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The architecture of the BubR1 tetratricopeptide tandem repeat defines a protein motif underlying mitotic checkpoint-kinetochore communication

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The accurate and timely transmission of the genetic material to progeny during successive rounds of cell division is sine qua non for the maintenance of genome stability. Eukaryotic cells have evolved a surveillance mechanism, the mitotic spindle assembly checkpoint (SAC), to prevent premature advance to anaphase before every chromosome is properly attached to microtubules of the mitotic spindle. The architecture of the KNL1-BubR1 complex reveals important features of the molecular recognition between SAC components and the kinetochore. The interaction is important for a functional SAC as substitution of BubR1 residues engaged in KNL1 binding impaired the SAC and BubR1 recruitment into checkpoint complexes in stable cell lines. Here we discuss the implications of the disorder-to-order transition of KNL1 upon BubR1 binding for SAC signaling and propose a mechanistic model of how BUBs binding may affect the recognition of KNL1 by its other interacting partners.

Keywords: Bub1, BubR1, KNL1, BubR1-KNL1, BubR1-Blinkin complex, spindle assembly checkpoint, kinetochore, tetratricopeptide repeat motif, chromosome instability, mitosis

Abbreviations: spindle assembly checkpoint, SAC; KNL1/Mis12/Ndc80 complexes network, KMN; tetratricopeptide repeat motif, TPR; anaphase-promoting complex or cyclosome, APC/C

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The spindle assembly checkpoint (SAC) is an evolutionarily conserved and essential self-regulatory mechanism of the eukaryotic cell cycle that prevents defects in the segregation of sister chromatids during mitosis.[1,2] Proper sister chromatid separation requires that microtubules of the mitotic spindle are attached correctly to the kinetochore, the large protein structure established on the centromere region of each chromatid. An outer ten-component kinetochore complex referred to as the KMN network (KNL1-Mis12-Ndc80 network) makes direct contact to microtubules and integrates microtubule binding with SAC activity. The SAC triggers anaphase delay in response to kinetochores incorrectly or not attached to the mitotic spindle. The large multi-domain protein kinases Bub1, BubR1 and Mps1 and the proteins Mad1, Mad2 and Bub3 are central components of the SAC that localize at incorrectly attached kinetochores. Mitotic checkpoint components display different dynamics at the kinetochore: Mad1 and Bub1 are stable components while BubR1, Mps1 and Mad2 are transient.[1,2] The kinetochore localization of SAC components is generally considered important for a proper checkpoint and stimulates the binding of Mad2 and the BubR1-Bub3 complex to Cdc20, thus leading to its inhibition. Cdc20 is an activator of the Anaphase Promoting Complex (APC/C), which is a large E3 ubiquitin ligase responsible for targeting Securin and Cyclin B1 for degradation leading to sister chromatid separation and mitotic exit, respectively.[3,4]

In addition to their functions in the checkpoint, Mps1, Bub1 and BubR1 play a role in establishing proper kinetochore-microtubule interactions.[5,6] Whether multiple binding sites exist on the kinetochore for these checkpoint components to perform their dual role is not clear. For instance, BubR1 interacts with the kinetochore components KNL1 and Cenp-E whereas electron microscopy (EM) data suggest multiple binding sites for BubR1 in the kinetochore and FRAP experiments indicate distinct pools of BubR1.[7,8] The fact that RNAi depletion of KNL1 but not that of CENP-E leads to BubR1

mislocalization indicates that KNL1 is the major binding partner for BubR1 at the kinetochore.[9] Furthermore, Bub1 and BubR1 can both form a complex with Bub3, a protein that also plays a role in kinetochore binding. Interestingly, the interacting partner(s) of Bub3 in the kinetochore is (are) not known. Despite the fact that there are many similarities in the mode of binding of Bub1 and BubR1 to the kinetochore, the dynamics at the kinetochore of the two proteins suggest that their binding is likely to be regulated differently.[10] The crystal structure of a BubR1-KNL1 complex that we have determined recently provides insights into this process and is the focus of the present report.

The kinetochore protein KNL1 (also often referred to as Blinkin, Spc105, AF15Q14 and CASC5)[11-13] is a predominantly intrinsically disordered protein that forms part of the KNL1/Mis12/Ndc80 (KMN) network and functions as a docking platform for multiple substrates. For instance, KNL1 C-terminal region interacts with the Nsl1 and Dsn1 components of the Mis12 complex[11,14] whereas its N-terminal region binds to the tetratricopeptide (TPR) motif of Bub1 and BubR1, an interaction that links the SAC with the KMN network. Furthermore, the N-terminal region recruits Protein Phosphatase 1 (PP1) to kinetochores, an interaction that is required to silence the SAC. Depletion of KNL1 of higher organisms by RNAi causes severe chromosome segregation defects that closely resemble the phenotypes associated with Bub1 and BubR1 protein exhaustion.[11,15]

The N-terminal of BubR1 is a domain organized as a triple tandem arrangement of the TPR motif, a protein motif defined by a consensus of 34 amino acids that are organized in a helix-loop-helix. The three TPR units of BubR1 (and Bub1) share features typical of other TPR motifs such as the presence of small and large hydrophobic residues located at specific positions within the helix-loop-helix and the assembly of the TPR units into a relatively extended structure to form a regular series of antiparallel α-helices rotated relative to one another by a constant 24 degrees. The uniform arrangement of neighboring α-helices gives rise to the formation of a right-handed superhelical structure with a continuous concave surface on one side and a contrasting convex surface on the other. Nevertheless, residues identified as well conserved in many TPRs[16] are poorly conserved in TPR Bub1 and TPR BubR1 from different species,[12] thus indicating that important deviations from the canonical 34-residue TPR motif are tolerated in these proteins. Essential for the stability of TPR tandem arrays are short-range and long-range interactions,[17] the disruption of which largely accounts for the instability of N-terminal truncated mutants of human Bub1 and BubR1[18] and yeast BubR1 (commonly referred to as Mad3).[19]

The crystal structure of a chimeric protein in which the TPR-containing region of human BubR1 was fused to the KNL1 fragment that binds BubR1 has been solved at 2.2 Å resolution. The structure revealed that TPR BubR1 undergoes little conformational change upon KNL1 binding. NMR experiments, which are exquisitely sensitive to chemical environment and local conformation, confirmed that the chimeric construct mimics the native BubR1-KNL1 interaction. For instance, the HSQC spectrum of the bound state and that of the chimera are essentially identical.[20] Furthermore, analysis of the chemical shift index revealed non-random coil shifts for residues of the KNL1 helix that is formed upon complex formation.[20] Although the architecture of the KNL1-BubR1 complex shows unique features when compared with the mode of ligand binding of TPRs that show high structure similarity with TPR Bub1 and TPR BubR1 (**Fig. 1A**), the recurrent use of residues defining the concave surface of structure-related TPRs[21] and the various roles of Bub1 and BubR1 in SAC signaling[22,23] suggest that TPRs of the latter proteins might contain more than one protein binding site (**Fig. 1B**). Such possibility seems particularly attractive in the case of BubR1 as its N-terminal region contains a highly conserved KEN box motif that binds Cdc20, an interaction that is essential for inhibition of the APC/C complex.[24-26] The N-terminal KEN box motif is predicted to be located within a region of low structural complexity that precedes the TPR tandem arrangement. Although it is unclear if, in addition to BubR1 residues defining the KEN box motif, those defining the TPR motif also participate in Cdc20 binding, some recent reports lend support to this notion.

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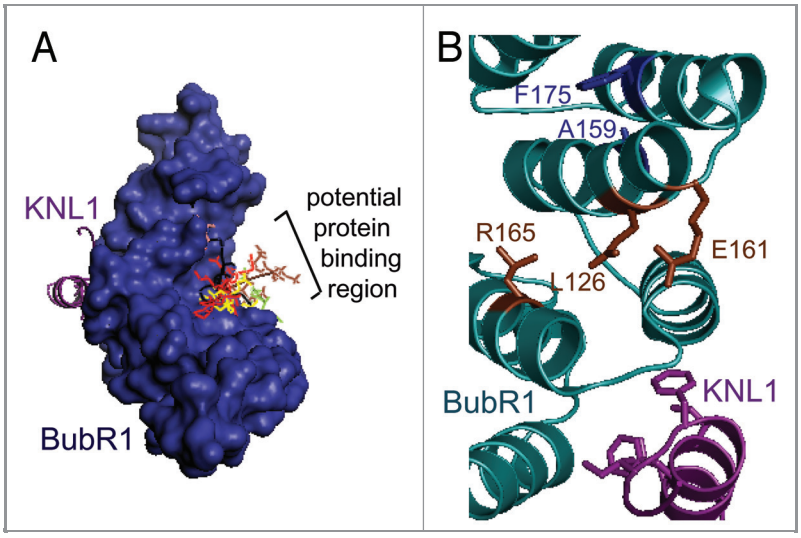

Figure 1. (A) A second protein-protein interaction region can exist in TPR Bub1 and/or TPR BubR1. (B) Cooperative interactions are established in the BubR1-KNL1 complex. Residue substitutions that compromise the stability of the TPR motif such as A159W and F175G also abrogate binding to Cdc20, Mad2 and the APC/C. In contrast, mutations that impair KNL1 binding such as L126A and E161A/R165A without affecting protein stability are able to bind Cdc20, Mad2 and the APC/C with similar affinity as the wild-type protein.

For instance, an independent study has shown that structure integrity of the TPR domain is required for the efficient binding of BubR1 to a Mad2-Cdc20 subcomplex.[27] More importantly, BubR1 mutations that compromise the stability of the TPR motif such as A159W and F175G also abrogate binding to Cdc20, Mad2 and the APC/C. In contrast, BubR1 mutations that impair KNL1 binding such as L126A and E161A/R165A do not affect protein stability and are also able to bind Cdc20, Mad2 and the APC/C with the same affinity as the wild-type protein. Because the A159W and F175G mutations but not L126A and E161A/R165A fail to restore mitotic timing defects upon BubR1 RNAi treatment, it was suggested that KNL1 binding was not required for BubR1 kinetochore localization or SAC function.[27] This interpretation is in conflict with our data in which we have observed that single substitution of BubR1 residues L126, E161, and R165 by alanine weakened the interaction but did not abolish it completely.[28] Our more recent yeast two-hybrid data and peptide mapping analysis coupled with ITC and mass spectrometry, in vivo studies in stable cell lines, NMR and X-ray crystallography lend further support to this notion.[29] For instance, the crystal structure of the complex revealed that the interaction of KNL1 (208–226) with TPR BubR1 is derived from extensive complementary hydrophobic interfaces implicating KNL1 residues I213, F215, F218, I219 and L222. These residues define a novel motif (I_{213}-x-*F*-x-x-*F*-*I*-x-*R*-L_{222}) that is essential for binding BubR1. KNL1 residue R221 contributes to the interaction through the establishment of salt bridges with BubR1 residues E103 and E107. In stable isogenic HeLa cell lines the specific interference with the interaction between KNL1 and N-terminal BubR1 leads to defects in the SAC and the impairment of BubR1 binding to Cdc20.[29] The fact that BubR1 L128A/L131A and Y141A/L142A still localize to the kinetochore and that these mutants bind KNL1 mimic peptides with much lower affinity than BubR1 wild type, indicate that a productive BubR1-KNL1 interaction involves multiple sites of contact or that BubR1 has several independent binding sites on the kinetochore. We have proposed that complex formation underlies a sequential zipper or Velcro mechanism in which KNL1 residues I213, F215, F218 and I219 dock into the BubR1 pockets before the residue R221 establishes a salt bridge with BubR1 E107. An important implication of such cooperative interactions is that they may lead to increased specificity and more sensitive regulation.

An intriguing possibility is that upon binding BubR1, Bub3 also contributes to the interaction with KNL1. Such a scenario would explain the early observation that a functional Bub3 binding site is required for kinetochore localization of BubR1.[30] However, it is currently unclear whether Bub3 makes direct contacts to KNL1 or binds to another kinetochore component. It can be anticipated that advances in super-resolution microscopy combined with defined point and deletion mutations of BubR1 and other SAC and kinetochore components will help to determine the precise contribution of TPR BubR1 and Bub3 in BubR1 kinetochore recruitment and the various roles of BubR1 in the SAC.

Given the high structure similarity between Bub1 and BubR1 TPRs[12,28] we anticipated that KNL1 conserved hydrophobic residues I177, T179, F182 and L186 of the Bub1 binding motif (I_{177}-x-*T*-x-x-*F*-*L*-x-x-L_{186}) should define a similar mode of interaction to that of BubR1-KNL1 (**Fig. 2**). The crystal structure of a Bub1-KNL1 complex reported more recently (Protein Data Bank no. 4AIG) confirmed the validity of our predictions.[31]

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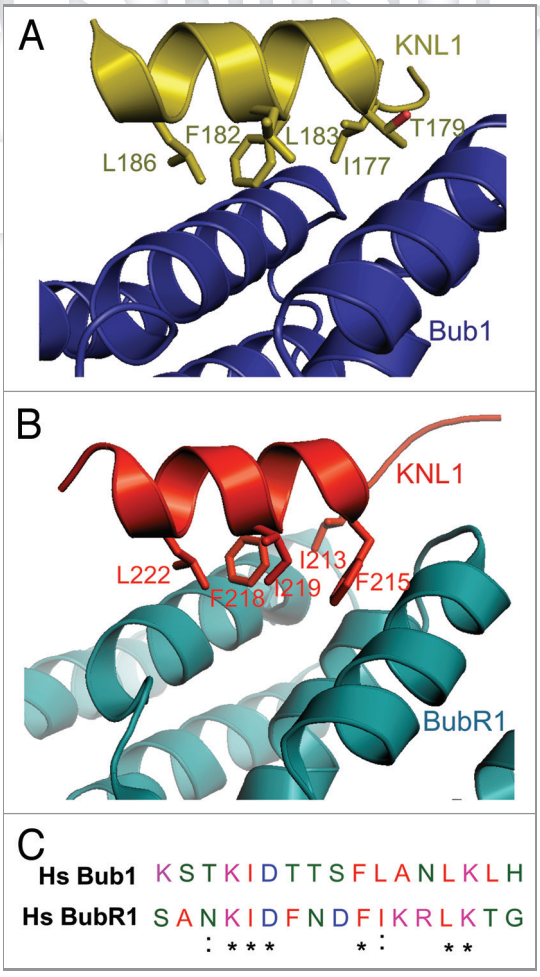

Figure 2. (A) Close-up of the conserved hydrophobic residues of KNL1 that bind Bub1, and (B) of those that bind human BubR1. (C) Amino acid sequence alignment of the TPR Bub1 and TPR BubR1 binding motifs present in N-terminal KNL1.

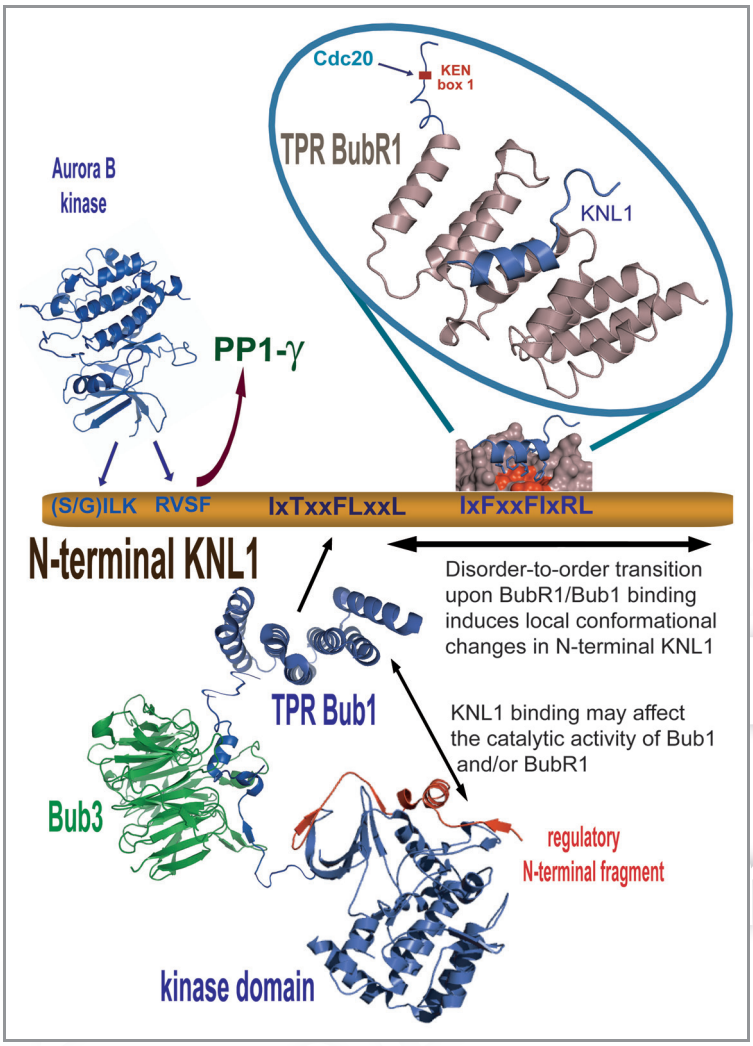

Figure 3. The observed disorder to order transition of KNL1 N-terminal fragments upon BubR1 and Bub1 binding suggests a mechanism of presentation of KNL1 unbound flexible regions to protein kinases, phosphates, etc. An analog molecular recognition mechanism important for Bub1 kinase activity may operate upon KNL1 binding.

Importantly, the BubR1-KNL1 and Bub1-KNL1 complex structures provide detail of the molecular determinants of the interaction such as the role of the TPR convex surface in binding KNL1 and a disorder-to-order transition of N-terminal KNL1 upon Bubs binding. Such a mode of binding should induce local conformational changes and modulate KNL1 interaction with other protein substrates. For instance, the disorder to order transition of KNL1 upon BubR1 binding may assist the presentation of unbound flexible regions of KNL1 to specific kinases and/or phosphatases (**Fig. 3**). Binding of TPR Bub1 to KNL1 may also lead to conformational changes of the N-terminal extension that activates Bub1 kinase domain (**Fig. 3**), an interesting regulatory feature defined from the crystal structure (Protein Data Bank no. 3E7E)[32]

The Mad3 protein (BubR1 homolog of yeast) is phosphorylated by Ipl1p (Aurora B homolog in yeast) and this is required for the SAC to respond to lack of tension.[26,33] Given the proximity of the PP1 binding site in KNL1 to that of the Bubs binding region,[34,35] it will be important to determine if Bub1 and/or BubR1 are directly dephosphorylated at this site and the role of such post-translational modification in SAC silencing.

Closing Remarks

The organization of the KNL1-BubR1 complex has provided structural details of the communication between the SAC and the kinetochore. It has revealed important features of how molecular recognition is achieved in this signaling system and provided compelling evidence that the TPR motif is essential for BubR1 function for the reasons we discussed previously. The unique architecture of the KNL1-BubR1 complex may assist the design and development of low molecular mass compounds able to interfere with protein–protein interactions that are relevant to the SAC. This in turn may represent new opportunities for the treatment of cancer.

Undoubtedly, the molecular understanding of how the enrichment of Bub1 and BubR1 in the kinetochore affects the interaction of KNL1 with Aurora B kinase, protein phosphatase 1γ, and microtubules will provide important insights into the regulation of kinetochore-mitotic checkpoint signaling. Future work should aim to define the role of post-translational modifications upon kinetochore composition, the regulation of its assembly, disassembly and the interaction of KNL1 with microtubules and SAC components in a temporal and spatial framework.

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