**Protein**

**Note**
THRSP is primarily a nuclear protein which is important in the regulation of lipid metabolism. It is induced by thyroid hormone, carbohydrate intake, adipose tissue differentiation, and lactation, and is inhibited by glucagon and conjugated linoleic acid. Expression of THRSP (Spot14) parallels that of fatty acid synthase in adipose, liver, and mammary tissue in bovine and murine species. Elevated expression of THRSP in human breast tumors is correlated with poor prognosis, whereas absence of expression is associated with longer survival.

**Description**
A driver of de novo saturated fatty acid synthesis in normal and malignant tissues, Spot14 (S14, THRSP) was named for its position on two-dimensional gels of in vitro translation products. The gene is rapidly induced by thyroid hormone in rat liver, and it is strongly activated by glucose metabolism. An acidic protein of approximately 16 kD, it is localized primarily in the nucleus; three domains are conserved from its ancestral protein, Strait1499, also known as Mig12 and S14-related protein.

From immunohistochemical studies, the temporal and spatial expression patterns of murine Spot14 and fatty acid synthase (FASN) were regulated in parallel in mammary epithelium during pregnancy, lactation, and involution. In cattle, milk fat depression is associated with production of conjugated linoleic acid (CLA) isomers as intermediates of fatty acid synthesis by rumen bacteria. Ingestion of a low forage, high oil diet leads to increased production of CLA, and this results in low milk fat content, and decreased expression of S14, FASN, sterol response element binding protein (SREBP), and responsive genes INSIG1 and INSIG2 in a coordinate manner. Breast epithelium does not express detectable levels of Spot14 or FASN in the resting state; however, during pregnancy and lactation, Spot14 and enzymes of lipid biosynthesis are expressed at high levels. Spot14 and FASN are expressed in most breast cancers, and high levels of Spot14 expression portend an aggressive course and high risk of recurrence, regardless of nodal status at diagnosis. Thus Spot14 represents a potential target for therapeutic intervention in cancer.

**Expression**
Spot14 protein is expressed primarily in tissues which synthesize fatty acids. These tissues include white and brown adipose tissue, breast tissue, and liver. Expression is observed in a variety of malignancies, and it is a component of the lipogenic tumor phenotype, e.g., in human breast cancer.

**Localisation**
By immunohistochemistry, Spot14 is localized primarily in the nucleus of rat liver, human mammary gland, and breast cancer cells.

**Function**
Spot14 is involved in the regulation of lipid biosynthesis. Its precise function is not known. It exists as a heterodimer in human cells which are actively synthesizing lipids. Triggers for the induction of Spot14, such as hormones or refeeding after fasting, also trigger FASN activity. Furthermore, siRNAs and anti-sense RNAs directed against Spot14 inhibit expression of genes coding the lipid-synthesizing enzymes.

**Homology**
Homologous proteins are found in cow, rat, mouse, chicken, dog, and chimpanzee, as well as other species. An acidic protein of approximately 16.4 kDa, human THRSP bears 99% homology to its counterpart in Pan troglodytes, 91% to that in Macaca mulatta, 82% to that in Mus musculus, and 80% to that in Rattus norvegicus (data from NCBI BLAST). Three domains are conserved from the ancestral S14-related peptide (Strait 11499, Mig12, S14-related protein).

**Mutations**
Note
Mutations have been characterized in the chicken. Single-nucleotide polymorphisms (SNPs) have been noted in cow, rat, mouse, and chimpanzee. The SNP database in NCBI lists 63 human SNPs for THRSP.

**Implicated in**

**Breast tumors**
Note
Along with cyclin D1, which shares the same amplicon at 11q13, S14 is amplified in about 20% of human breast cancers. Although cyclin D1 is a human and murine mammary oncogene, it was the concomitant overexpression of S14 and lipogenic enzymes in aggressive breast tumors that prompted investigation of the role of fatty acid metabolism in metastasis and recurrence of breast tumors. In an immunohistochemical study of invasive breast tumors, high levels of S14 expression correlated with reduced disease-free survival, irrespective of nodal status at diagnosis; there were no recurrences among those whose tumors expressed low levels of S14, even after prolonged follow-up. S14 expression levels did not segregate with cyclin D1, Her-2/neu amplification status, or hormone receptor status. Thus it appears that S14 promotes a virulent, lipogenic phenotype in breast tumors.
Aberrant hepatic lipogenesis and hepatic steatosis

Note
The relationship between lipid metabolism and disease is further corroborated by the finding in human hepatocytes that the pregnane X receptor (PXR), which is a nuclear receptor regulating xenobiotic and drug metabolism, upregulates lipogenesis via S14. Stimulation of PXR also enhances expression of the cd36 gene, which permits the uptake of exogenous fatty acids by cells, and also stimulates de novo lipogenesis as well as upregulation of the enzymes involved in lipid synthesis. Knockdown by short interfering RNAs to PXR, S14, or FASN abrogates lipid synthesis. S14-directed fatty acid synthesis has also been implicated in aberrant hepatic lipogenesis and hepatic steatosis.

Obesity

Note
It is possible that Spot14 plays a role in the regulation of lipid storage in humans. Whereas nonobese humans downregulate the level of Spot14 in response to fasting, obese subjects do not. Postfasting levels of glucose, insulin, and ketones did not differ between the two groups. The abnormal downregulation of Spot14 in adipose tissue of obese subjects implies that Spot14 may be important to the acquisition or maintenance of obesity in humans.

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