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LAMP GENE- Structure, Function and Involvement in Cancer

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Abstract: ***The LAMP1 gene in humans produces the lysosomal-associated membrane protein 1 (LAMP-1), also known as lysosome-associated membrane glycoprotein 1 and CD107a (Cluster of Differentiation 107a). The human LAMP1 gene is found in region 3, band 4 of chromosome 13's long arm (q). These glycoproteins, which are typically found across lysosomal membranes, have a long, heavily glycosylated end on the luminal side of the membrane with N-linked carbon chains and a short, cytoplasm-expose C-terminal tail. A structure resembling a hinge exists in the extracytoplasmic region, and it is capable of forming disulphide bridges that are similar to those found in human immunoglobulin A Cancer cells frequently express LAMP1 and LAMP2 on their cell surfaces, especially tumours with a high propensity to metastasize, such melanoma and colon cancer, which has been found to be correlated with the propensity to metastasize. Danon disease, which is brought on by a change (mutation) in the LAMP2 gene. Currently, case reports and databases have identified approximately 160 distinct LAMP2 gene variants that have the potential to cause Danon disease. The prognosis has been shown to be most adversely affected by mutations that result in the total lack of the LAMP2 protein.***

Keywords: LAMP gene, Carcinoma, Chromosome 13, Danon's disease

I. INTRODUCTION

The LAMP1 gene in humans produces the lysosomal-associated membrane protein 1 (LAMP-1), also known as lysosome-associated membrane glycoprotein 1 and CD107a (Cluster of Differentiation 107a) (1, 2). The human LAMP1 gene is found in region 3, band 4 of chromosome 13's long arm (q). (2,3)

A member of the family of Lysosome-associated membrane glycoproteins, Lysosomal-associated membrane protein 1 is a glycoprotein (4,5). At least 76 different types of normal tissue cells express the type I transmembrane protein LAMP-1 glycoprotein at high or moderate levels (6,7). It serves to supply selectins with carbohydrate ligands and is typically found across lysosomal membranes (8). Additionally, CD107a has been demonstrated to be a degranulation marker on lymphocytes including CD8+ and NK cells. (9) and might potentially be involved in the differentiation and spread of tumour cells.

II. STRUCTURE OF LAMP

These glycoproteins, which are typically found across lysosomal membranes, have a long, heavily glycosylated end on the luminal side of the membrane with N-linked carbon chains and a short, cytoplasm-exposed (8) C-terminal tail (6). A structure resembling a hinge exists in the extracytoplasmic region, and it is capable of forming disulphide bridges that are similar to those found in human immunoglobulin A (8)

. A 40 kDa polypeptide core and 18 N-glycosylation sites to aid in the addition of sugar chains are two further features of the LAMP-1 glycoproteins' structure (8).

- Lysosomal proteases cannot degrade the glyocoprotein because of the polylactosamine attachments (10).
- Large amounts of polylactosaminoglycan and sialic acid to pass through the trans-Golgi cisterns (10).
- The poly-N-acetyllactosamine groups that interact with selectin and other glycan-binding proteins (11).

III. FUNCTIONS OF LAMP

50% of all lysosomal membrane proteins are made up of the LAMP1 and LAMP2 glycoproteins (6), which are hypothesised to play a role in lysosomal integrity, pH, and catabolism (6, 11). Due to enhanced expression of LAMP2 glycoproteins caused by LAMP1 gene deficits, LAMP1 and LAMP2 expression are related (11). Therefore, it is believed that the two have comparable in vivo functions. While the LAMP1 deficient phenotype is little different from the wild type due to LAMP2 up regulation, the LAMP1/LAMP2 double deficient phenotype results in embryonic death, making it difficult to pinpoint the exact role of LAMP1 (6,11).

The LAMP1 glycoproteins are primarily found throughout lysosomal membranes, but under specific conditions they can also be expressed across the cell's plasma membrane (11). By lysosomal fusion with the cell membrane, (12) LAMP1 expression at the cell surface is possible (13, 14). LAMP1 cell surface expression can bind to selectins and facilitate cell-cell adhesion (15). In light of this, cells with migratory or invasive activities, such as cytotoxic T cells, platelets, and macrophages (16), have cell surface expression of LAMP1. Cancer cells (16, 17) frequently express LAMP1 and LAMP2 on their cell surfaces, especially tumours with a high propensity to metastasize, such melanoma (16) and colon cancer, which has been found to be correlated with the propensity to metastasize (11).

IV. ROLE OF LAMP IN CANCER

LAMP1 expression has been seen on the surface of tumour cells for a variety of cancer types, notably in tumours that have a high propensity for metastasis, such as melanoma (16, 17) colon cancer (16, 17), and pancreatic cancer (18,19). LAMP1 is hypothesised to assist in mediating cell-cell adhesion (17) and migration (15, 18), and its shape is correlated with tumour cell differentiation and metastatic capacity. In fact, LAMP1 and LAMP2 interact with E-selectin and galectins to mediate the adherence of certain cancer cells to the extracellular matrix, with the LAMPs acting as ligands for the cell-adhesion molecules (17).
LAMP-1 cell membrane expression has been found in the subsequent cancer types:
Astrocytoma, Colon adenocarcinoma, Melanoma, Pancreatic adenocarcinoma, and Human Fibrosarcoma (17, 18, 19).

V. LAMP-RELATED ILLNESS

Danon disease, which is brought on by a change (mutation) in the LAMP2 gene. Currently, case reports and databases have identified approximately 160 distinct LAMP2 gene variants that have the potential to cause Danon disease. The prognosis has been shown to be most adversely affected by mutations that result in the total lack of the LAMP2 protein. Clinically, some mutations that result in a partial LAMP2 protein shortage might be less serious. In many cases, the condition is passed down through the parents, usually the mother who has a much higher chance of surviving to adulthood than the normal affected male. Only a select few men may be in good enough health to father their own children without a heart transplant. Although they have not been extensively reported, new genetic alterations (sporadic mutations) may possibly be to blame for the first incidence in a family. A 50% probability exists that each child born to affected moms will inherit the gene mutation (both sons and daughters). The genetic flaw will be passed to all of the daughters and none of the sons of affected fathers who are healthy enough to conceive children. This inheritance pattern is consistent with that of other X-linked genetic diseases.
Females are partly shielded from the effects of the gene abnormalities that result in Danon illness since they have two X chromosomes (whereas males only have one). This is explained by the fact that each woman with Danon disease have two X chromosomes: one with a gene mutation causing the disease and the other with a healthy copy of the LAMP2 gene. Females are protected by the X chromosome, which also has the normal LAMP2 gene, which partially explains why symptoms in females are less severe and don't manifest until adulthood. However, some Danon disease patients have developed to the point where they require a heart transplant. This gene's (LAMP2) genetic traits are passed on as an X-linked dominant trait.
The interaction of the genes for a specific trait found on the chromosomes inherited from the mother and father determines the presence of genetic illnesses.
Genetic illnesses known as X-linked recessive genetic disorders are brought on by a faulty gene on the X chromosome. Females have two X chromosomes, but one of them is "shut off," meaning that none of its genes are active. Females who carry a disease gene on one of their X chromosomes are susceptible to developing the condition. Because the defective gene is often shut down on the X chromosome in carrier females, these individuals typically do not exhibit symptoms of the condition. A male has one X chromosome, and if he inherits an X chromosome with a disease gene, the condition will manifest in him. All of a man's daughters will be carriers of the disease gene he carries if he has an X-linked ailment. Because males usually convey their Y chromosome rather than their X chromosome to male progeny, a male cannot pass an X-linked gene to his sons. With each pregnancy, female carriers of X-linked disorders have a 25% chance of having a daughter who is also a carrier, a 25% risk of having a daughter who is not a carrier, a 25% chance of having a son who has the disease, and a 25% chance of having an unaffected son. An faulty gene on the X chromosome also causes X-linked dominant disorders like Danon disease, however in these uncommon diseases, only females carrying the aberrant gene are affected. More severely impacted than females by an aberrant gene are males, and many of these men do not survive. Males with Danon disease can live to adulthood, but their medical issues and the common requirement for a heart transplantation probably prevent them from having children.

It is unclear how the LAMP2 protein, which is produced from the LAMP2 gene, works. It seems that the lysosomes in the cell depend on the LAMP2 protein to operate properly. . Lysosomes are tiny organelles found inside cells that break down specific chemicals and compounds in the body. They are frequently compared to waste disposal facilities. Cellular waste builds up when the lysosomes do not operate properly. Glycogen is one such product that can accumulate, and in certain individuals, excess glycogen seen on a skeletal muscle biopsy is used to support the diagnosis of Danon disease. It's crucial to understand, though, that a single muscle biopsy does not necessarily show signs of excess glycogen.

VI. DIAGNOSIS

There are LAMP-2 protein antibodies available, and muscle biopsy tissue staining for the lack of LAMP-2 protein is another viable but uncommon diagnostic method. Women with Danon illness are likely to have normal LAMP-2 antibody levels, but if testing is done, results should be taken cautiously because they could be falsely negative.

The gold standard for diagnosis at the moment is LAMP2 gene genetic testing, which is available in specialised genetics labs. Reduced or even absent amounts of the LAMP-2 protein, the gene product of the LAMP2 gene, are predicted by the majority of genetic abnormalities causing Danon disease. LAMP2 genetic testing is the best that is currently available, despite the fact that its sensitivity is unknown. The non-invasive nature of DNA-based testing and the inclusion of LAMP2 gene testing in genetic diagnostic panels for hypertrophic cardiomyopathy make this approach the most popular means of diagnosis.

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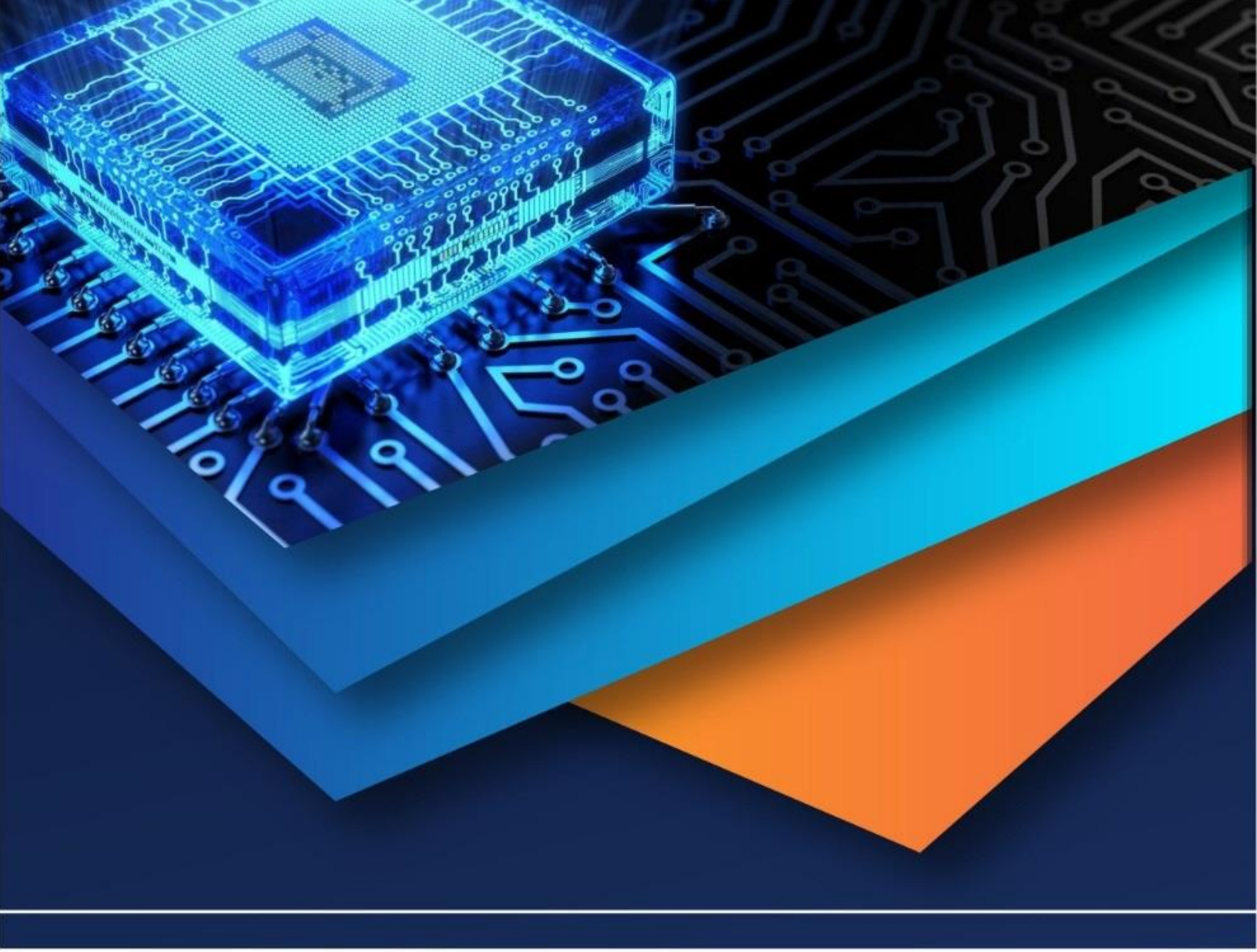

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