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Review Article

The Usage of Lysosomal Antibodies during the Study of Lysosome Structure and Functions: A Review

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Abstract

Lysosomes are involved in cellular waste degradation and recycling, along with cellular signaling and energy metabolism. Lysosomal storage disorders occur due to the abnormality in genes which are encoding lysosomal proteins. This work aims to emphasize the usage of different lysosomal antibodies during the study of the structure and functions of lysosomes and the investigation of different types of pathological diseases related to lysosomal functions. This may present the characteristics of those antibodies according to a classification that mainly depends on the localization of their targets.

Keywords: lysosome, lysosomal antibody, lysosomal marker, autophagy

Introduction:

The lysosome is an intracellular organ with an acidic interior due to the presence of acidic hydrolases and membrane proteins [3]. They are going to be found in most of the all-being cells. Lysosomes appear as dense bodies among the cytoplasm, typically as a perinuclear pattern. Lysosomes are restricted by a phospholipid-bilayer. It has high carbohydrate content, because of heavily glycosylated lysosomal membrane proteins. There are twenty-five lysosomal membrane proteins are acknowledged. To protect the membrane of the lysosome from the lytic enzymes within the lysosome, glycosylation of the lysosomes at their luminal, domains form the glycocalyx. And additionally, lysosomes contain Intra lysosomal membranes, wherever the membrane degradation happens.

The acidic setting of the lysosome maintained by the lysosomal v-ATPase, combined with a pantheon of luminal hydrolases, leads to an organelle that is fitted to the breakdown [2] of major macromolecules, together with lipids, polysaccharides, and proteins. After degradation, free fatty acids, monosaccharides, and amino acids are transported to the cytoplasm using specific permeases and reused in the anabolic process. [2].

Biogenesis of the lysosome.

Lysosome biogenesis models are classified into two types: "kiss and run" and "hybrid." "In the "kiss and run" model, late endosomes deliver their contents to lysosomes via transient fusion events, whereas in the "hybrid" model, late endosomes and lysosomes fuse completely to form hybrid organelles, and lysosomes are then formed via selective retrieval of late endosomal components from the hybrid organelles." [4]

Autophagy

All eukaryotes have autophagy, which is a lysosome-based breakdown mechanism. Autophagosomes are double-membrane vesicles that form during autophagy. It engulfs intracellular materials, including cytosol, and then merges with the lysosome to form the autolysosome, a hybrid organelle that degrades the absorbed intracellular contents [13].

The important role of lysosomes in the normal functioning of the cell suggests the need to study them in the modeling of experimental pathology. For this, there are a number of molecular markers characterizing the functions of lysosomes.

Lysosome marker antibodies

Lysosome marker antibodies will help researchers better understand the structure and function of lysosomes. Lysosome markers can help researchers figure out what role (or roles) a protein plays in a variety of tasks involving or controlled by the lysosome. Furthermore, lysosome marker antibodies are utilized to follow the fusion of the lysosome with the autophagosome just before the autolysosome contents are degraded. Antibodies to lysosome markers are designed to reliably identify the primary cell organ targets. It is separated into two groups based on the

location of those objectives[12]. When tracking lysosomal proteins via lysosomal antibodies, we can use either western blot, immunohistochemistry, flow cytometry, immunocytochemistry, or the ELISA method.

1) Lysosomal membrane markers

Before autolysosome breakdown, lysosomal membrane markers are utilized to track fusion with the autophagosome. Molecular Probes for finding and tracking lysosomal membranes made with red or green fluorescent proteins.

2) Markers for Lysosomal Contents

Acidic organelles are targeted at nanomolar concentrations using molecular probes that permeate cells. They are available in several colors, including deep red, to enable multiplexing with other fluorescent markers.

Lysosomal membrane markers

1) ATG5 Antibody

The protein ATG5 is a key component of autophagy and may play a role in the apoptotic process. It contributes to mitochondrial quality maintenance after oxidative damage, negative modulation of the innate antiviral immune response and lymphocyte growth and proliferation, MHC II antigen presentation, and adipocyte differentiation. By interacting with the Fast-associated protein with a death domain, it induces autophagic cell death.

APG5 could play a role in the apoptotic process, possibly through the cytoskeleton's modification. The ATG5-ATG12 conjugate forms a cup-shaped separation membrane that detaches from the membrane shortly before or shortly after autophagosome formation. Innate immune response proteins including RIG-I and VISA (also known as IPS-1) bind with the compound, suppressing type I interferon production and allowing virus multiplication in host cells. Spinocerebellar ataxia is one of the diseases linked to ATG5 malfunction.

In Atg5 mutant cells, maintaining cells in a low pH buffer reduces intracellular pH and restores late endosome/lysosome biogenesis. Due to decreased recruitment of a V1-ATPase subunit to acidic organelles, late endosomal components are recovered from hybrid organelles, resulting in an acidic organelle pH increase. As a result, the retromer is unable to extract late endosomal particles from hybrid cell organelles since it is pH-dependent. [5]. As a result, Atg5 regulates late endosome and lysosome biogenesis by modulating lysosomal pH. [4, 5].

2) ATG12 Antibody

ATG12, a member of the autophagy protein family, forms a conjugate with ATG5 that exhibits ubiquitin-protein ligase (E3)-like activity in autophagy for protein lipidation. This compound also binds to innate immune response proteins including RIG-I and VISA, which inhibits type I interferon production while allowing viral replication in host cells. In the presence of ATG7, ATG12 has been demonstrated to interact with ATG10 in human embryonic kidney cells. There are at least two ATG12 isoforms identified. Autophagy, the process of bulk breakdown of cellular proteins via an autophagosomic-lysosomal route, is essential for normal cell growth control and may be impaired in tumor cells. It aids in the maintenance of cellular resources during fasting as well as the proper cycling of cytosolic components. TOR (Target of Rapamycin) inhibits this process by phosphorylating the autophagy protein APG1 [17].

3) Beclin 1 Antibody

Beclin 1 is essential for autophagy. It is a key member of the PI3K complex, which is responsible for the synthesis of phosphatidylinositol 3-phosphate. Different PI3K complex forms are thought to have a function in multiple membrane trafficking pathways: PI3KC3-C1 is engaged in autophagosome induction, while PI3KC3-C2 is involved in autophagosome maturation and endocytosis. Beclin 1 is also involved in antiviral host defense [18].

Beclin 1 Antibody in IHC

To identify breast cancer and liver cancer, we can use Beclin1 monoclonal antibody Immunohistochemical examination of paraffin-embedded tissues, followed by DAB staining.

4) LC3B Antibody

“In humans, LC3B (Autophagy Marker Light Chain 3B)is encoded by the MAP1LC3B (Microtubule-associated proteins 1A/1B light chain 3B) gene. LC3B is required for neurogenesis and is involved in microtubule assembly. According to recent research, LC3B plays an important part in autophagy, a process that includes the mass destruction of cytoplasmic components." [7] Three human LC3 isoforms undergo post-translational modifications during autophagy. Macroautophagy is the primary inducible process for complete cytoplasmic turnover in eukaryotic cells. The development of double-membrane-bound autophagosomes that enclose the cytoplasmic substance to be eliminated characterizes it. The creation of double-membrane-bound autophagosomes that enclose the cytoplasmic constituent to be destroyed in a membrane-bound structure before fusing with the lysosome is termed macroautophagy [13]. LC3B is a microtubule-associated protein that helps microtubules bind with cytoskeleton components physically. LC3B may affect cancer, aging, metabolic and neurological illnesses, as well as cardiovascular and pulmonary ailments.

Therefore, the ATG5, ATG12, Beclin1, and LC3B antibodies that are mentioned above can be classified as autophagy-related antibodies.

5) CD34 Antibody

CD34 is a highly glycosylated monomeric surface protein identified on many stem cells. CD34 may act as a surface receptor that governs the adhesion, differentiation, and proliferation of hematopoietic stem cells and other progenitors via receptor-mediated endocytosis. CD34 expression is assumed to reflect a specific stage of hematopoietic development in both in vitro and in vivo situations, with altered adhering qualities and expanding and differentiating capabilities [6]. CD34 may function as a scaffold for lineage-specific glycan binding, allowing stem cells to attach to lectins produced by stromal cells or other bone marrow components. CD34 is thought to help selectins recognize carbohydrate ligands. The intracellular chain of the CD34 antigen is phosphorylated by active protein kinase C, indicating a possible role in signal transduction.CD34 deficiency is linked to two diseases: dermatofibrosarcoma and neurofibroma.

6) CD63 Antibody

The tetraspanin glycoprotein CD63 (LAMP-3, lysosome-associated membrane protein-3) is found in various cell types' late endosomes and secretory vesicles. CD63 can also be detected in the plasma membrane after a cell has been triggered. The presence of CD63, on the other hand, does not entail mast cell activation. Melanoma and Hermansky-Pudlak Syndrome are two diseases that have been associated with CD63. During platelet activation, CD63 is a glycoprotein that is expressed on activated platelets. ME491, a melanoma antigen, and PTLGP40, a platelet antigen, are all synonymous with CD 63.

7) CD68 Antibody

CD68 (Macrosialin) is a 110-kDa integral membrane glycoprotein found in monocytes and macrophages' lysosomes, as well as dendritic cells and peripheral blood granulocytes. CD68 may be engaged in phagocytic activities such as intracellular lysosomal metabolism and extracellular cell-cell and cell-pathogen interactions in tissue macrophages. CD68 is

indicated by tonsil reticulocytes, histiocytic lymphoma, acute myeloid leukemia, and granulocyte sarcoma. A variety of human malignancies, including Acute Myeloid Leukemia, have been revealed to have enhanced CD68 expression on CD34+ cells[21].

8) CXCR4 Antibody

CXCR4 is a member of the G-protein-coupled chemokine receptor family that serves as a co-receptor for X4 HIV-1 entrance into CD4+ cells. CXCR4 has been identified as a co-receptor for HIV-2 binding to CD4 via envelope glycoprotein 120, promoting Env-mediated virus fusion. CXCR4 can potentially act as the sole receptor for HIV-2 binding to CD4 host cells in some situations[22].CXCR4 is a C-X-C chemokine CXCL12/SDF-1 signaling receptor that increases intracellular calcium ion levels and activates MAPK1/MAPK3.CXCR4 is an extracellular ubiquitin receptor that increases the rise of intracellular calcium ions while decreasing cellular cAMP levels. [10]. CXCR4 is also involved in hematopoiesis and the creation of the heart ventricular septum, as well as playing a critical part in gastrointestinal vascularization, most likely via controlling vascular branching and/or remodeling events in endothelial cells. CXCR4 is implicated in cerebellar development and may affect hippocampal-neuron survival in the CNS. CXCR4 binds to bacterial lipopolysaccharide (LPS) and mediates the inflammatory response generated by LPS, including monocyte TNF production. CXCR4 antibodies prevent HIV-1 and HIV-2 from fusing and infecting human target cells. HIV binding sites are found in CXCR4's amino-terminal domain and second extracellular loop.

9) LAMP 1 Antibody

LAMP1 (lysosome-associated membrane protein-1) and LAMP-2 are important components of the lysosomal membrane, and 1-2 percent of total CD107a is also detected on the plasma membrane[25]. LAMP1 is a highly glycosylated membrane protein with a putative signal peptide, 18 N-linked glycosylation sites, a single membrane-spanning region, and a short cytosolic tail. The LAMP proteins are involved in lysosome formation and are necessary for lysosome-phagosome fusion[24]. LAMP1 is an integral membrane protein of type 1 that travels from the trans-Golgi network to endosomes and finally to lysosomes LAMP1 translocation to the plasma membrane is dependent on a carboxyl-terminal tyrosine-based motif after cell activation. Cell surface LAMP1 (and LAMP2) have been demonstrated to increase human peripheral blood mononuclear cells (PBMC) adhesion to vascular endothelium, suggesting that they may be involved in PBMC adherence to the site of inflammation. LAMP1 positivity is increased in neurons and glial cells surrounding senile plaques in Alzheimer's disease (AD) patients, and it is seen in medullary epithelial cells, single macrophages, and lymphocytes in acute thymic involution.

10) LAMP 2 Antibody

LAMP2 (Lysosome-associated membrane glycoprotein 2) belongs to the membrane glycoprotein family. LAMP2 connects selectins to carbohydrate ligands and may play a role in tumor cell metastasis as well as lysosome protection, maintenance, and adhesion. LAMP2 is a 46 kDa polypeptide before posttranslational modification. Mature, functioning LAMP2 is heavily glycosylated with a wide range of N-linked and O-linked oligosaccharides, with a total molecular weight of about 100-130 kDa. LAMP 2 comprises a broad amino-terminal intra-lysosomal domain, a hydrophobic transmembrane region, and a short carboxy-terminal cytoplasmic tail. LAMP2 is used to track a kind of autophagy known as chaperone-mediated autophagy[25]. LAMP 2 comprises a broad amino-terminal intra-lysosomal domain, a hydrophobic transmembrane region, and a short carboxy-terminal cytoplasmic tail. LAMP-2A, -2B, and 2C are the three variant versions of the LAMP protein. LAMP2, together with CD107a/LAMP-1, is a significant component of the lysosomal membrane. LAMP proteins are involved in lysosome biogenesis and are essential for lysosome-phagosome fusion, and LAMP2 is a key regulator in effective phagosomal maturation. LAMP2 loss induces autophagosome buildup in various organs, resulting in cardiomyopathy and myopathy (Danon's disease).

11) PDGFRB Antibody

PDGFRb is a tyrosine kinase receptor on the cell surface for platelet-derived growth factor family members. Mitogens for mesenchymal cells are these growth agents. Whether a functional receptor is a homodimer or a heterodimer of platelet-derived growth factor receptor alpha and beta polypeptides is determined by the growth factor bound to a receptor monomer. [14]. The granulocyte-macrophage colony-stimulating factor and macrophage-colony stimulating factor receptor genes surround the gene on chromosome 5; all three genes may be involved in the 5-q syndrome. A translocation between chromosomes 5 and 12, which connects this gene to the translocation's ETV6, leukemia gene, causes chronic myeloproliferative disease with eosinophilia.

12) TLR3 Antibody

TLR3 (Toll-like receptor 3) is important in pathogen identification and innate immune activation. TLRs identify pathogen-associated molecular patterns produced on infectious pathogens and mediate the release of cytokines required for successful immune development. TLR3 is only found in the dendritic subpopulation of leukocytes and is most common in the placenta and pancreas. TLR3 recognizes dsRNA from a viral infection and activates NF-kappaB, causing type I interferon to be produced. The TLR family is a phylogenetically conserved innate immune mediator that is required for microbial identification. So far, TLRs have been found to activate the MyD88/interleukin-1 receptor-associated kinase (IRAK) signaling pathway. TLR3 is the only human TLR that does not use MyD88 as an adaptor molecule, instead of using TRIF in a signaling pathway that leads to the activation of IRF-3 and NF-kB downstream[34]. TLR3 activation induces not just Type I interferon but also other inflammatory cytokines, resulting in DC maturation. TLR3 has been shown to identify viral double-stranded (ds) RNA, a molecular signature linked to viral infection. It has recently been demonstrated that it can identify viruses such as Influenza A and West Nile Virus.

13) TLR7 Antibody

TLR7 is essential for pathogen identification and innate immune activation. Infections with single-stranded RNA viruses, such as influenza virus and vesicular stomatitis virus, activate TLR7[31]. TLR7 is mostly expressed in the lung, placenta, and spleen, and it is closely related to another member of the TLR family, TLR8[33]. TLR7 also activates NF-kappaB, secretes cytokines, and initiates an inflammatory response via MyD88 and TRAF6. TLR7 recognizes pathogen-associated molecular patterns (PAMPs) expressed on infectious pathogens and mediates the release of cytokines required for successful immune development.

02) Markers for Lysosomal Contents

1) IGF2R Antibody (Insulin-Like Growth Factor 2 Receptor)

IGF2R, also named MPRI, Mannos-6-Phosphate Receptor, belongs to the MRL1/IGF2R family. This receptor performs a variety of tasks, including lysosomal enzyme intracellular trafficking, transforming growth factor-beta activation, and insulin-like growth factor 2 degradation. This gene's mutation or loss of heterozygosity has been linked to an increased risk of hepatocellular cancer [11]. Phosphorylated lysosomal enzymes are transported to lysosomes by IGF2R from the Golgi complex and the cell surface. IGF2R is a phosphomannosylated lysosomal enzyme that binds to mannose-6-phosphate receptors in the Golgi apparatus and transports the resulting receptor-ligand complex to an acidic prelyosomal compartment, where the low pH promotes the complex's dissociation. IGF2 is also bound by this receptor. By binding DPP4, IGF2R acts as a

positive regulator of T-cell coactivation. This antibody targets IGF2R and assesses its function.

2) MPO Antibody

The hemoprotein myeloperoxidase (MPO) is extensively produced in neutrophils and released upon their activation. MPO antibodies are used to assess patients who may have immune-mediated vasculitis. Myeloperoxidase is a tetrameric complex with two glycosylated alpha chains and two unglycosylated beta chains that are covalently linked. Anti-neutrophil cytoplasm antibodies (ANCA), the serological markers for some systemic vasculitis such as periarteritis nodosa, microscopic polyarteritis, and pulmonary eosinophilic granulomatosis, have traditionally targeted myeloperoxidase (Churg-Strauss syndrome)[32]. Anti-myeloperoxidase autoantibody levels in rheumatoid arthritis range from low to moderate. Myeloperoxidase has recently been discovered to play a role in the onset and progression of cardiovascular disease. Myeloperoxidase has strong pro-inflammatory capabilities and may play a role in tissue damage. Myeloperoxidase is being considered as one of the most promising cardiac indicators right now.
Myeloperoxidase is a component of polymorphonuclear(PMN) leukocytes' host defense system, and it is responsible for microbicidal activity against a variety of pathogens. In physiologic circumstances, MPO catalyzes the formation of hypohalous acids, specifically hypochlorous acid.

3) PAK Antibody

PAK proteins function as effectors that connect Rho GTPases to cytoskeleton remodeling and nuclear signaling. PAK proteins belong to the serine/threonine p21-activating kinase family that includes PAK1, PAK2, PAK3, and PAK4[28]. These proteins serve as targets for the tiny GTP binding proteins Cdc42 and Rac. PAK1 is a protein that affects cell motility and morphology.

4) Rab Antibody

Rab proteins belong to the Ras-like GTPase family that is involved in intracellular protein transport. The docking and fusing of transport vesicles between different compartments within the cell is the responsibility of various members of the 40+ member Rab family [29]. Mannose 6-phosphate receptors must be transported from the late endosome to the trans-Golgi network, and Rab 9 is required for this. Rab 9 allows cells to recycle essential cellular trafficking components more efficiently by promoting receptor delivery.

5) Anti Ovalbumin Antibody.

Ovalbumin is the major protein found in egg white, and Anti Ovalbumin Antibody identifies it. Ovalbumin accounts for about 60-65% of total protein. Ovalbumin shares sequence and three-dimensional similarity with the serpin superfamily, although it is not a serine protease inhibitor like most serpins. Ovalbumin's function is unclear, but it is considered to be a storage protein. Ovalbumin can cause allergic reactions in humans [8]. When recognizing Ovalbumin, Western Blot, Immuno cytochemistry, and ELISA can be used.

Future directions

By all accounts and based on verified results, lysosomal antibodies help in the identification of the structure and functions of lysosomes, as well as play a key role in the diagnosis of disorders involving lysosomal functions.

This could aid in the early detection of diseases including lysosomal storage disorders and malignancies, among others. This may aid in the initiation of treatment at an early stage of the disease, thus increasing the patient's chances of recovery.

We may also utilize this as a method of checking the success of the treatment for the diseases mentioned above by improving the methodologies. Using lysosomal antibodies, for example, we can check lysosomal function after commencing the therapy process. Then we may assess the improvement in lysosome function that the medication may have caused. We can then determine whether or not to continue with the treatment.

Thus, lysosomal antibodies are currently used exclusively as a diagnostic tool in experimental and clinical medicine, but with further development they can be used as a therapeutic tool, especially in the treatment of cancer and a number of other diseases caused by insufficient functions of apoptosis.

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Conflict of interest statement
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