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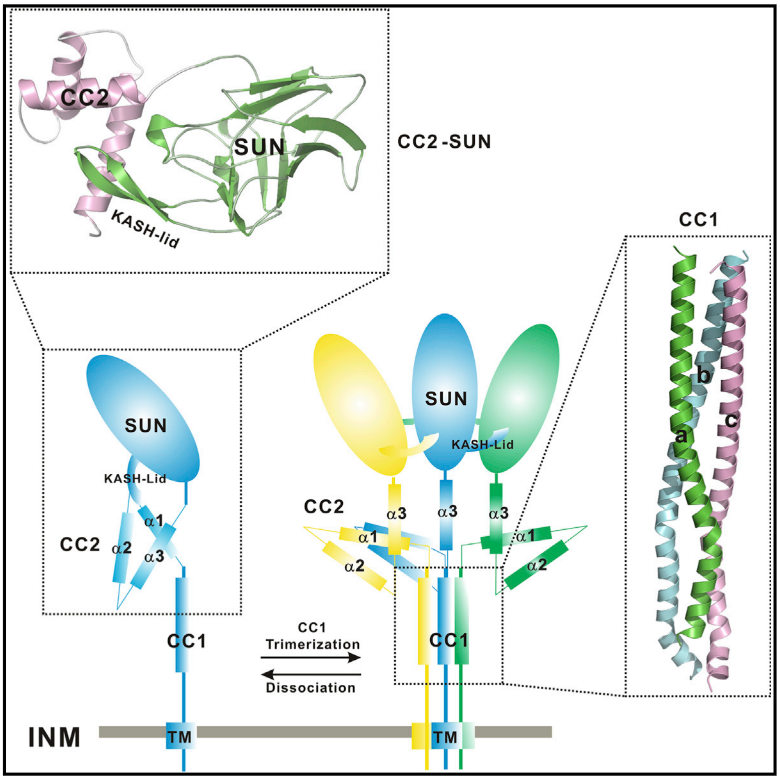
Coiled-Coil Domains of SUN Proteins as Intrinsic Dynamic Regulators

Graphical Abstract



Highlights

- The two coiled-coil domains of SUN2 exhibit distinct oligomeric states
- CC2 forms a three-helix bundle to lock the SUN domain in an inactive conformation
- CC1 is a trimeric coiled coil for the trimerization and activation of the SUN domain
- The two coiled-coil domains of SUN2 act as the intrinsic dynamic regulators

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In Brief

SUN proteins contain at least one predicted coiled-coil domain preceding the SUN domain. Nie et al. determine the crystal structures of the different fragments including the coiled-coil and SUN domains from SUN2, which provide the molecular mechanism underlying the internal coiled-coil-mediated regulation of SUN proteins.

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Coiled-Coil Domains of SUN Proteins as Intrinsic Dynamic Regulators

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SUMMARY

SUN proteins are the core components of LINC complexes that span across the nuclear envelope for nuclear positioning and migration. SUN proteins contain at least one predicted coiled-coil domain preceding the SUN domain. Here, we found that the two coiled-coil domains (CC1 and CC2) of SUN2 exhibit distinct oligomeric states. CC2 is a monomer in solution. The structure of the CC2-SUN monomer revealed that CC2 unexpectedly folds as a three-helix bundle that interacts with the SUN domain and locks it in an inactive conformation. In contrast, CC1 is a trimer. The structure of the CC1 trimer demonstrated that CC1 is an imperfect coiled coil for the trimerization and activation of the SUN domain. Modulations of CC1 and CC2 dictate different oligomeric states of CC1-CC2-SUN, which is essential for LINC complex formation. Thus, the two coiled-coil domains of SUN2 act as the intrinsic dynamic regulators for controlling the SUN domain activity.

INTRODUCTION

The nuclear envelope (NE) is a double-membrane structure that includes the inner and outer nuclear membranes (INM and ONM, respectively), and serves as a physical barrier to partition the nuclear and cytoplasmic environments (Hetzer, 2010; Shimi et al., 2012; Wilson and Berk, 2010). More than 60 putative integral membrane proteins have been found to reside in either the INM or the ONM to decorate the NE and secure the structural integrity (Schirmer et al., 2003). Moreover, these NE-resident proteins often function together to form protein complexes that span across the NE and connect the nuclear lamina to the cytoskeleton, and thus are referred to as linkers of nucleoskeleton and cytoskeleton (LINC) (Razafsky and Hodzic, 2009; Starr and Fridolfsson, 2010).

LINC complexes are formed by coupling of KASH (Klarsicht, ANC-1, and Syne/Nesprin Homology) and SUN (Sad1 and UNC-84) proteins from the ONM and INM, respectively (Crisp et al., 2006). KASH proteins are featured with a single transmembrane helix and a short C-terminal tail penetrating the perinuclear space (together known as the KASH domain) (Starr and Fischer, 2005; Wilhelmsen et al., 2006). The N-terminal regions of KASH proteins are exposed in the cytoplasm, where they can associate with the cytoskeleton (Luxton and Starr, 2014; Mellad et al., 2011). SUN proteins harbor at least one transmembrane segment and a C-terminal family-specific SUN domain that can bind to the KASH domain within the lumen of the NE (Starr and Fridolfsson, 2010; Tzur et al., 2006). In contrast to KASH proteins, the N-terminal regions of SUN proteins are exposed in the nucleoplasm and contain signature motifs that are required for interacting with the nuclear lamina (Gruenbaum et al., 2005; Haque et al., 2006). Thus the formation of LINC complexes by KASH and SUN proteins at the NE establishes the physical linkage between the cytoskeleton and nuclear lamina, which is instrumental for the mechanical force transmission from the cytoplasm to the nuclear interior, and is essential for cellular processes such as nuclear positioning and migration, centrosome-nucleus anchorage, and chromosome dynamics (Burke and Roux, 2009; Chang et al., 2015; Hiraoka and Dernburg, 2009; Zhou and Hanna-Rose, 2010). In mammals, LINC complexes can be assembled by at least four KASH proteins (Syne/Nesprin-1 to -4) and two widely expressed SUN proteins (SUN1 and SUN2) (Mellad et al., 2011; Starr and Fridolfsson, 2010). Defects of these proteins are also related to a broad spectrum of muscle pathologies (e.g., Emery-Dreifuss muscular dystrophy and dilated cardiomyopathy) and neuronal disorders (such as lissencephalies) (Cartwright and Karakesisoglou, 2014; Fridkin et al., 2009; Mejat and Misteli, 2010).

Recognition between the SUN and KASH domains in the perinuclear space is pivotal for the formation of LINC complexes (Sosa et al., 2013; Tapley and Starr, 2013). Recent structural studies of the SUN domain of SUN2 demonstrated that it adopts a β-sandwich fold with a long flexible loop (namely, the KASH-lid) (Sosa et al., 2012; Zhou et al., 2012). A short segment preceding the SUN domain forms a parallel three-stranded coiled coil to drive the formation of a homo-trimer (Sosa et al., 2012). The structure of the LINC (SUN-KASH) complex further revealed that the flexible KASH-lid in the apo-SUN domain becomes well folded in the complex and forms a β hairpin, which intimately pairs with the KASH domain and anchors it in the protomer interfaces of the SUN domain homo-trimer (Sosa et al., 2012; Wang et al., 2012). In addition, the extreme C-terminal proline-rich tail of the KASH domain inserts into a tailor-made pocket within the SUN domain (Sosa et al., 2012). Thus, the extensive multivalent interactions between the SUN and KASH domains