THE EMBO JOURNAL

Manuscript EMBO-2011-78796

Structural basis for cell surface patterning through NetrinG-NGL interactions

Elena Seiradake, Charlotte H Coles, Pavel V Perestenko, Karl Harlos, R.A. Jeffrey McIlhinney, Alexandru R Aricescu and E Yvonne Jones

Corresponding author: E. Yvonne Jones, Oxford, University of

Review timeline:

Submission date:	13 July 2011
Editorial Decision:	22 August 2011
Revision received:	24 August 2011
Accepted:	25 August 2011

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 22 August 2011

Thank you for submitting your manuscript to the EMBO Journal. Your study has now been seen by two referees and their comments are provided below.

As you can see, the referees find the study interesting, very insightful and suitable for publication in the EMBO Journal basically as is. I am therefore very pleased to proceed with acceptance of the paper for publication here. Before doing so, Ref #2 has a minor text change and a suggestion for figure 1 that I would like to ask you to take into consideration in a revised version. When you submit the revised manuscript please also include the appropriate PDB accession codes.

When preparing your letter of response to the referees' comments, please bear in mind 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, please visit our website:
http://www.nature.com/emboj/about/process.html

Best

Editor
The EMBO Journal

REFEREE REPORTS

Referee #1 (Remarks to the Author):

Seiradake et al. report X-ray crystal structures of NetrinG2, NGL3, and NetrinG1-NGL1 and

NetrinG2-NGL2 complexes. A conserved interface is observed, and mutagenesis and loop-swap experiments validate the observed interface. These are long-awaited and important structures that will have a large impact in both the axon guidance and signaling/molecular recognition fields. The manuscript is clearly written, marvelously brief, and work meticulously carried out and documented. I strongly recommend publication as is in EMBO J.

Referee #2 (Remarks to the Author):

This is a fascinating manuscript that provides substantial novel insight into the structural basis of NetrinG - NGL interactions. The structural insights obtained were then used to elegantly test the hypothesis that relatively short sequences are sufficient to determine the binding specificity between specific partners. The authors demonstrate that transferring amino acid sequences between different NGLs results in dramatic switching between preferred netrinG binding partners. Similar analysis of the NetrinGs revealed that the NGL binding site is not as modular. They then developed an assay using a cells line that demonstrates the specificity of cell surface localization of NetrinG - NGL binding, and demonstrate cell surface sorting to sites of cell - cell interactions based on the specificity of the NetrinG - NGL interaction.

The paper provides relatively little background on the cell biology of the netrinG - NGL interaction, but the comments that are made are accurate. The reference Sun et al 2011 on page 2 should be changed to Lai Wing Sun et al 2011.

The figures are clearly presented. It would be helpful to the reader if the loop I, II, and III labels used in Figure 2 for the domains of the NetrinGs that interact with the NGLs were also included in Figure 1.

1st Revision - authors' response 24 August 2011

Point-by-point response to the referee comments:

Referee #1 (Remarks to the Author):

Seiradake et al. report X-ray crystal structures of NetrinG2, NGL3, and NetrinG1-NGL1 and NetrinG2-NGL2 complexes. A conserved interface is observed, and mutagenesis and loop-swap experiments validate the observed interface. These are long-awaited and important structures that will have a large impact in both the axon guidance and signaling/molecular recognition fields. The manuscript is clearly written, marvelously brief, and work meticulously carried out and documented. I strongly recommend publication as is in EMBO J.

Referee #2 (Remarks to the Author):

This is a fascinating manuscript that provides substantial novel insight into the structural basis of NetrinG - NGL interactions. The structural insights obtained were then used to elegantly test the hypothesis that relatively short sequences are sufficient to determine the binding specificity between specific partners. The authors demonstrate that transferring amino acid sequences between different NGLs results in dramatic switching between preferred netrinG binding partners. Similar analysis of the NetrinGs revealed that the NGL binding site is not as modular. They then developed an assay using a cells line that demonstrates the specificity of cell surface localization of NetrinG - NGL binding, and demonstrate cell surface sorting to sites of cell - cell interactions based on the specificity of the NetrinG - NGL interaction.

The paper provides relatively little background on the cell biology of the netrinG - NGL interaction, but the comments that are made are accurate. The reference Sun et al 2011 on page 2 should be changed to Lai Wing Sun et al 2011.

The figures are clearly presented. It would be helpful to the reader if the loop I, II, and III labels

used in Figure 2 for the domains of the NetrinGs that interact with the NGLs were also included in Figure 1.

Author response: We thank the reviewers for their enthusiastic support and helpful comments.

- We changed the reference Sun et al 2011 to Lai Wing Sun et al 2011

- We included labels for loop I, II and III in Figure 1.

