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Gene Section
Review

HELLS (Helicase, Lymphoid-Specific)

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Abstract

Review on HELLS, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: LSH, PASG, SMARCA6

HGNC (Hugo): HELLS

Location: 10q23.33

Note

HELLS (helicase, lymphoid specific) is a member of the SNF2 family of chromatin remodelling proteins that utilize ATP to alter the structure and packaging of chromatin (Jarvis et al., 1996). These changes in chromatin together with changes in other epigenetic mechanisms such as DNA methylation and histone modifications alter cellular processes such as transcription, mitosis, meiosis, and DNA repair.

HELLS has been shown to be important for stem cell gene control, Hox gene control, DNA methylation, DNA repair, meiosis, and chromatin packaging of repetitive DNA (Dennis et al., 2001; Yan et al., 2003b; De La Fuente et al., 2006; Myant et al., 2008; Burrage et al., 2012).

HELLS belongs to the SNF2 family of chromatin remodelling proteins.

This group of proteins are involved in altering chromatin structure by hydrolyzing ATP and moving nucleosomes. HELLS has orthologues in mouse, Xenopus laevis, Danio rerio, Arabidopsis thaliana, and Saccharomyces cerevisiae among others.

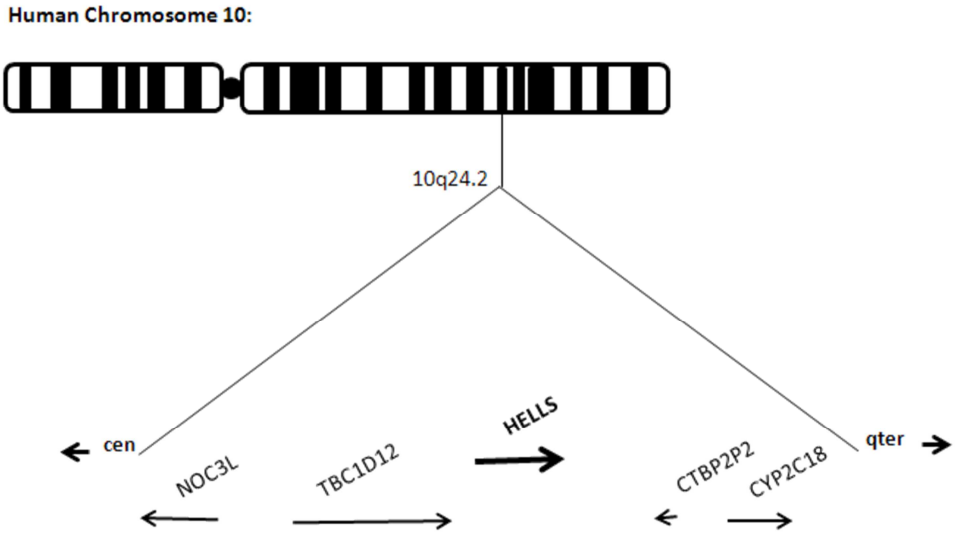

Figure 1. The HELLS gene is located on the long arm of human chromosome 10 at position 24.2. HELLS is found from base pair 94545767 to 94602871 base pair (GRCh38 assembly). Neighboring genes are shown.

Figure 2. The HELLS protein contains the helicase ATP binding and helicase C-terminal domains as identified by Prosite. It additionally contains a nuclear localization signal.

The best studied is the mouse gene called Lsh (lymphoid specific helicase) that resides on a syntenic region of mouse chromosome 19 (Geiman et al., 1998).

DNA/RNA

Description

The HELLS gene consists of 22 exons spanning 57104 base pairs. It is highly expressed in embryonic stem cells, proliferating lymphoid cells/tissue, and germ cells. In stem cells, expression decreases upon differentiation. HELLS is additionally expressed at a lower level in many tissues of the developing embryo. In normal adult somatic tissue, expression is low with the exception of proliferating lymphocytes.

Transcription

The HELLS gene produces a transcript of 3163 bp. Ten alternatively spliced isoforms have been detected. The functional relevance of most of these splice variants is currently unknown. One, variant 1 containing a 44 ntd insertion between exons 3 and 4, creates an additional exon and has been associated with non-small cell lung cancer (NSCLC) (Yano et al., 2004). An additional variant, variant 9, contains a 75 ntd deletion in exon 18 and has been associated with acute myelogenous leukemia an acute lymphoblastic leukemia (Lee et al., 2000).

Pseudogene

None.

Protein

Description

HELLS protein consists of 838 amino acids with a predicted size of 97 kD. Since Lsh is a member of the SNF2 chromatin remodeling protein family, it contains the ATP binding and C-terminal helicase domains of this subfamily of helicases.

Localisation

Nuclear.

Function

HELLS functions as a chromatin remodeling family member linking multiple epigenetic mechanisms including histone modifications and DNA methylation (Dennis et al., 2001; Yan et al., 2003a; Yan et al., 2003b; Huang et al., 2004; Fan et al., 2005; Zhu et al., 2006; Xi et al., 2007; Myant et al., 2008). Knockout mice die perinatally with defects in lymphocyte proliferation, embryonic growth, and kidney development (Geiman et al., 2001; Geiman and Muegge, 2000).

Loss leads to global DNA methylation changes including global hypomethylation at repetive sequences, as well as both hypo and hypermethylation of single copy genes (Myant et al., 2011; Tao et al., 2011b; Dunican et al., 2013; Yu et al., 2014).

HELLS has been identified as a marker of mammalian stem cells with expression decreasing upon differentiation.

Reduction in expression of HELLS leads to prolonged expresssion of stem cell genes implicating this protein as having a role in stem cell gene silencing (Xi et al., 2009).

HELLS has been also implicated in DNA repair (Burrage et al., 2012).

HELLS is additionally involved in meiosis with its loss leading to reduced proliferation and differentiation of germ cells with defects in synapsis (de la Fuente et al., 2006; Zeng et al., 2011).

Homology

HELLS exhibits homology with other SNF2 family members like SNF2H, SNF2L, CHD1, CHD2, CHD3, CHD4, CHD5, CHD6, CHD7, CHD8, CHD9, BRG1, and BRAHMA. While other SNF2 family members contain additional domains such as chromodomains, bromodomains, BRK, PHD, and RING fingers, HELLS protein does not. Because of this lack of additional domains, Lsh does not fit into any of the other subfamilies of SNF2 members but appears to represent a distinct subfamily of SNF2 factors. By homology, it is most closely related to the CHD and SNF2H/L (ISWI) subfamily.

Mutations

Note

Hells^{tm1Kmu}

There are two mutant mouse models of HELLS. The original knockout mouse generated by the Muegge lab (Hells^{tm1Kmu}) deleting the helicase domains of I, Ia, and part of two that are included in exons 6 and 7.

These mutant mice die perinatally with embryonic growth retardation (Geiman et al., 2001). These null embryos have kidney defects such as necrosis and globule formation in tubules (Geiman et al., 2001). Murine embryonic fibroblasts display early senescence in culture and mitotic defects (Fan et al., 2003).

Since HELLS is highly expressed in developing and activated lymphoid tissue, lymphoid development and function was studied using a radiation chimera.

Null embryos display lymphoid defects in thymocyte development with a partial blockage in transitioning from CD4/CD8 double negative to double positive T lymphocytes.

This partial arrest in lymphocyte development leads to a reduction in mature T and B lymphocytes (Geiman et al., 2000).

In addition, activation of lymphocytes leads to apoptosis intead of cell proliferation (Geiman et al., 2000).

Molecular studies on this mouse led to identifying HELLS as a gene necessary for DNA methylation and important for correct chromatin packaging and histone methylation (Dennis et al., 2001; Yan et al., 2003b ; Huang et al., 2004; Myant et al., 2011; Tao et al., 2011b; Yu et al., 2014).

Hells^{tm1Rarc}

Another mutant mouse model of Hells was developed in the Arceci lab designated Hells^{tm1Rarc}. This mouse model was generated from a hypomorphic allele of HELLS by deleting exons 10, 11, and 12 (Sun et al., 2004). The deleted section includes several helicase domains of HELLS (III, IV, and part of II) but not the ATPase domain. This mutant mouse also shows growth retardation but approximately 40% of mice survive to several weeks of age unlike the Muegge mouse model which die at birth. Additionally, these mice exhibit signs of premature aging with defects such as graying hair and balding, low fat deposition, and unstable gate among others (Sun et al., 2004). The premature aging defects seen in this mouse model are likely the result of replicative senescence caused by increased expression of the p16 tumor suppressor gene in these HELLS mutant mice. Molecular analysis demonstrated profound DNA methylation loss and aberrant expression of repeat sequences (Sun et al., 2004; Dunican et al., 2013).

Implicated in

Acute myelogenous leukemia, acute lymphoblastic leukemia

Note

When the HELLS gene was first characterized, it was found to be located in a break point region of the human genome frequently associated with leukemia at 10q23-10q24 (Geiman et al., 1998). Subsequently, an in-frame 75 ntd deletion in exon 18 (variant 9) of the HELLS gene was found in 57% of accute myelogenous leukemia and 37% of acute lymphoblastic leukemia patient samples tested but not in normal lymphoid tissue examined (Lee et al., 2000). This deletion leads to the loss of 25 amino acids and includes part of one of the conserved SNF2 family helicase domain. This same variant was also detected in both normal and non-small cell lung cancer patient samples raising the possibility that variant 9 is also expressed in some normal tissue (Yano et al., 2004).

Erythroleukemia

Note

The mouse HELLS gene (Lsh) has been implicated in the development of erythroleukemia based on animal studies involving the original knockout mouse model (Hells^{tm1Kmu}) (Fan et al., 2008). Since these mice die at birth, hematopoiesis was studied using a reconstitution model (Geiman et al., 2001). Hells -/- mice had defective hematopoiesis (Fan et al., 2008). In a subset of mice reconstituted with Hells-/- cells, erythroleukemia developed which is normally a rare spontaneous event in mice. Hells loss leads to hypomethylation of repetitive elements throughout the genome (Huang et al., 2004; Dunican et al., 2013). This hypomethylation was found to occur in these Hells null mouse hemaotopoietic progenitor cells at retroviral elements within the PU.1 oncogene leading to overexpression of the gene (Fan et al., 2008). Increased PU.1 gene expression is linked to erythroleukemia.

Non-small cell lung cancer (NSCLC)

Note

A 44 ntd insertion between exons 3 and 4 (variant 1) was detected in 26% of non-small cell lung cancer samples but in none of the normal tissue samples (Yano et al., 2004). This insertion through exon creation of a sequence of intronic origin is predicted to lead to premature termination of translation leading to a 97 amino acid protein. The truncated protein may act as a dominant negative protein. This truncated HELLS may also lose its normal nuclear localization since at least part of the nuclear localization signal (NLS) would be affected.

Head and neck cancer

Note

HELLS is a downstream target of the FOXM1 transcription factor (Waseem et al., 2010). Both HELLS and FOXM1 have been found to be overexpressed in head and neck cancer such as oraopharyngeal squamous cell carcinoma (Janus et al., 2011). High expression of both genes correlates with tumor stage 3 or higher. Additionally, HELLS expression was found to increase in progression from normal to dysplasia and then squamous cell carcinoma and metastasis in head and neck cancer (Waseem et al., 2010). Because of this, HELLS has been proposed as a biomarker for early detection and progression of head and neck cancer. Additionally, HELLS is known to be involved in control of p16 tumor suppressor gene expression through repression with reduction in HELLS leading to increased p16 expression. FOXM1 also suppresses p16, likely through HELLS induction (Teh et al., 2012). This also leads to a DNA methylation profile in primary oral keratinocytes that is similar to human head and neck cancer (Teh et al., 2012).

Breast cancer

Note

The HELLS gene has been found to be mutated in 3% of invasive breast cancer samples. Most are an amplification or upregulation of the HELLS gene but there are also some that have deletion or downregulation (Colak et al., 2013). HELLS was proposed to be a possible marker for progression from pre-invasive ductal carcinoma in situ (DCIS) to invasive ductal carcinoma (IDC). Additionally, the HELLS gene is located in a copy number alteration chromosomal region (Colak et al., 2013). Furthermore, depletion of HELLS in a breast cancer cell line reduced DNA methylation at several tumor suppressor genes. This resulted in de-repression of genes involved in proliferation, and altered several growth characteristics of breast cancer cells in vitro including anchorage independent growth in soft agar and the ability to migrate in a wound healing assay (Tao et al., 2011a).

Skin squamous cell carcinoma

Note

The role of HELLS in skin tumorigenesis was explored by overexpressing a deltaNp63alpha isoform of the p63 gene (Keyes et al., 2011). HELLS is a direct transcriptional target of deltaNp63alpha. HELLS had been implicated in senescence before by targeting the p16 tumor supressor gene. In this study, p16 was found not to be involved. Instead, increased deltaNp63alpha led to upregulation of HELLS expression. This caused senescence bypass, increased stem like cells and tumorigenesis in human primary keratinocytes.

Melanoma

Note

HELLS was identified as a gene having elevated expression in aggressive metastatic tumor cells lines compared to cell lines from less aggressive primary tumors (Ryu et al., 2007).

HELLS mRNA was also detected in the blood of patients with different stages of melanoma. The level of HELLS mRNA in patient blood was significantly higher in patients with metastatic melanoma than those with localized primary tumors (Kim et al., 2010).

This work also found that HELLS expression in blood appears to be a better biomarker for metastatic melanoma than the currently used standard (Kim et al., 2010).

These results suggest that HELLS may be a useful biomarker of melanoma presence and progression and a possible target for intervention.

Prostate cancer

Note

The HELLS protein specifically interacts with E2F3, a transcription factor uniquely amplified in some human tumors.

The expression of E2F3 is inversely correlated with patient survival. HELLS and E2F3 are co-overexpressed in prostate carcinomas at the most aggressive stages.

The association of HELLS and E2F3 occurs at several E2F target genes that control cell cycle entry.

Depletion of HELLS in a prostate cancer cell line reduced the induction of E2F target genes and impaired growth suggesting that HELLS may contribute to the malignant progression of tumors (von Eyss et al., 2012).

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