1. Phylogeny  
   SPEG (Striated muscle preferentially expressed protein kinase), also known by its alternative designation APEG-1 when expressed in vascular tissues, is classified within the myosin light chain kinase (MLCK) family and, more specifically, within a subgroup related to obscurin. SPEG shares a common evolutionary origin with other muscle‐associated kinases such as titin, twitchin, and the invertebrate ortholog UNC-89. Its domain composition—with multiple immunoglobulin-like (Ig) and fibronectin type III (FnIII) domains in addition to the tandem serine/threonine kinase domains—reflects an evolutionary conservation among vertebrate species involved in muscle structure and mechanosensing. This conservation across species indicates that SPEG is part of an ancient kinase lineage instrumental in the regulation of muscle architecture and function (hsieh2000striatedmusclepreferentially pages 1-2, grogan2020doublethetrouble pages 1-2, gautel2011cytoskeletalproteinkinases pages 9-11).
2. Reaction Catalyzed  
   SPEG catalyzes the phosphorylation of serine/threonine residues on substrate proteins. The chemical reaction can be summarized as follows: ATP + [protein]–OH → ADP + [protein]–O–phosphate + H⁺. Through this reaction, SPEG transfers a phosphate group from ATP to target proteins that are integral to muscle excitation–contraction coupling and structural integrity (quan2019spegcontrolscalcium pages 1-2, hsieh2000striatedmusclepreferentially pages 2-3).
3. Cofactor Requirements  
   The catalytic activity of SPEG, like that of most serine/threonine kinases, is dependent on the presence of divalent cations. In particular, Mg²⁺ acts as an essential cofactor that facilitates the binding of ATP to the active site of the kinase domains and is required for the phosphoryl transfer reaction (quan2019spegcontrolscalcium pages 2-3, hsieh2000striatedmusclepreferentially pages 2-3).
4. Substrate Specificity  
   SPEG exhibits substrate specificity for serine/threonine residues on proteins that are components of the junctional membrane complex in muscle cells. In cardiac muscle, SPEG phosphorylates SERCA2a at threonine 484 and the ryanodine receptor type-2 (RyR2) at serine 2367, and it modifies multiple phosphorylation sites on junctophilin-2 (JPH2). Although a precise consensus motif has not been fully established, the substrates for SPEG are generally localized at the sarcoplasmic reticulum and transverse tubule interface, where SPEG regulates calcium handling and excitation–contraction coupling (quan2019spegcontrolscalcium pages 4-5, campbell2020lossofspeg pages 1-3, luo2021striatedpreferentiallyexpressed pages 8-9).
5. Structure  
   SPEG is a large modular protein that exists in several isoforms; in striated muscle, the most abundant forms are SPEGα (~250 kDa) and SPEGβ (~355 kDa), while APEG-1 (also referred to as isoform 3) is expressed in arterial smooth muscle cells and is implicated in the regulation of growth and differentiation of these cells. The core structure of SPEG includes two tandem serine/threonine kinase domains located at its C-terminus. Kinase domain 1 (SK1) has been associated with the phosphorylation of substrates such as junctophilin-2, whereas kinase domain 2 (SK2) is linked to the phosphorylation of SERCA2a. In addition, the protein contains multiple N-terminal Ig-like domains and fibronectin type III (FnIII) domains that mediate protein–protein interactions and likely serve scaffolding functions. Conserved catalytic residues, including key aspartate residues within the active site of each kinase domain, have been identified, and a calmodulin-binding motif is present in the regulatory region of SK1. This multi-domain architecture supports both the enzymatic and formative roles of SPEG in muscle cells (hsieh2000striatedmusclepreferentially pages 3-5, grogan2020doublethetrouble pages 6-8, quan2019spegcontrolscalcium pages 5-7, luo2021striatedpreferentiallyexpressed pages 2-4).
6. Regulation  
   SPEG regulation occurs at several levels. The kinase domains of SPEG can undergo autophosphorylation, which is thought to modulate its catalytic activity. In cardiac muscle, upstream regulators such as protein kinase B (PKB) and calcium/calmodulin-dependent protein kinase II (CaMKII) further modify SPEG activity through phosphorylation of residues within the regulatory regions, particularly affecting the SK2 domain which is central to SERCA2a phosphorylation. In addition, alternative splicing produces distinct isoforms—SPEGα and SPEGβ in striated muscles and APEG-1 in vascular smooth muscle cells—with the latter being implicated in growth and differentiation signalling. The binding of SPEG to specific partners within the junctional membrane complex, such as RyR2, JPH2, and components of the myospryn complex, also contributes to its spatial regulation and substrate selection (hsieh2000striatedmusclepreferentially pages 5-6, grogan2020doublethetrouble pages 6-8, quan2019spegcontrolscalcium pages 7-9, luo2021striatedpreferentiallyexpressed pages 7-8).
7. Function  
   SPEG is central to the regulation of calcium homeostasis and structural integrity in muscle tissue. In cardiac and skeletal muscles, SPEG phosphorylates key proteins that govern excitation–contraction coupling. The phosphorylation of SERCA2a by the SK2 domain enhances its oligomerization and activity, thereby promoting efficient calcium reuptake into the sarcoplasmic reticulum. Concurrently, SPEG-mediated phosphorylation of RyR2 at serine 2367 serves to modulate calcium release, reducing diastolic calcium leak and maintaining proper rhythmic contraction. Phosphorylation of junctophilin-2 (JPH2) contributes to the stabilization of the transverse tubule system. Defects in SPEG function have been linked to severe muscle disorders, including centronuclear myopathy, dilated cardiomyopathy, and arrhythmogenic conditions such as atrial fibrillation. In arterial smooth muscle cells, the APEG-1 isoform (also previously designated as isoform 3) is expressed and has been implicated in the regulation of cell growth and differentiation, thereby influencing vascular remodeling and possibly contributing to the maintenance of vascular tone (quan2019spegcontrolscalcium pages 7-9, campbell2020lossofspeg pages 15-16, grogan2020doublethetrouble pages 8-9, luo2021striatedpreferentiallyexpressed pages 9-11, li2024integratedmulti‐omicsapproach pages 10-12).
8. Other Comments  
   No specific small-molecule inhibitors targeting SPEG have been identified in the current peer-reviewed literature. Mutations in SPEG, particularly those affecting the kinase domains, are associated with congenital muscle disorders such as centronuclear myopathy and dilated cardiomyopathy, as well as with arrhythmias in the heart. In addition, SPEG deficiency in cardiomyocytes has been linked to mitochondrial dysfunction, reduced ATP production, and increased oxidative stress. The APEG-1 isoform, which is expressed in vascular smooth muscle cells, may have a distinct role in regulating cellular growth and differentiation. These findings underscore the clinical relevance of SPEG in both striated and smooth muscle pathophysiology (campbell2020lossofspeg pages 15-16, li2024striatedpreferentiallyexpressed pages 14-15, luo2021striatedpreferentiallyexpressed pages 9-11).
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