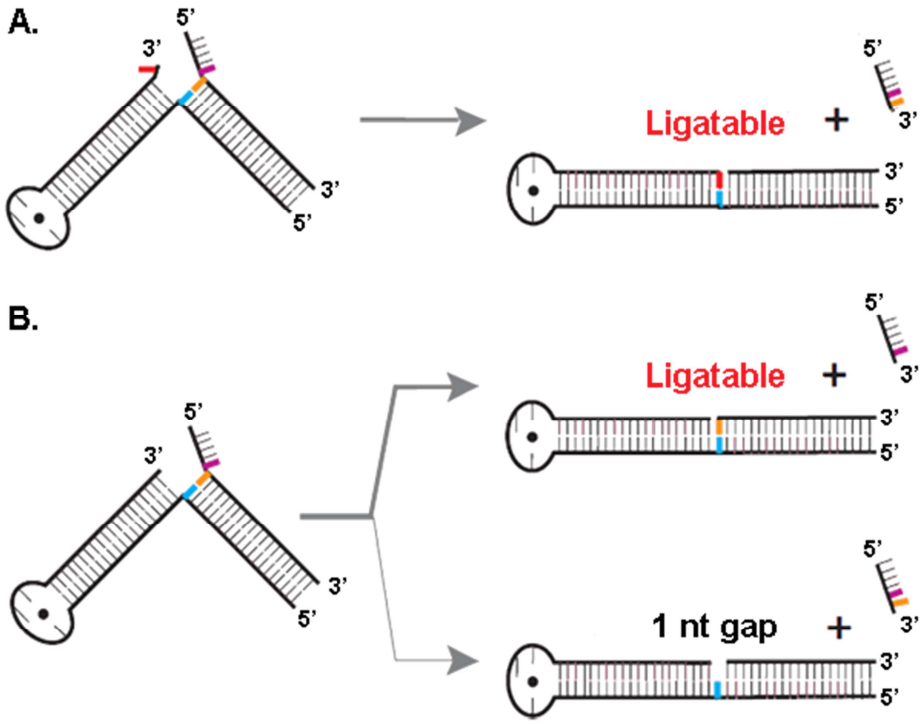

Figure 4. The 3'-flap directs cleavage to ensure that all dsDNA product is ligatable.
A. Schematic illustration of the cleavage products of the double-flap substrate. The 3'-flap is red, the last nucleotide of the 5'-flap is purple, and the downstream duplex terminal base pair is shown in blue and orange. After cleavage, the purple and orange nucleotides are part of the ssDNA product. For the dsDNA product, the red nucleotide forms a base-pair with the blue nucleotide to create a ligatable nick. **B.** In a similar manner, cleavage on the single flap substrate, which lacks the red nucleotide, occurs predominantly between the purple and orange nucleotide to create a 5-nucleotide ssDNA product and a ligatable dsDNA product. To a lesser degree, cleavage also occurs at the nucleotide one nucleotide into the downstream duplex to create a 6-nucleotide ssDNA product and a single nucleotide gap dsDNA product. Note: the substrates used in Figure 3 are static structures (i.e., they do not have the ability to equilibrate as in vivo substrates do). See following references for more detail (Kaiser et al., 1999; Kao et al., 2002; Sharma et al., 2004; Nazarkina et al., 2008).

Implicated in

Prostate cancer

Oncogenesis

A gene expression profile comparing normal, primary tumor, and metastatic prostate tissue samples showed that FEN1 expression is up-regulated in primary and metastatic tumor tissue along with other DNA replication and repair genes (LaTulippe et al., 2002). The level of FEN1 expression has also been positively correlated with tumor Gleason score, and thus, tumor dedifferentiation (Lam et al., 2006). Furthermore, aggressive forms of prostate cancer as defined by the ability to form tumors in SCID mice show a five-fold or greater increase in FEN1 expression in comparison to a nontumorigenic clone (Freedland et al., 2003).

Pancreatic cancer

Oncogenesis

Using cDNA microarrays, a global gene expression profile of pancreatic adenocarcinoma identified FEN1 as one of 103 previously unidentified genes that were expressed at higher levels in comparison to normal tissue (Iacobuzio-Donahue et al., 2003).

Gastric cancer

Oncogenesis

Using cDNA microarrays and semi-quantitative RT-PCR, FEN1 was shown to be up-regulated in comparison to normal tissue (Kim et al., 2005). Furthermore, using a cancer profiling array and immunohistochemistry, FEN1 was also shown to be up-regulated in stomach cancer (Singh et al., 2008).

Lung cancer

Oncogenesis

FEN1 levels were elevated in small cell and non-small-cell cancers in comparison to normal lung controls (Sato et al., 2003). Furthermore, using a cancer profiling array and immunohistochemistry, FEN1 was also shown to be up-regulated at the mRNA and protein level in lung cancer (Singh et al., 2008; Nikolova et al., 2009).

Brain cancer

Oncogenesis

Gene expression patterns in neuroblastomas were analyzed using microarrays and confirmed by RT-PCR to show that neuroblastomas with unfavorable clinical

outcome express FEN1 at levels 2.7-fold higher than neuroblastomas detected by mass screening (Krause et al., 2005), thereby implying that FEN1 expression level in neuroblastoma could be diagnostic of clinical outcome. Futhermore, FEN1 expression levels are higher in glioblastoma multiforme, primary astrocytoma, anaplastic astrocytoma, and oligoastrocytoma as determined by Western blotting (Nikolova et al., 2009).

Breast cancer

Oncogenesis

A cancer profiling array and immunohistochemistry showed increased levels of FEN1 expression at the mRNA and protein levels. In addition, increased expression is likely due to promoter hypomethylation. Furthermore, this study showed that increased FEN1 expression is positively correlated with advanced or higher grace breast tumors (Singh et al., 2008).

Testicular cancer

Oncogenesis

Western blotting analysis showed increased levels of FEN1 in 14 out of the 17 seminomas (Nikolova et al., 2009).

Other cancers

Oncogenesis

Overexpression of FEN1 at the mRNA level has also been detected in uterine, colon, ovarian, and kidney cancer tissues (Singh et al., 2008). In summary, expression of FEN1 is commonly increased to facilitate cell proliferation in cancer cells due to the pivotal role of FEN1 in DNA replication. However, partial or complete loss of function is also known to facilitate the development of cancer by causing genomic instability in eukaryotes (Navarro et al., 2007; Zheng et al., 2007; Larsen et al., 2008).

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