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Research Article

Formation of long and winding nuclear F-actin bundles by nuclear c-Abl tyrosine kinase

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ABSTRACT

The non-receptor-type tyrosine kinase c-Abl is involved in actin dynamics in the cytoplasm. Having three nuclear localization signals (NLSs) and one nuclear export signal, c-Abl shuttles between the nucleus and the cytoplasm. Although monomeric actin and filamentous actin (F-actin) are present in the nucleus, little is known about the relationship between c-Abl and nuclear actin dynamics. Here, we show that nuclear-localized c-Abl induces nuclear F-actin formation. Adriamycin-induced DNA damage together with leptomycin B treatment accumulates c-Abl into the nucleus and increases the levels of nuclear F-actin. Treatment of c-Abl-knockdown cells with Adriamycin and leptomycin B barely increases the nuclear F-actin levels. Expression of nuclear-targeted c-Abl (NLS-c-Abl) increases the levels of nuclear F-actin even without Adriamycin, and the increased levels of nuclear F-actin are not inhibited by inactivation of Abl kinase activity. Intriguingly, expression of NLS-c-Abl induces the formation of long and winding bundles of F-actin within the nucleus in a c-Abl kinase activity-dependent manner. Furthermore, NLS-c-AblΔC, which lacks the actin-binding domain but has the full tyrosine kinase activity, is incapable of forming nuclear F-actin and in particular long and winding nuclear F-actin bundles. These results suggest that nuclear c-Abl plays critical roles in actin dynamics within the nucleus.

Introduction

Non-receptor-type tyrosine kinases act as cytoplasmic signaling molecules and play important roles in various cellular events, such as cell proliferation, differentiation, migration, and apoptosis. The non-receptor-type tyrosine kinase c-Abl is composed of a Src homology (SH) 3 domain, an SH2 domain, a kinase catalytic domain, and the unique last exon region. The last exon region is important for the localization and functions of c-Abl, because it contains three nuclear localization signals (NLSs), a nuclear export signal (NES), a DNA-binding domain, and an actin-binding domain [1,2]. The c-Abl actin-binding domain consists of the monomeric actin (globular actin, G-actin)- and polymeric actin (filamentous actin, F-actin)-binding domains, which cooperatively bundle F-actin in vitro [3]. Cytoplasmic c-Abl is known to play roles in actin dynamics, including actin polymerization and F-actin assembly, in the cytoplasm [4,5].

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Several tyrosine kinases and phosphatases are involved in nuclear events [6,7]. Our previous studies showed that Lyn, a member of non-receptor-type Src-family tyrosine kinases (SFKs), is present in the nucleus although Lyn does not seem to have any NLSs [8–10]. Nuclear localization of Lyn is enhanced by inhibition of its kinase activity, Crm1-dependent nuclear export or lipid modifications [9]. Unlike SFKs, c-Abl has three NLSs and an NES, which enable c-Abl to shuttle between the cytoplasm and the nucleus [11]. DNA damage stimulates nuclear translocation of c-Abl, and nuclear c-Abl is involved in DNA damage responses through its activation mediated by ATM-dependent phosphorylation [12–15].

Actin, a major component of the cytoskeleton, is highly abundant in the cytoplasm. Nonetheless, actin, in both monomeric and polymeric