1. Phylogeny  
   Serine/threonine-protein kinase ATR, encoded by the ATR FRP1 gene (UniProt Q13535), belongs to the phosphatidylinositol 3‐kinase‐related kinase (PIKK) family, a large and evolutionarily conserved group of atypical protein kinases that includes ATM, DNA‐PK, mTOR, SMG1, and TRRAP (foote2015druggingatrprogress pages 1-2). Orthologs of ATR are widely distributed among eukaryotes, demonstrating its fundamental role in maintaining genome stability, and its evolutionary history has been traced back to common ancestral kinases present in the last eukaryotic common ancestor (LECA) (foote2015druggingatrprogress pages 2-4, rakshambikai2015typicalandatypical pages 29-36). Within the human kinome, ATR is grouped with other serine/threonine kinases that play central roles in the DNA damage response, and it is closely related to ATM and DNA–PK given their joint involvement in the cellular response to genotoxic stress (foote2015druggingatrprogress pages 1-2, moret2020aresourcefor pages 54-55). Its classification in the atypical protein kinase (aPK) fold group further distinguishes it from the more conventional eukaryotic protein kinases (ePKs) by virtue of its large size and unique regulatory domains (moret2020aresourcefor pages 54-55, attwood2021trendsinkinase pages 13-14).
2. Reaction Catalyzed  
   ATR functions as a serine/threonine kinase that catalyzes the phosphorylation reaction in which ATP donates its terminal phosphate group to a hydroxyl group on target protein substrates. In this reaction, ATP and the protein substrate yield ADP and a phosphorylated protein (with either serine or threonine residues modified) along with a proton (H⁺) as a by‐product (foote2015druggingatrprogress pages 1-2, foote2015druggingatrprogress pages 9-10).
3. Cofactor Requirements  
   The catalytic activity of ATR, similar to that of other serine/threonine protein kinases, necessitates the coordination of cofactors. In particular, the reaction requires ATP as the phosphate donor, and this process is facilitated by the presence of divalent cations, notably Mg²⁺, which help stabilize the ATP–enzyme complex and promote the transfer of the phosphate group to the substrate (foote2015druggingatrprogress pages 2-4, foote2015druggingatrprogress pages 5-6).
4. Substrate Specificity  
   ATR exhibits substrate specificity by preferentially phosphorylating serine and threonine residues that are immediately followed by a glutamine residue, conforming to the consensus sequence [ST]-Q (foote2015druggingatrprogress pages 1-2). This sequence specificity is characteristic of several DNA damage response kinases, ensuring that ATR targets a defined set of substrates involved in cell cycle checkpoint signaling and DNA repair (foote2015druggingatrprogress pages 1-2, blazquez2020potentialforprotein pages 1-2).
5. Structure  
   ATR is an exceptionally large protein with a modular structure composed of several distinct domains that coordinate its catalytic activity and regulatory interactions. The N-terminal region comprises multiple HEAT (Huntingtin, EF3, PP2A, TOR1) repeats that form elongated, solenoid-like structures and mediate protein–protein interactions essential for ATR recruitment to sites of DNA damage (foote2015druggingatrprogress pages 1-2, stach2013functionalanalysesof pages 53-58). Following the HEAT repeats, the FAT (FRAP-ATM-TRRAP) domain is present and contributes to maintaining the structural integrity and proper folding of the kinase (stach2013functionalanalysesof pages 53-58). Centrally located is the kinase domain, which adheres to the classic bilobal architecture found in eukaryotic protein kinases – a smaller N-terminal lobe primarily composed of β-sheets and a larger C-terminal lobe rich in α-helices. This catalytic domain contains key motifs, including the glycine-rich loop (G-loop) for ATP binding, the conserved DFG motif that coordinates a magnesium ion for catalysis, and an activation loop (A-loop) that undergoes phosphorylation-dependent conformational changes necessary for full enzymatic activity (foote2015druggingatrprogress pages 16-17, attwood2021trendsinkinase pages 7-9). The extreme C-terminal region harbors the FATC domain, a conserved motif essential for proper kinase function and stability (stach2013functionalanalysesof pages 53-58). Together, these domains create an organized structure wherein regulatory interactions are integrated with catalytic function, enabling ATR to respond to replication stress and DNA damage (foote2015druggingatrprogress pages 1-2, moret2020aresourcefor pages 54-55).
6. Regulation  
   ATR is tightly regulated by multiple mechanisms to ensure that its kinase activity is induced only under conditions of genotoxic stress. Activation occurs predominantly through the recruitment of ATR to sites of DNA damage by binding to replication protein A (RPA)-coated single-stranded DNA (ssDNA), a common intermediate during replication fork stalling or resection at double-strand break sites (foote2015druggingatrprogress pages 1-2, foote2015druggingatrprogress pages 17-18). The binding partner ATR-interacting protein (ATRIP) is essential for localizing ATR to these DNA structures and facilitating subsequent activation (foote2015druggingatrprogress pages 1-2). Additionally, mediator proteins such as TopBP1 enhance ATR activity through direct interactions that promote its active conformation (foote2015druggingatrprogress pages 14-16). Post-translational modifications, including phosphorylation events within the activation loop and other regulatory regions, modulate ATR’s activity and stability, while ubiquitylation and interactions with poly(ADP-ribose) and ubiquitin-related proteins (e.g., the recruitment of UBA1 by poly(ADP-ribose)) further influence its signaling efficacy (kumbhar2018recruitmentofubiquitinactivating pages 16-16, foote2015druggingatrprogress pages 10-11). These regulatory mechanisms collectively ensure that ATR is deployed only when necessary to safeguard genome integrity.
7. Function  
   ATR plays a crucial role as a DNA damage sensor and effector kinase in the cellular response to genotoxic stress. It is activated in response to various forms of DNA damage, including ionizing radiation, ultraviolet light, and replication fork stalling, thereby initiating a signaling cascade that culminates in cell cycle checkpoint activation (foote2015druggingatrprogress pages 1-2, foote2015druggingatrprogress pages 16-17). One of the primary substrates of ATR is checkpoint kinase 1 (CHK1), whose phosphorylation at specific serine residues (e.g., Ser-345) triggers cell cycle arrest and provides time for DNA repair processes to be executed (foote2015druggingatrprogress pages 17-18, foote2015druggingatrprogress pages 10-11). In addition to CHK1, ATR phosphorylates a variety of proteins involved in replication fork stabilization, DNA repair pathways, and chromatin remodeling, all of which contribute to the maintenance of genomic stability and cell survival under stress conditions (foote2015druggingatrprogress pages 1-2, foote2015druggingatrprogress pages 9-10). Loss or inhibition of ATR function has been shown to result in replication defects, accumulation of DNA breaks, and ultimately genomic instability, which underscores its essential role in both normal cellular physiology and the response to anticancer therapies (foote2015druggingatrprogress pages 17-18, foote2015druggingatrprogress pages 19-20).
8. Other Comments  
   A number of small molecule inhibitors targeting ATR have been developed with the aim of sensitizing cancer cells to DNA-damaging agents. Notable examples include VX-970 (also known as VE-822), AZ20, and AZD6738, which have demonstrated potent and selective inhibition of ATR kinase activity in preclinical cancer models (foote2015druggingatrprogress pages 12-14, foote2015druggingatrprogress pages 14-14). These inhibitors are particularly effective in tumors deficient in ATM or those exhibiting high levels of replication stress, thereby exploiting synthetic lethal interactions (foote2015druggingatrprogress pages 19-20). In addition to its role in cancer therapy, mutations in ATR are associated with Seckel Syndrome—a developmental disorder characterized by growth retardation and microcephaly—highlighting its importance in human development and organismal viability (foote2015druggingatrprogress pages 1-2, foote2015druggingatrprogress pages 17-18). While several ATR inhibitors are in various stages of clinical development, none have yet received regulatory approval, and ongoing research is focused on improving their pharmacological profiles and understanding their potential in combination regimens (attwood2021trendsinkinase pages 19-20, panzeca2023newindoleand pages 18-24).
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