Gcn5 and PCAF negatively regulate interferon β production through HAT-independent inhibition of TBK1


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Review timeline:
- Submission date: 30 April 2014
- Editorial Decision: 04 June 2014
- Correspondence: 13 June 2014
- Revision received: 30 July 2014
- Editorial Decision: 20 August 2014
- Revision received: 24 August 2014
- Editorial Decision: 27 August 2014
- Correspondence: 28 August 2014
- Revision received: 02 September 2014
- Accepted: 04 September 2014

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.)

Editor: Nonia Pariente

1st Editorial Decision 04 June 2014

Thank you for your submission to EMBO reports. We have now received reports from the two referees that were asked to evaluate your study, which can be found at the end of this email. As you will see, although both referees find the topic of interest and in principle suited to EMBO reports, they also raise several concerns that would need to be addressed before publication of your study can be considered.

Given that both provide constructive suggestions on how to strengthen different aspects of the study, I would like to give you the opportunity to revise your manuscript. Please note that it is EMBO reports policy to undergo one round of revision only and thus, acceptance of your study will depend on the outcome of the next, final round of peer-review.

From referee 1’s report, the additional analyses would need to be included and new ChIP-Seq experiment to assess H3K9ac levels at TSS in the absence of both Gcn5 and PCAF would need to be provided.

With respect to referee 2’s report, given the strong emphasis of EMBO reports on the physiological
relevance of the findings it publishes, it would be crucial to address several of the concerns, especially in view of the modest increase in IFN production upon loss of GCN5 and PCAF. Mutant GCN5 would need to be expressed at physiological levels, basal IFN expression tested and whether cells remain responsive to viral infection. In addition, the effects of non-catalytic PCAF should be assessed. However, please note that the elucidation of how GCN5 repression is relieved during viral infection and whether other non-IFN-related genes are also regulated by catalytically inactive HATs would be beyond the scope of this study and would not need to be addressed during revision.

From an editorial standpoint, both the text of your study and the number of figures exceed the format of EMBO reports. At 46,750 characters, your text will need to be shortened by 16,750 to conform to our length limitations, and we can maximally publish 5 figures in the main manuscript. The presentation of a merged the Results and Discussion section, which we require, will help to eliminate some redundancy inherent to their presentation separately and allow you to better accommodate the necessary additional discussions/data. In addition, although basic Materials and Methods required for understanding the experiments performed must remain in the main text, additional detailed information necessary to repeat them may be included as Supplementary Material. Lastly, the conceptual novelty of the first part of the results section and of figure 1 is limited by your previous demonstration that GCN5/PCAF-mediated H3K9ac is dispensable for gene expression. Thus, figure 1 is the best candidate to be moved to the supplement and this part of the text could be more succinctly summarized.

I look forward to seeing a revised form of your manuscript when it is ready. In the meantime, please contact me if I can be of any help.

REFEREE REPORTS:

Referee #1:

In their work, Jin et al. examine the effects of Gcn5/PCAF depletion on global gene expression. These enzymes are thought to globally facilitate gene transcription through their activity as histone acetyltransferases (namely lysine 9 acetylation of histone 3, H3K9ac). This assumption is based largely on the fact that the modification is enriched at the gene transcription start sites. However, Jin et al. observe that only ~1000 of the ~13,000 active genes in fibroblasts are affected by the depletion of Gcn5/PCAF. The great majority (~800) of those ~1000 genes show the expected reduction in gene expression in the Gcn5/PCAF-depleted cells. Yet Jin et al. focus their attention on the 224 up regulated genes, many of which belong to the interferon-stimulated genes (ISGs). The subsequent experiments of Jin et al. tell us essentially two things: that lysine 9 acetylation of histone 3 is dispensable for activation of the interferon b gene, and that Gcn5/PCAF actually inhibits the expression of that gene. These findings are robustly and convincingly documented; they are new and of general interest to the molecular biology community.

This is a generally strong manuscript based on solid experimental data. In my view the understanding of the significance of H3K9ac for gene transcription would benefit from additional information about this modification for the ~1000 genes differentially expressed in cells with and without Gcn5/PCAF. In Figure 1a the authors show the abundance of H3K9ac for three groups of genes based on their expression levels. However, I could not find how the expression levels (low, medium, high) are defined. In addition, nothing is said about H3K9ac of genes that are repressed as compared to those that are up regulated in the Gcn5/PCAF-deficient cells. Are there any global correlations between H3K9 acetylation and the sensitivity to or the consequences of Gcn5/PCAF depletion? While the answers to these questions are hidden in the data the authors already have, the answer to another rather basic question may require an additional experiment. It is unclear at present how depletion of Gcn5/PCAF actually affects H3K9ac at transcription start sites. In Figure 1a the authors use ChIP-seq to correlate H3K9ac and gene expression in cells that express Gcn5, but the respective data for Gcn5/PCAF-depleted cells are not available. The authors state that loss of both Gcn5 and PCAF "profoundly reduces" levels of H3K9ac and refer to their previous work (Jin et al. 2011), but western blot results are shown there that cannot fully clarify the issue.
Referee #2:

In this study, the authors examine the role of GCN5 and PCAF in IFN induction. It has been previously shown that H3K9 acetylation at the IFN-beta promoter correlates with gene activation and that this mark is conferred by the related HAT enzymes, GCN5 and PCAF. Using cells from conditional knockout mice, the authors show that elimination of both GCN5 and PCAF leads to a complete loss of detectable H3K7 acetylation globally and a loss of induction of H3K9-Ac at the IFN-beta promoter in response to polyIC. Surprisingly, loss of these HATs led to an increase rather than a decrease in IFN expression. Although the level of expression was extremely low, it caused an increase in basal expression of antiviral genes. This increase in basal antiviral genes appeared to be due to IFN, since it was dependent on all the major components of the IFN pathway, including IRF3, IFNAR, and TBK1. Moreover, they found that reintroduction of GCN5 restored repression of basal IFN pathway genes, and that this could be accomplished by expression of a catalytically impaired version of GCN5, suggesting a non-HAT mechanism of repression. Indeed, they showed that ectopically expressed or purified GCN5 was could interact with TBK1 and impair its enzymatic activity in vitro. They conclude from these data that GCN5 (and presumably PCAF) redundantly inhibit TBK1 enzymatic function in the absence of viral infection to repress the pathway.

The data presented support the authors' conclusion that loss of GCN5 and PCAF cause a modest increase in spontaneous IFN production, leading to establishment of at least a modest antiviral state. What remains unclear is the physiologic significance of this work. The authors conclude that GCN5 is a natural inhibitor of TBK1 enzymatic function, though a direct interaction/inhibition mechanism. However, it remains unclear how polyIC or viral infection leads to IFN production in wild type cells, since ectopic expression of either wild type or mutant GCN5 completely repressed this response. In order to conclude that GCN5 inhibits TBK1 though a non-enzymatic mechanism, it is critical to express mutant GCN5 at physiological levels and show that spontaneous basal IFN expression is repressed but the cells remain responsive to viral infection. In addition, it would be very helpful to understand how this hypothetical repressive action of GCN5 is relieved during IFN induction by viral infection. It should also be shown that non-catalytic PCAF exerts the same biochemical effects as GCN5, since presumably these proteins function redundantly. Finally, since many non-IFN-related genes were identified as upregulated in HAT mutant cells, it will be of interest to understand if their expression is similarly controlled by non-enzymatic HATs.

Correspondence - authors 13 June 2014

Thank you very much for your highly efficient handling of our manuscript.

We agree entirely with referee 1's comments and will do a new ChIP-Seq experiment to assess H3K9ac levels at TSS in the absence of both Gcn5 and PCAF.

We appreciate referee 2's generally positive comments. We will address referee 2's concerns on the physiological relevance of our findings by expressing ectopic Gcn5/PCAF (wild type and mutant) at physiological levels and test both basal and polyIC-induced IFN expression. We will use polyIC, a widely used mimic of virus infection, instead of virus infection. The reason is because the first author Qihuang Jin, who will do the revision experiments, has moved to Dr. Sharon Dent's lab in Texas two years ago and no longer has access to VSV, an infectious virus provided by our collaborator at NIH.

Thanks again for your efforts. We will try our best to address all points raised by the two referees and will send the revised version back within 2-3 months.
Response to referees

Referee #1:

We appreciate the comments and suggestions of the referee and our responses to address the referee’s questions are detailed below:

Q1: In Figure 1a the authors show the abundance of H3K9ac for three groups of genes based on their expression levels. However, I could not find how the expression levels (low, medium, high) are defined.

We now include the definition of the expression levels in the Supplemental Material and Methods as the following: “In order to show the correlation between H3K9ac on TSS and gene expression levels, we selected three groups of genes to represent different expression levels (high, medium, and low), and for each group we calculated the average abundance of H3K9ac on TSS of genes. Specifically, we collected all the genes detected by RNA-Seq (i.e., genes with tag number no smaller than 10 in at least one of the samples) and ranked them by their expression levels in the retroviral Vec-infected cells. The top, medium and lowest 1000 genes are selected to represent the high-, medium-, and low-expression genes.”

Q2: In addition, nothing is said about H3K9ac of genes that are repressed as compared to those that are up regulated in the Gcn5/PCAF-deficient cells. Are there any global correlations between H3K9 acetylation and the sensitivity to or the consequences of Gcn5/PCAF depletion?

As shown in the new Fig. S1A-B, genes with lower levels of promoter H3K9ac, which associate with lower expression levels in the control cells, are more sensitive to the loss of Gcn5/PCAF and show more significant changes of expression in the double KO (dKO) cells.

Q3: It is unclear at present how depletion of Gcn5/PCAF actually affects H3K9ac at transcription start sites.

To address this comment, we performed ChIP-Seq of H3K9ac in retroviral Cre- and Vec-infected PCAF""; Gcn5""; MEFs (Gcn5/PCAF dKO and control cells, respectively). The results show near-complete depletion of H3K9ac on the TSSs in the dKO cells (Fig. S1C-I). These results are consistent with our previous report that Gcn5/PCAF dKO causes ~19-fold decrease of global H3K9ac levels in MEFs (Jin et al., EMBO J 2011).

Referee #2:

We appreciate the comments and suggestions of the referee and our responses to address the referee’s questions are detailed below:

Q1. However, it remains unclear how polyIC or viral infection leads to IFN production in wild type cells, since ectopic expression of either wild type or mutant GCN5 completely repressed this response.

We apologize for not labeling the values in the original Fig. 4b (now Fig. 3G). As shown in the updated Fig. 3G, poly(I:C) treatment induced low levels of IFN in the Vec cells. The loss of Gen5 in the Cre cells resulted in ~30-70 fold increase of poly(I:C)-induced IFN production. Ectopic expression of either wild-type or mutant Gen5 in the Cre cells reduced poly(I:C)-induced IFN production levels close to those observed in the Vec cells.

Q2. In order to conclude that GCN5 inhibits TBK1 through a non-enzymatic mechanism, it is critical to express mutant GCN5 at physiological levels and show that spontaneous basal IFN expression is repressed but the cells remain responsive to viral infection.
To address this comment, we expressed ectopic wild-type and non-catalytic mutant Gcn5 at physiological levels in the double KO (dKO) cells (Fig. S6A). As shown in Fig. S6B-D, both wild-type and mutant Gcn5, when expressed at physiological levels, inhibit basal and poly(I:C)-induced IFN production as well as up-regulation of ISGs in the dKO cells. These results further indicate that Gcn5 inhibits innate immune signaling and TBK1 through a non-enzymatic mechanism.

Q3. In addition, it would be very helpful to understand how this hypothetical repressive action of GCN5 is relieved during IFN induction by viral infection.

As the Editor mentioned in the decision letter, this issue is outside of the scope of this manuscript. We will try to address this issue in future publications.

Q4. It should also be shown that non-catalytic PCAF exerts the same biochemical effects as GCN5, since presumably these proteins function redundantly.

We expressed ectopic wild-type PCAF and non-catalytic mutants, PCAF-Δ579-608 and PCAF-Δ609-624 in the dKO cells. Unlike the wild-type PCAF, the two mutants can’t rescue H3K9ac in the dKO cells (Fig. S6E). However, both wild-type and mutant PCAF behave like Gcn5 and inhibit basal and poly(I:C)-induced IFN production as well as up-regulation of ISGs in the dKO cells (Fig. 6F-H).

Q5. Finally, since many non-IFN-related genes were identified as upregulated in HAT mutant cells, it will be of interest to understand if their expression is similarly controlled by non-enzymatic HATs.

We selected five non-IFN-related, highly up-regulated genes from Table S2 and analyzed their expression by qRT-PCR. As shown in the figure below, the expression of these genes is similarly controlled by the non-catalytic Gcn5 mutant D608A.

![Gene expression](attachment:image)

Thank you for the submission of your revised study to EMBO reports. We have now received the reports from referees 1 and 2. As you will see, although referee 1 is now supportive of publication, referee 2 raises several minor but important issues, which would need to be clarified before we can
accept your study for publication.

We have thus decided to open an exceptional additional round of revision for your study, in order for you to address these outstanding concerns. If they are adequately addressed, we will be happy to accept your manuscript for publication. Please provide your revised study within two months.

Several of the outstanding points call for additional comments. In this regard, please note that we have recently decided to flexibilize our format and, thus, you may add the necessary discussion, as needed.

I look forward to seeing a revised form of your manuscript when it is ready. In the meantime, please contact me if I can be of any assistance.

REFEEEREE REPORTS:

Referee #1:
The authors have addressed the questions I had raised in a thorough and satisfactory manner.

Referee #2:
The authors have revised this study in response to previous critiques. Their data show that cells lacking PCAF and GCN5 display increased gene expression of IFN and IFN-stimulated genes, leading to decreased susceptibility to viral infection. Mechanistically, they show that TBK1 interacts with GCN5, resulting in reduced catalytic activity. They conclude the cytoplasmic GCN5 serves as a repressor of TBK1 activity through a physical interaction model that does not require lysine acetyltransferase activity.

The data clearly show that cells lacking PCAF/GCN5 express higher levels of IFN and IFN-stimulated genes, and respond more robustly to stimulation, e.g., polyIC treatment. There are several peculiarities about this study that deserve more comment from the authors.

1. Perhaps more striking than the increased responsiveness of their DKO cells to polyIC is the limited response observed from the parental wild type cells. Most studies of mouse embryo fibroblasts in the literature have documented substantial levels of IFN induction in response to polyIC, while relatively low levels were seen in this study. Are the PCSF-/- MEF defective for IFN production?

2. The data present make a strong case that the entire phenotype is due to deregulated TBK1 activity, leading to constitutive secretion of very low levels of IFN, cause increased expression of downstream genes. However, the amounts of IFN detected in culture supernatants would not be expected to produce the observed changes in gene expression of antiviral protection, since they are substantially below 1 u/ml. This suggests that something in addition to IFN is produced and cooperates with IFN to produce the observed results. The authors should treat WT cells with recombinant IFN at the concentration detected in this study to determine if IFN alone can reproduce the results.

3. IFN target genes have been shown to be transiently expressed in response to IFN stimulation. In contrast, the authors observe substantial levels of constitutive ISG gene expression in response to chronic IFN exposure. To determine if the loss of TBK1 repression leading to increased IFN production is indeed the mechanism underlying the observed antiviral signature, the authors should treat cells chronically as describe in (2) above with recombinant IFN and determine if chronic IFN exposure reproduces the results. If not, speculation on additional mechanisms would be in order.

4. The authors found that 69 of 224 unregulated genes were immune related. A question is whether the induction of all 224 genes is due to dysregulated TBK1 activity and/or chronic IFN exposure. In the Response to Critique they show data on 5 genes that are also unregulated by GCN5 loss and
repressed by non-catalytic GCN5. However, the genes shown are all probably regulated by IFN. Are any of the genes in Table S2 not regulated by IFN but dependent on TBK1? Put another way, it is important to understand if all the unregulated gene expression is due to increased TBK1 activity, suggesting a single mechanism for the repressive activity of GCN5.

Response to Referee 2

“The authors have revised this study in response to previous critiques. Their data show that cells lacking PCAF and GCN5 display increased gene expression of IFN and IFN-stimulated genes, leading to decreased susceptibility to viral infection. Mechanistically, they show that TBK1 interacts with GCN5, resulting in reduced catalytic activity. They conclude the cytoplasmic GCN5 serves as a repressor of TBK1 activity through a physical interaction model that does not require lysine acetyltransferase activity.

The data clearly show that cells lacking PCAF/GCN5 express higher levels of IFN and IFN-stimulated genes, and respond more robustly to stimulation, e.g., polyIC treatment.”

We appreciate the referee’s efforts. We are grateful that referee 2 agrees with the major conclusion of our manuscript.

“1. Perhaps more striking than the increased responsiveness of their DKO cells to polyIC is the limited response observed from the parental wild type cells. Most studies of mouse embryo fibroblasts in the literature have documented substantial levels of IFN induction in response to polyIC, while relatively low levels were seen in this study. Are the PCSF-/- MEF defective for IFN production?”

In the literature, polyIC-induced IFN production in MEFs varies a lot and depends on the protocols and the cell lines used. We followed the protocol from Nahum Sonenberg’s lab. In Figure 2d of Sonenberg lab’s Nature paper (Colina et al., 2008), polyIC induces ~10-20 ng/ml IFNα in the supernatant of wild type MEFs. In Figure 3C of Sonenberg lab’s Nature Immunology paper (Herdy et al., 2012), polyIC induces ~5-10 ng/ml IFNβ in the supernatant of wild type MEFs. In our hands, polyIC induces ~50 ng/ml of IFNβ in the supernatant of the PCAF-/-;Gcn5<sup>lox/lox</sup> MEFs (Figure 3C). At the mRNA level, polyIC induces dramatic increases of both IFNα and IFNβ in these cells (Figure 3G). Thus, the PCAF<sup>-/-</sup>;Gcn5<sup>lox/lox</sup> MEFs are not defective for IFN production.

Most importantly, the conclusion of our paper that Gcn5 and PCAF repress IFN production in cells is supported not only by data from MEFs but also by data from two other different cell types, macrophages (Figure 3E) and brown preadipocytes (Figure S2).

“2. The data present make a strong case that the entire phenotype is due to deregulated TBK1 activity, leading to constitutive secretion of very low levels of IFN, cause increased expression of downstream genes. However, the amounts of IFN detected in culture supernatants would not be expected to produce the observed changes in gene expression of antiviral protection, since they are substantially below 1 u/ml. This suggests that something in addition to IFN is produced and cooperates with IFN to produce the observed results. The authors should treat WT cells with recombinant IFN at the concentration detected in this study to determine if IFN alone can reproduce the results.”

We do not agree with the referee’s comment that the amounts of IFN detected in culture supernatants are substantially below 1 u/ml. As shown in Figure 3A, the Gcn5/PCAF dKO MEFs
produce both IFNα (~14 pg/ml) and IFNβ (~1.8 pg/ml) in the supernatant. If we assume the activity of IFNα secreted from the dKO cells is similar to that of recombinant IFNα from Schering Corporation (~ 2.6 × 10^8 IU/mg protein, https://www.drugs.com/drp/interferon-alfa-2b-recombinant.html), the activity of IFNα alone in the supernatant is ~ 3.6 IU/ml. While the IFNα/β levels in the supernatant of the dKO MEFs are low, they are sufficient to induce significant ISG expression in WT MEFs (Figure S4). The detected IFN concentrations likely underestimate the actual IFN production from the dKO cells, because the high affinity IFN receptors on the cell surface would bind and deplete IFNα/β from the supernatant. This also makes it very difficult for us to decide which dosage of IFNα/β should be used to do the experiments suggested by the referee.

Importantly, depletion of the IFN receptor in the dKO cells blocks the up-regulation of ISGs and reverses cell resistance to VSV infection (Figure 4A-C). While we can’t rule out the possibility that something in addition to IFN is produced and contributes to the observed results, our data indicate that the observed phenotype of the dKO cells is mainly due to IFN production (also see the updated Discussion).

“3. IFN target genes have been shown to be transiently expressed in response to IFN stimulation. In contrast, the authors observe substantial levels of constitutive ISG gene expression in response to chronic IFN exposure. To determine if the loss of TBK1 repression leading to increased IFN production is indeed the mechanism underlying the observed antiviral signature, the authors should treat cells chronically as describe in (2) above with recombinant IFN and determine if chronic IFN exposure reproduces the results. If not, speculation on additional mechanisms would be in order.”

Knockdown of TBK1 or inhibition of TBK1 kinase activity in the dKO cells blocks IFN production and prevents upregulation of ISGs and cell resistance to VSV infection (Figure 4), indicating that loss of repression of TBK1 is the major mechanism underlying the observed phenotype in the dKO cells. However, we don’t rule out the possibility that additional mechanisms may contribute to the observed results. For example, Gcn5 has been shown to repress NF-κB activity (Mao et al., 2009). NF-κB promotes the production of IFNβ and pro-inflammatory cytokines (Honda and Taniguchi, 2006; Sun et al., 2010). Loss of Gcn5/PCAF in cells would increase the transcriptional activity of NF-κB, which promotes the production of not only IFNβ but also pro-inflammatory cytokines. Such a mechanism may contribute to the observed phenotype in the dKO cells (also see the updated Discussion).

“We agree with the editor that this issue is beyond the scope of this study (see the Decision Letter). We will address this issue in future publications.

References:


3rd Editorial Decision 27 August 2014

I have now had time to go through the minor revision of your study in response to the final concerns from referee 2, and consider you have adequately addressed the issues raised. I am therefore writing with an 'accept in principle' decision, which means that I will be happy to accept your manuscript for publication once a few minor issues/corrections have been addressed, as follows.

- It is a precondition for publication in EMBO reports that authors agree to make all data that cannot be published in the journal itself freely available, where possible in an appropriate public database. In the case of ChIP-seq and RNA-seq datasets, they can be deposited, for example, in GEO. This should be specified in the main text in the first instance where the data are mentioned, with the relevant accession code (which can also be included in the Methods section under the appropriate subheading).

- Most of the figures include graphs with error bars. Please ensure that all relevant figures and supplementary figures have been generated according to proper statistical analysis procedures (n at least 3), and all figure legends include information on the number of independent experiments measured, the type of error bars, what the bars represent and statistical test applied to the data (if applicable).

- As a standard procedure, we edit the title and abstract of manuscripts to make them more accessible to a general readership. Please find the edited versions at the end and let me know if you do NOT agree with any of the changes.

- Every EMBO reports paper now includes a 'Synopsis' to further enhance its discoverability. Synopses are displayed on the html version and they are freely accessible to all readers. The synopsis includes a short standfirst text -I have added my proposal for this text below- as well as 2-3 one sentence bullet points that summarise the paper. These should be complementary to the abstract -i.e. not repeat the same text. This is a good place to include, as appropriate, key acronyms and quantitative and organism (yeast, mammalian cells, etc) information. We would thus need you to supply a 550 pixels wide by 400 pixels high graphic outlining the main message of the study, and the bullet points to accompany the standfirst. Something readable in the above specified dimensions based on the model in figure 5L would be perfect.

Do let me know if you would like to modify the standfirst blurb:

"This study shows that, contrary to the current model and despite their recruitment to the IFNβ promoter, Gcn5 and PCAF negatively regulate IFNβ production. They do so in a histone acetyltransferase-independent manner, through the inhibition of TBK1.

2-3 bullet points"

After all remaining corrections have been attended to, you will receive an official decision letter from the journal accepting your manuscript for publication in the next available issue of EMBO reports. This letter will also include details of the further steps you need to take for the prompt
Gcn5 and PCAF negatively regulate interferon β production through HAT-independent inhibition of TBK1

Viral infection triggers innate immune signaling, which in turn induces interferon β (IFNβ) production to establish innate antiviral immunity. Previous studies showed that Gcn5 (Kat2a), a histone acetyltransferase (HAT) with partial functional redundancy with PCAF (Kat2b), and Gcn5/PCAF-mediated histone H3K9 acetylation (H3K9ac), are enriched on the active IFNβ gene promoter. However, whether Gcn5/PCAF and H3K9ac regulate IFNβ production is unknown. Here we show that Gcn5/PCAF-mediated H3K9ac correlates with, but is surprisingly dispensable for, the expression of endogenous IFNβ and the vast majority of active genes in fibroblasts. Instead, Gcn5/PCAF repress IFNβ production and innate antiviral immunity in several cell types in a HAT-independent and non-transcriptional manner: by inhibiting the innate immune signaling kinase TBK1 in the cytoplasm. Our results thus identify Gcn5 and PCAF as negative regulators of IFNβ production and innate immune signaling.

Correspondence - authors 28 August 2014

This is great! Thank you for your highly efficient and professional handling of our manuscript. In the future, we will send more manuscripts to EMBO Reports and EMBO Journal.

We will modify the manuscript and prepare the graphic outline and synopsis according to your instructions. I really like the title, abstract and the standfirst blurb that you suggested.

We are in the process of submitting the ChIP-seq and RNA-seq data to GEO. Once we receive a GEO accession number, we will be able to submit the revised manuscript.

3rd Revision - authors’ response 02 September 2014

We have modified the manuscript and prepared the graphic outline and synopsis according to your instructions.

4th Editorial Decision 04 September 2014

I am very pleased to accept your manuscript for publication in the next available issue of EMBO reports.

Thank you for your contribution to EMBO reports and congratulations on a successful publication.