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An allosteric mechanism to displace nuclear export cargo from CRM1 and RanGTP by RanBP1

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Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)

1st Editorial Decision 13 April 2010

Thank you for submitting your manuscript for consideration at The EMBO Journal. It has now been seen by two referees, whose comments are shown below. The referees find the study to be of a high technical quality and interesting and both recommend publication in the EMBO Journal after very minor revision. As a consequence pending these minor revisons we are happy to accept the paper for publication.

When you submit a revised version to the EMBO Journal, please make sure you upload a letter of response to the referees' comments. Please note that when preparing your letter of response to the referees' comments that this will form part of the Review Process File, and will therefore be available online to the community. For more details on our Transparent Editorial Process initiative, please visit our website: http://www.nature.com/emboj/about/process.html

Thank you for the opportunity to consider your work for publication. I look forward to your revision.

Yours sincerely,

Editor
The EMBO Journal

REFEREE COMMENTS

Referee #1 (Remarks to the Author):

The recognition of NES by CRM1 and RanGTP has been explained by a couple of CRM1 structures published in 2009. It is generally accepted that the release of RanGTP (by RanBP1 and RanGAP) and the positive cooperativity between cargo and Ran for CRM1 is responsible for dissociating cargo in the cytoplasm. However, the mechanism by which RanBP1 exerts in function in this process is unclear. Previous work of the Imp-beta-Ran-RanBP1 complex have suggested that the Ran effector increases dissociation rate of the GTPase from the importin. The authors have very elegantly and rigorously shown that binding of RanBP1 stimulates NES release by inducing conformational change in the NES-binding cleft of CRM1. The paper is also beautifully written. This unexpected finding should be published immediately after some minor revisions.

Minor comments:

Page 4, 1st sentence: shouldn't Monecke et al Science 2009 also be referenced? The 4th sentence, " The binary CRM1-Spn1....., between helices 11A and 12A." could then be specifically referenced to Dong et al, 20009a. Similarly, the 1st sentence of page 5 concerning the role of trimethylguanosine-capped oligonucleotide in releasing Spn1 should be referenced to both Dong et al, 2009b and Monecke et al., 2009.

Referee #3 (Remarks to the Author):

Koyama and Matsuura present a very interesting structural, mutational and biochemical analysis of the process by which Leucine-rich Nuclear Export Signals (NESs) are displaced from the export receptor CRM1 by the combined presence of RanGTP and RanBP1 or RanBP2. They show that The joint binding of RanBP1 and RanGTP induces a large change in the conformation of the intra Heat repeat 9 loop such that it moves into a position from which it acts to close the NES-binding cleft between Heat repeats 11 and 12 of CRM1. Using a FRET assay, they show that this effect speeds up the dissociation of the PKI NES from CRM1 by between 100- and 1000-fold. The manuscript also contains data that helps explain how RanBP1 binding helps destabilise RanGTP-CRM1 interaction and why RanBP3 and Nup2, two other proteins that have RanBP folds, do not act to destabilise CRM1 export complexes.
It has always seemed probable that the effects of the Ran system on import and export receptors would be to induce conformational changes in the receptors and thus mediate large changes in the cargo binding affinity. This, however, to my knowledge, represents a the best example to date of this principle, which I predict will turn out to be much more generally important as more structural intermediates in the assembly and disassembly of import and export complexes are elucidated and can be compared. Provided referees expert in the structural aspects of the analysis find no major technical problems, I therefore strongly support publication and have no detailed criticism of the manuscript to make.

1st Revision - authors' response 14 April 2010

Referee #1
Minor comments:

Page 4, 1st sentence: shouldn't Monecke et al Science 2009 also be referenced? The 4th sentence, "The binary CRM1-Spn1....., between helices 11A and 12A." could then be specifically referenced to Dong et al, 2009a. Similarly, the 1st sentence of page 5 concerning the role of trimethylguanosine-capped oligonucleotide in releasing Spn1 should be referenced to both Dong et al, 2009b and Monecke et al., 2009.

We have quoted the Monecke et al 2009 paper accordingly.

Referee #3 did not raise any issues.

Thank you for your time and consideration.

