



Fig. 3 A potential model for CD19 "processive amplification" of Lyn activity.⁵⁶ **(A)** Following BCR cross-linking, Lyn and other Src-family PTKs become activated. Lyn then phosphorylates tyrosines within the ITAMs of CD79a and CD79b. Syk is then recruited to tandem phosphotyrosines and becomes activated. **(B)** Following BCR and/or CD19 cross-linking, Lyn phosphorylates exposed CD19-Y⁵¹³. **(C)** Lyn then binds phosphorylated CD19-Y⁵¹³ via its SH2 domain, and phosphorylates CD19-Y⁴⁸² through "processive phosphorylation". Following phosphorylation, the closed structure of the CD19 cytoplasmic domain is relaxed, exposing other potential sites for phosphorylation. **(D)** Phosphorylated CD19-Y⁴⁸² recruits another Lyn molecule, which leads to Lyn transphosphorylation and/or autophosphorylation and the formation of a Src-family PTK amplification loop. This leads to phosphorylation of CD19-Y³⁹¹ and Vav recruitment. **(E)** Vav may then be phosphorylated by activated Lyn, leading to the activation of downstream signaling pathways and MAPK activation. Once activated, Lyn may lose its SH2 domain-binding affinity and release CD19, thereby allowing the recruitment of unactivated Lyn into the CD19-mediated Src-family PTK amplification loop. Additionally, Lyn release from CD19 may allow the tandem SH2 domains of PI 3-kinase to interact with CD19-Y⁴⁸² and CD19-Y⁵¹³. **(F)** CD19 amplification of Src-family PTK activation (most likely Lyn) leads to optimal CD22 phosphorylation. Tyrosine phosphorylated CD22 in turn recruits SHP1, which may regulate CD19 or its associated kinases by dephosphorylation.

biological properties attributed to CD19.⁵⁶ We call this process "processive amplification". That CD19 directly amplifies Lyn activation was revealed using *in vitro* kinase assays with purified Lyn in the presence or absence of recombinant CD19.²¹ Incubation of Lyn

with ATP results in Lyn autophosphorylation. However, adding CD19 cytoplasmic domain protein to a Lyn kinase assay dramatically upregulates both CD19 and Lyn phosphorylation. CD19 also upregulates Lyn phosphorylation of exogenous substrate. Results iden-