1. Phylogeny –  
   Obscurin (OBSCN), also known as OBSCN‐b, KIAA1556, or KIAA1639, is a giant muscle protein that belongs to a family of titin‐related, multidomain proteins with kinase capacity. It is evolutionarily conserved among vertebrates and shares orthology with the invertebrate protein UNC-89, which is expressed in Caenorhabditis elegans, and with other giant muscle proteins such as SPEG and Obsl1. Obscurin is classified within the group of tandem myosin light chain kinase (MLCK) homologs and Rho guanine nucleotide exchange factor (Rho-GEF) proteins. Its evolutionary lineage indicates that the ancestral vertebrate obscurin already possessed dual kinase domains before gene duplication events in the MLCK family occurred. This evolutionarily conserved architecture is evident from domain‐level comparisons and sequence homology analyses across species (sutter2004orthologousrelationshipof pages 5-8, young2001obscurinagiant pages 1-2, manring2017obscurefunctionsthe pages 1-2).
2. Reaction Catalyzed –  
   Obscurin functions as a serine/threonine protein kinase. In its catalytic reaction, it transfers a phosphate group from ATP to a target protein’s serine or threonine residue. The general reaction catalyzed is:  
   ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This reaction underpins its role in phosphorylating substrates such as N-cadherin (CDH2) and the sodium/potassium-transporting ATPase subunit (ATP1B1), as predicted by similarity with other members of the MLCK family (fleming2021exploringobscurinand pages 12-14, marston2017obscurinvariantsand pages 5-5).
3. Cofactor Requirements –  
   The kinase activity of obscurin is dependent on divalent cations. As is typical for serine/threonine protein kinases, its catalytic function requires Mg²⁺ ions. The Mg²⁺ serves as a cofactor that coordinates with ATP during the phosphate transfer reaction (fleming2021exploringobscurinand pages 12-14).
4. Substrate Specificity –  
   Obscurin phosphorylates serine/threonine residues on protein substrates. By similarity to other muscle kinases, its substrate specificity includes targets involved in muscle adhesion and excitation–contraction coupling. Its kinase domains are reported to phosphorylate N-cadherin (CDH2) and the Na⁺/K⁺-ATPase beta subunit (ATP1B1), and it is predicted to recognize motifs enriched in serine/threonine residues with flanking charged amino acids. While an explicit consensus substrate motif for obscurin has yet to be fully defined, the substrate specificity is consistent with that of related MLCK family kinases that typically target basic motifs adjacent to the phosphorylated residue (fleming2021exploringobscurinand pages 12-14).
5. Structure –  
   Obscurin is a giant, multidomain protein with an approximate molecular weight of 800 kDa. Its domain organization comprises: • An N-terminal region containing numerous tandem immunoglobulin-like (Ig) domains and fibronectin type III (Fn3) domains that provide a scaffolding and structural function essential for sarcomere assembly. These domains are homologous to those found in titin and have been implicated in the organization of thick filaments into A bands (benian2015titinandobscurin pages 1-2, manring2017obscurefunctionsthe pages 10-11).  
   • Adjacent to the Ig and Fn3 domains, there is an IQ motif that binds calmodulin in a calcium-independent manner, contributing to the regulation of protein interactions during myofibrillogenesis.  
   • A Src homology 3 (SH3) domain is present, followed by a tandem arrangement of Rho guanine nucleotide exchange factor (RhoGEF) domains that participate in downstream signaling related to cytoskeletal dynamics (young2001obscurinagiant pages 1-2).  
   • A pleckstrin homology (PH) domain is embedded in the structure, which binds phosphatidylinositol 3,4-bisphosphate (PtdIns(3,4)P2) and phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P2) with high affinity. This domain likely governs subcellular targeting and contributes to the integration of membrane signals (fleming2021exploringobscurinand pages 1-2).  
   • The obscurin-B isoform includes two serine/threonine kinase domains, which are arranged in tandem at the C-terminus. These catalytic domains contain the conserved glycine-rich loop for ATP binding, a catalytic loop with a histidine/lysine cluster, and the DFG motif that coordinates the divalent metal ion cofactor. Owing to its large size, high-resolution full-length 3D structures have not been determined; however, individual domains have been characterized by crystallography and homology modeling (manring2017obscurefunctionsthe pages 10-11, fleming2021exploringobscurinand pages 12-14, benian2015titinandobscurin pages 1-2).
6. Regulation –  
   Obscurin is subject to multiple regulatory mechanisms: • Autophosphorylation is a key regulatory process within its kinase domains. For example, the kinase domain (designated OK1 in some studies) can phosphorylate an adjacent inter-kinase region, thereby modulating its subcellular localization and catalytic activity (fleming2021exploringobscurinand pages 12-14, manring2017obscurefunctionsthe pages 12-13).  
   • Protein-protein interactions also play a major role in obscurin regulation. It interacts with titin, myomesin, and small ankyrin 1 isoforms to stabilize its localization at the M-band and sarcoplasmic reticulum, thereby integrating structural and signaling functions. These interactions may indirectly regulate its kinase activity by influencing its conformational state (blondelle2019murineobscurinand pages 1-2, kuntrogianni‐konstantopoulos2006obscurinmodulatesthe pages 1-2).  
   • Although direct evidence for regulation by other post-translational modifications (such as ubiquitination) is not detailed in these sources, interactions with components of the ubiquitin ligase machinery have been observed, suggesting that degradation and turnover may also be modulated through such mechanisms (grogan2019unravelingobscurinsin pages 11-12).  
   • The dynamic exchange between different isoforms produced by alternative splicing further contributes to its regulation under varying developmental and physiological conditions (manring2017obscurefunctionsthe pages 9-10).
7. Function –  
   Obscurin is expressed predominantly in striated muscles, including both skeletal and cardiac tissue. Its biological functions include: • Structural Roles: Obscurin provides a critical scaffold that organizes myofibrillar components during myofibrillogenesis. By mediating interactions with titin, myomesin, and ankyrin isoforms, obscurin helps maintain the integrity of the sarcomere, particularly the assembly of myosin into A bands and the stabilization of the M-band (blondelle2019murineobscurinand pages 1-2, grogan2019unravelingobscurinsin pages 3-4).  
   • Signaling Functions: As a serine/threonine kinase, obscurin participates in phosphorylation events that are important for the regulation of cell–cell adhesion and membrane excitability. It has been predicted to phosphorylate N-cadherin (CDH2) and the Na⁺/K⁺-ATPase beta subunit (ATP1B1), suggesting roles in modulating intercellular communication and ion transport (fleming2021exploringobscurinand pages 1-2).  
   • Membrane Association: The PH domain of obscurin binds significantly to phosphatidylinositides such as PtdIns(3,4)P2 and PtdIns(4,5)P2, which may target obscurin to discrete membrane regions and coordinate signaling events required for sarcolemmal integrity and the organization of the sarcoplasmic reticulum (fleming2021exploringobscurinand pages 1-2, hu2020proteomicanalysisof pages 1-2).  
   • Myofibrillogenesis: Obscurin’s integration into the sarcomere is implicated in the proper assembly and alignment of myofibrils, an essential process for muscle contraction and overall muscle metabolism (grogan2019unravelingobscurinsin pages 6-8, manring2017obscurefunctionsthe pages 7-9).
8. Other Comments –  
   Obscurin is also alternatively described as Obscurin-RhoGEF or Obscurin-myosin light chain kinase, reflecting its multifunctional domain architecture. Mutations in the OBSCN gene have been associated with inherited cardiomyopathies, including hypertrophic, dilated, and left ventricular non-compaction forms, thereby underscoring its clinical relevance in cardiac muscle pathology (grogan2019unravelingobscurinsin pages 16-16, grogan2019unravelingobscurinsin pages 16-17).  
   In addition, related proteins such as Obsl1 are known to cause 3M-growth syndrome when mutated, which further emphasizes the importance of this protein family in maintaining muscle cell structure and function (blondelle2019murineobscurinand pages 12-12).  
   No specific inhibitors of obscurin have been well characterized to date; however, its kinase activity and role in muscle signaling and structure have made it a target of interest in the development of therapeutic strategies for muscle disorders (benian2015titinandobscurin pages 1-2).  
   The alternative splicing that generates multiple isoforms, including those with or without kinase domains, suggests a complex regulation that permits fine-tuning of its functional roles during muscle development and in response to physiological stress (fleming2021exploringobscurinand pages 1-2, manring2017obscurefunctionsthe pages 9-10).
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   young2001obscurinagiant pages 10-11;  
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