Abstract The phosphatidylinositol (PI)-3 kinase (PI3K) pathway plays a central role in regulating many biological processes via the generation of the key second messenger PI-3,4,5-trisphosphate (PI-3,4,5-P3). This membrane-associated phospholipid, which is rapidly, albeit transiently, synthesized from PI-4,5-P2 by PI3K in response to a diverse array of extracellular stimuli, attracts pleckstrin homology (PH) domain-containing proteins to membranes to mediate its many effects. To ensure that the activation of this pathway is appropriately suppressed/terminated, the ubiquitously expressed tumor suppressor PTEN hydrolyzes PI-3,4,5-P3 back to PI-4,5-P2 while the 145-kDa hemopoietic-restricted SH2-containing inositol 5′-phosphatase, SHIP (also known as SHIP1), the 104-kDa stem cell-restricted SHIP (sSHIP) and the more widely expressed 150-kDa SHIP2 hydrolyze PI-3,4,5-P3 to PI-3,4-P2. In this review we will concentrate on the properties of the three SHIPs, with special emphasis being placed on the role that SHIP plays in cytokine-induced signaling.

Abbreviations BCR: B cell receptor · BMMCs: Bone marrow derived mast cells · Epo: Erythropoietin · ES Cells: embryonic stem cells · GM-CSF: Granulocyte macrophage colony stimulating factor · IL-3: Interleukin-3 · IP4: Inositol-1,3,4,5-tetrakisphosphate · M-CSF: Macrophage colony stimulating factor · PH: Pleckstrin homology · PI3K: Phosphatidylinositol-3 kinase · PI-3,4,5-P3: Phosphatidylinositol-3,4,5-trisphosphate · SHIP: Src homology 2 containing inositol 5′-phosphatase ·
5'-phosphatase · SF: Steel Factor · sSHIP: Stem cell SHIP · TCR: T cell receptor · TPO: Thrombopoietin · WT: Wild type

Introduction

It is now well established that the phosphatidylinositol (PI)-3 kinase (PI3K) pathway plays a central role in regulating many cellular decisions. These include, depending on the cell type, survival, adhesion, movement, proliferation, differentiation, and end cell activation (Krystal 2000). A key second messenger in this pathway is the membrane-associated PI-3,4,5-trisphosphate (PI-3,4,5-P3), which is present at low levels in unstimulated cells but is rapidly synthesized from PI-4,5-P2 by PI3K in response to a diverse array of extracellular stimuli. This transiently generated PI-3,4,5-P3 attracts pleckstrin homology (PH) domain-containing proteins to the plasma membrane to mediate its effects (Rameh and Cantley 1999; Huber et al. 1999). To ensure that the activation of this pathway is appropriately suppressed/terminated, the ubiquitously expressed tumor suppressor PTEN hydrolyzes PI-3,4,5-P3 back to PI-4,5-P2 (Maehama and Dixon 1998; Stambolic et al. 1998) while the 145-kDa hemopoietic-restricted SH2-containing inositol 5'-phosphatase, SHIP (also known as SHIP1; Huber et al. 1999), the 104-kDa stem cell-restricted SHIP (sSHIP; Tu et al. 2001) and the more widely expressed 150-kDa SHIP2 (Pesesse et al. 1997; Wisniewski et al. 1999; Pesesse et al. 1998; Muraille et al. 1999) break it down to PI-3,4-P2 (Fig. 1A). The fact that almost 50% of human cancers contain biallelic inactivating mutations of PTEN (Cantley and Neel 1999) highlights the importance of these phospholipid phosphatases in preventing uncontrolled cell growth. In this review we concentrate on the properties of the three SHIPs, with special emphasis on the role that SHIP plays in cytokine-induced signaling.

The properties of SHIP, sSHIP, and SHIP2

In 1996, we (Damen et al., Lioubin et al., and Kavanaugh et al.) independently cloned the cDNA of a 145-kDa intracellular protein that became both tyrosine phosphorylated and associated with the adaptor protein, Shc, after cytokine, growth factor, or immunoreceptor stimulation of hemopoietic cells (Liu et al. 1994). Its predicted amino acid sequence revealed an amino-terminal SH2 domain that binds preferentially to the sequence pY(Y/D)X(L/I/V) (Osborne et al. 1996), a centrally located 5'-phosphatase domain that selectively hydrolyzes PI-3,4,5-P3, and inositol-1,3,4,5-tetrakisphosphate (IP4) in vitro (Damen et al. 1996) and in vivo (Huber et al. 1999a; Valderrama-Carvajal et al. 2002), two NPXY sequences that, when phosphorylated, bind the phosphotyrosine binding (PTB) domains of Shc (Huber et al. 1999), Dok1 (Sattler et al. 2001), and Dok2 (Tamir et al. 2000), and a critical proline rich C-terminus that binds a subset of SH3-containing proteins (Wisniewski et al. 1999).

During murine development, SHIP is first detectable, by RT-PCR, in 7.5-day postcoitus mouse embryos (coincident with and dependent upon the onset of hemopoiesis) and its protein expression pattern in the embryo appears restricted to hemopoietic cells (Liu et al. 1998). In the adult mouse, SHIP protein expression is also restricted to hemopoietic cells (and to spermatids; Liu et al. 1998). Also noteworthy is that SHIP protein expression ap-