1. Phylogeny  
   Tyrosine‐protein kinase Lyn is a member of the Src family kinases (SFKs), which belong to the non‐receptor tyrosine kinase group in the human kinome. Lyn is evolutionarily related to other SFK members such as c‐Src, Fyn, Hck, Blk, Lck, and Yes, and it is phylogenetically assigned to the Src B subgroup, sharing a common origin with these kinases that can be traced back to the early eukaryotic ancestors (ubau2013functionalcharacterizationof pages 15-18, huang2016directedevolutionof pages 1-2). Orthologs of Lyn and its related SFKs are found in vertebrates, consistent with the conserved nature of signaling modules established in the Last Eukaryotic Common Ancestor (LECA) (corwin2016decipheringhumancytoplasmic pages 13-16).
2. Reaction Catalyzed  
   Tyrosine-protein kinase Lyn catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to a tyrosine residue on substrate proteins. The chemical reaction can be summarized as:  
   ATP + [protein]-L-tyrosine → ADP + [protein]-L-tyrosine-phosphate + H⁺ (ubau2013functionalcharacterizationof pages 15-18, loris2007exploringstructureand pages 49-52).
3. Cofactor Requirements  
   The kinase activity of Lyn is dependent on the presence of divalent cations, with Mg²⁺ serving as a necessary cofactor in the catalytic transfer of phosphate from ATP to substrate proteins (loris2007exploringstructureand pages 49-52).
4. Substrate Specificity  
   Lyn phosphorylates substrate proteins by recognizing specific amino acid motifs surrounding target tyrosine residues. Although an exact consensus motif has not been exhaustively defined in the provided texts, biochemical analyses indicate a preference for substrates exemplified by the LYNtide peptide, where studies report a Km in the low micromolar range and demonstrably higher catalytic efficiency for Lyn compared to related kinases such as Syk (sun2022targetingproteinproteininteractions pages 125-130). Moreover, motif-based phosphorylation studies using yeast models and computational predictions indicate that Lyn, along with other Src family kinases, phosphorylates substrates within sequence contexts that include proline-rich flanking regions and specific surrounding amino acids; these motifs have been linked to downstream signaling components such as immunoreceptor tyrosine-based activation and inhibitory motifs (corwin2016decipheringhumancytoplasmic pages 152-155, corwin2016decipheringhumancytoplasmic pages 146-149).
5. Structure  
   Lyn is organized into several well-defined domains that are characteristic of SFKs. At the N-terminus, a short unique region contains myristoylation and palmitoylation sites that mediate membrane association and subcellular localization, particularly to cholesterol-rich lipid rafts (ubau2013functionalcharacterizationof pages 6-8, ubau2013functionalcharacterizationof pages 64-68). Adjacent to the unique region is the Src homology 3 (SH3) domain, which plays a critical role in mediating protein–protein interactions by binding to proline-rich motifs; this domain has been a target for engineered affinity reagents such as FN3 monobodies that exhibit high specificity for Lyn (huang2016directedevolutionof pages 1-2, huang2016directedevolutionof pages 6-7). Following the SH3 domain is the SH2 domain, which recognizes phosphorylated tyrosine residues on partner proteins, thereby facilitating the assembly of signaling complexes (ubau2013functionalcharacterizationof pages 15-18, corwin2016decipheringhumancytoplasmic pages 16-18). The C-terminal region comprises the kinase catalytic (SH1) domain, which contains essential catalytic features such as the activation loop, C-helix, and a regulatory tail that harbors a key inhibitory tyrosine residue (Tyr530 in the human enzyme) and an activation loop tyrosine (Tyr419) whose phosphorylation status modulates kinase activity (ubau2013functionalcharacterizationof pages 15-18, loris2007exploringstructureand pages 138-143). Overall, the three-dimensional structure of Lyn, as predicted by crystal structures and AlphaFold models, reveals a bilobal kinase domain typical of protein kinases with a conserved ATP-binding cleft and regulatory elements that dictate its allosteric activation (loris2007exploringstructureand pages 49-52).
6. Regulation  
   Lyn activity is finely regulated through multiple mechanisms. Key regulatory post-translational modifications include phosphorylation events; phosphorylation of the C-terminal tyrosine residue (Tyr530) by C-terminal Src kinase (Csk) promotes an auto-inhibited conformation, while autophosphorylation of the activation loop tyrosine (Tyr419) facilitates full kinase activation (ubau2013functionalcharacterizationof pages 15-18, corwin2016decipheringhumancytoplasmic pages 73-76). Additionally, Lyn is subject to dephosphorylation by protein tyrosine phosphatases such as PTPα, which can subsequently activate the kinase (ubau2013functionalcharacterizationof pages 15-18). Ubiquitination by E3-ubiquitin ligases such as CBL further contributes to its regulation by marking activated kinases for proteasomal degradation (ubau2013functionalcharacterizationof pages 18-21, corwin2016decipheringhumancytoplasmic pages 10-13). Moreover, Lyn’s subcellular localization, dictated by lipid modifications, permits its compartmentalized function; its proper targeting to, or aberrant distribution from, lipid rafts critically influences its ability to engage in specific signaling interactions, such as those downstream of the B-cell receptor (ubau2013functionalcharacterizationof pages 64-68, ubau2013functionalcharacterizationof pages 70-73). Interaction with adaptor proteins, and the consequent phosphorylation of immunoreceptor tyrosine-based inhibitory motifs (ITIMs), recruits phosphatases including SHP-1, SHP-2, and SHIP-1 which act as negative regulators of signaling cascades (ubau2013functionalcharacterizationof pages 89-91, corwin2016decipheringhumancytoplasmic pages 152-155).
7. Function  
   Lyn plays a central role in the regulation of both innate and adaptive immune responses. It is predominantly expressed in hematopoietic cells, with high expression in B lymphocytes, where it is both necessary for initiating B-cell receptor (BCR) signaling and for mediating the subsequent down-regulation and termination of the response (ubau2013functionalcharacterizationof pages 1-5, ubau2013functionalcharacterizationof pages 54-58). Lyn phosphorylates a broad range of substrates, including proteins involved in B-cell activation such as CD79A, CD79B, CD19, and CD22, as well as downstream signaling effectors like SYK, BTK, and components of the MAPK cascade (ubau2013functionalcharacterizationof pages 73-76, corwin2016decipheringhumancytoplasmic pages 152-155). In addition to its critical function in B-cell signaling, Lyn is involved in the regulation of integrin signaling, responses to growth factors and cytokines, and plays an important role in hematopoiesis, platelet function, and the inflammatory response to bacterial lipopolysaccharide (ubau2013functionalcharacterizationof pages 68-70, sun2022targetingproteinproteininteractions pages 79-82). It is also implicated in the control of cell survival, proliferation, and apoptosis across various cell types, acting both as a positive and as a negative modulator depending on cellular context. Lyn’s downstream signaling involves regulation of phosphatidylinositol 3-kinase (PI3K) activity, subsequent activation of AKT1, and modulation of the MAP kinase cascade, which includes kinases such as ERK1/2 and JNKs (ubau2013functionalcharacterizationof pages 54-58, corwin2016decipheringhumancytoplasmic pages 178-180). Through its ability to phosphorylate inhibitory motifs on receptors or adaptors, Lyn recruits phosphatases that attenuate signal transduction, thus contributing to immune self-tolerance and regulating inflammatory responses (ubau2013functionalcharacterizationof pages 89-92, chylek2014phosphorylationsitedynamics pages 15-16).
8. Other Comments  
   Several inhibitors have been used experimentally to target Lyn kinase activity. For example, Dasatinib, an FDA-approved tyrosine kinase inhibitor, exhibits potent inhibition of Lyn with an IC₅₀ in the low nanomolar range (huang2016directedevolutionof pages 17-18). Other compounds such as SU6656, a Src family selective inhibitor, have been employed in functional studies to assess Lyn’s role in leukemic cell proliferation, notably in acute lymphoblastic leukemia (ubau2013functionalcharacterizationof pages 38-42, ubau2013functionalcharacterizationof pages 73-76). Disease associations for Lyn include its involvement in various hematologic malignancies such as acute lymphoblastic leukemia and chronic lymphocytic leukemia, as well as reported implications in several solid tumors where aberrant expression or mislocalization can affect cellular proliferation and survival (ubau2013functionalcharacterizationof pages 50-54, ubau2013functionalcharacterizationof pages 68-70). Additionally, altered Lyn signaling has been linked to defects in immune regulation and inflammatory responses, which are central to autoimmune conditions (ubau2013functionalcharacterizationof pages 12-15, corwin2016decipheringhumancytoplasmic pages 10-13).
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