1. Phylogeny  
   BRSK1, also known as SAD-B or Brain‐selective kinase 1, is a member of the AMP‐activated protein kinase (AMPK)–related kinase family and is classified within the larger serine/threonine (Ser/Thr) kinase superfamily. Members of this family are evolutionarily conserved across metazoans, with orthologs described in mammals as well as in lower organisms such as Caenorhabditis elegans and Drosophila; these kinases trace their lineage back to a common ancestral AMP‐activated kinase that has diversified in animal evolution (bright2008investigatingtheregulation pages 1-1, 1-2).
2. Reaction Catalyzed  
   BRSK1 catalyzes the phosphorylation reaction in which a phosphate group is transferred from adenosine triphosphate (ATP) to the hydroxyl group of a serine or threonine residue in target proteins. The overall chemical reaction can be represented as follows:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This classical kinase reaction underlies the post-translational modification processes regulated by BRSK1 (bright2008investigatingtheregulation pages 8-9).
3. Cofactor Requirements  
   The catalytic activity of BRSK1, like that of other serine/threonine kinases, is dependent on the presence of divalent metal ions which serve as essential cofactors. In general, magnesium ions (Mg²⁺) are required to coordinate ATP binding and to facilitate the phosphate-transfer reaction. This dependency on Mg²⁺ is a common feature among protein kinases and is central to the catalytic mechanism of BRSK1 (bright2008investigatingtheregulation pages 2-3).
4. Substrate Specificity  
   BRSK1 phosphorylates a number of downstream substrates that are crucial for neuronal polarization, cell cycle regulation, and centrosome duplication. Notably, BRSK1 is known to phosphorylate:  • CDC25B and CDC25C, which are key regulators of cell cycle progression by mediating dephosphorylation of cyclin-dependent kinases;  
    • MAPT/TAU, a microtubule-associated protein, where phosphorylation events (for example, reported at Thr-529 and Ser-579) modulate microtubule binding properties;  
    • RIMS1, a component implicated in synaptic vesicle regulation;  
    • TUBG1 and TUBG2 (gamma-tubulins), whose phosphorylation is involved in the control of centrosome duplication; and  
    • WEE1, a kinase that is inhibited upon phosphorylation at Ser-642, thereby affecting cell cycle checkpoints in postmitotic neurons.  
   Although no single consensus sequence has been definitively established for BRSK1 from the current context, these substrates contain target serine or threonine residues embedded within motifs that support efficient recognition and catalysis by BRSK1 (bright2008investigatingtheregulation pages 8-9).
5. Structure  
   BRSK1 displays a modular domain organization that is characteristic of the AMPK-related kinase family. The N-terminal region contains the canonical serine/threonine kinase domain, which encompasses several conserved motifs, including the nucleotide-binding GxGxxG motif located in the N-terminal lobe, the critical VAIK motif for ATP positioning, and the activation loop (T-loop) where phosphorylation at a conserved threonine residue (Thr189 in human BRSK1) is essential for catalytic activation. This kinase domain also harbors unique redox-sensitive cysteine residues; experimental studies using recombinant proteins have demonstrated that these cysteines can form intramolecular disulfide bonds under oxidative conditions, thereby modulating enzymatic activity (bendzunas2025redoxregulationand pages 5-7).

Following the catalytic domain is a ubiquitin-associated (UBA) domain. Although in many kinases the UBA domain is traditionally implicated in binding ubiquitin, in BRSK1 it is believed to function as a regulatory module that helps maintain an open conformation of the kinase and may also confer stability or influence subcellular localization. In addition, BRSK1 possesses a proline-rich region (PRR) and a kinase-associated (KA1) domain at its C-terminus; the KA1 domain typically contains an autoinhibitory sequence (AIS) that can interact with the kinase domain to modulate its activity. A distinctive structural feature of BRSK1 compared with canonical Ser/Thr kinases is the presence of a CPE motif in the activation segment instead of the more common APE motif. This substitution results in a unique arrangement of cysteine residues that are involved in reversible oxidation events, which add an additional layer of regulatory control under varying redox conditions (bendzunas2025redoxregulationand pages 5-7, 7-9).

The overall three-dimensional structure, as suggested by AlphaFold models and supported by biochemical studies, indicates that the central kinase domain forms the catalytic core, with its regulatory domains flanking this core to ensure proper spatial-temporal regulation. Key catalytic features include the phosphoacceptor site in the T-loop, a hydrophobic spine that stabilizes the active conformation, and a well-defined C-helix that is essential for coordinating the catalytic machinery. The redox-sensitive cysteine residues that are strategically located near the T-loop and within the CPE motif contribute to both the conformational flexibility and the redox-dependent modulation of kinase activity (bendzunas2025redoxregulationand pages 7-9).

1. Regulation  
   BRSK1 is subject to multiple regulatory inputs that converge to control its kinase activity in a spatial and temporal manner. One principal mechanism involves phosphorylation by the upstream kinase LKB1. LKB1, which is constitutively active, phosphorylates a conserved threonine residue (Thr189 in BRSK1) in the activation loop, a modification that is essential for enzyme activation and subsequent substrate phosphorylation (bright2008investigatingtheregulation pages 1-2, 8-9).

In addition to this phosphorylation event, BRSK1 is dynamically regulated by the cellular redox state. Several studies have demonstrated that reducing agents such as dithiothreitol (DTT) enhance BRSK1 kinase activity, whereas oxidizing conditions brought about by agents like hydrogen peroxide (H₂O₂) result in significant inhibition of its catalytic function. The underlying mechanism is based on the reversible oxidation of conserved cysteine residues within the kinase domain. These cysteines can form intramolecular disulfide bonds under oxidative conditions, which sterically hinder the proper arrangement of the catalytic segments and reduce enzyme activity; conversely, reduction of these disulfide bonds restores the active conformation of the kinase (bendzunas2025redoxregulationand pages 5-7, 7-9, 14-15).

This dual regulation—via phosphorylation on the T-loop and via cysteine oxidation—provides BRSK1 with a sensitive mechanism to integrate metabolic and redox signals in neuronal cells, thereby coordinating cellular responses to energy levels and oxidative stress without the need for additional upstream signals.

1. Function  
   BRSK1 plays a critical role in the regulation of several cellular processes, particularly in neurons where it is predominantly expressed. As a serine/threonine–protein kinase, BRSK1 phosphorylates a variety of substrates that are directly involved in the establishment and maintenance of neuronal polarity. For instance, phosphorylation of MAPT/TAU influences microtubule dynamics, which is essential for axon specification and synaptic function. In addition, BRSK1 phosphorylates CDC25B and CDC25C, which are key regulators of the cell cycle, thereby contributing to the checkpoint response during the UV-induced DNA damage response.

BRSK1 also phosphorylates WEE1 at Ser-642 in postmitotic neurons; this phosphorylation event down-regulates WEE1 activity and is associated with the maintenance of neuronal polarity. Another important substrate is represented by gamma-tubulin isoforms TUBG1 and TUBG2, whose phosphorylation by BRSK1 is fundamental for centrosome duplication and the proper translocation of gamma-tubulin complexes to the centrosome. Moreover, BRSK1 has been implicated in the regulation of neurotransmitter release through its phosphorylation of RIMS1 in synaptic vesicles, thereby affecting synaptic signaling in the central nervous system (bright2008investigatingtheregulation pages 8-9).

The tissue-specific expression of BRSK1 is highly enriched in the brain, where it coordinates several signaling pathways critical for neuronal development and function. By integrating cues from metabolic and redox signals via its unique regulatory mechanisms, BRSK1 acts as a pivotal node in pathways that regulate cell polarity, synaptic transmission, and cell cycle progression in neural tissues.

1. Other Comments  
   Currently, no highly selective inhibitors have been established specifically for BRSK1. However, research on inhibitors targeting related members of the AMPK-related kinase family suggests that compounds such as GW296115, which has been shown to inhibit BRSK2 in cellular studies, might serve as a starting point for the development of BRSK1 inhibitors (tamir2020gainoffunctiongeneticscreen pages 3-5). In addition, the dysregulation of BRSK1 activity has functional implications in neurodegenerative processes due to its role in TAU phosphorylation, as well as in cell cycle regulation through its effects on CDC25 phosphatases and WEE1. Although direct disease mutations in BRSK1 have not been extensively documented in the available literature, defects in upstream regulators such as LKB1 have been linked to various cancers. Thus, aberrant BRSK1 signaling may contribute to pathological conditions associated with defects in neuronal polarity and centrosome duplication (bright2008investigatingtheregulation pages 8-9, bendzunas2025redoxregulationand pages 7-9).
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