P2695

Characterizing ESCO1's Interaction with Chromatin

Jeff Schoen[1,2], Annelise Poss[1], Eulália Lima da Silva[1], Jingrong Chen[1], Erin Floyd[1], and Susannah Rankin[1,2]

1. Cell Cycle and Cancer Biology program, Oklahoma Medical Research Foundation
2. Cell Biology department, University of Oklahoma Health Sciences Center

OKLAHOMA MEDICAL RESEARCH FOUNDATION

The UNIVERSITY of OKLAHOMA Health Sciences Center

Abstract

ESCO1 is an acetyltransferase enzyme that regulates chromosome organization and gene expression by modifying Cohesin, a key regulator of genome architecture. Cohesin organizes DNA into loops and is critical for normal chromosome structure and function. Acetylation of the SMC3 subunit of Cohesin by ESCO1 stabilizes Cohesin on DNA, promoting long residence time at functional sites. Factors that shape when, where, or how ESCO1 stabilizes Cohesin are not understood.

We have found that tethering ESCO1 to a specific location in the nucleus results in gross local rearrangement of chromatin. Strikingly, this local chromatin rearrangement occurs independently of ESCO1's acetyltransferase activity and does not occur through Cohesin. We have mapped this activity to a 35 amino acid motif within ESCO1 and shown that this region of ESCO1 binds directly to DNA, with a likely preference for single stranded DNA. Deletion of this DNA binding domain (DBD) leads to a reduction in chromatin-bound ESCO1.

We hypothesize that the ESCO1 DBD directs it to preferred binding sites where it regulates Cohesin and gene expression. Experiments are ongoing to complete the characterization of the DBD, define how it is regulated, and characterize its impact on Cohesin localization and gene expression. With these experiments, we will define the biological impact of ESCO1's DNA binding activity.

Introduction

Fig 1: Esco1 and Esco2 have evolved as the human orthologs to the essential yeast protein Eco1

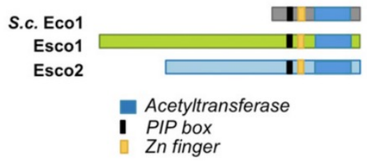


Fig 2: Esco1 and Esco2 have distinct roles in chromatin organization

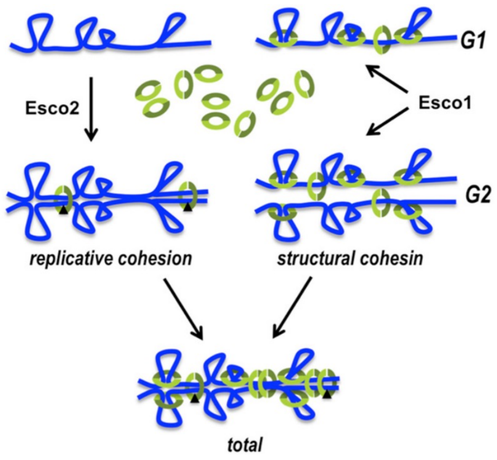
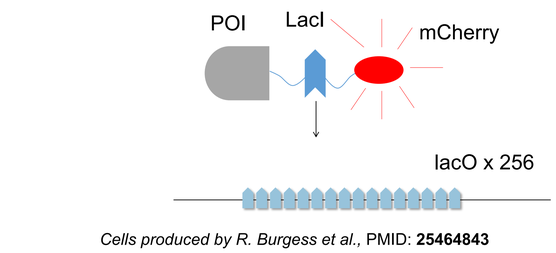


Fig 3: Tethered Esco1 rearranges local chromatin



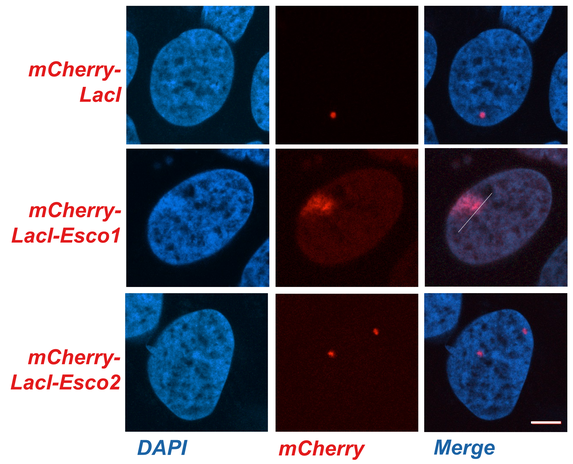


Fig 4: Mapping this activity identified a short fragment of Esco1 capable of spatially rearranging chromatin

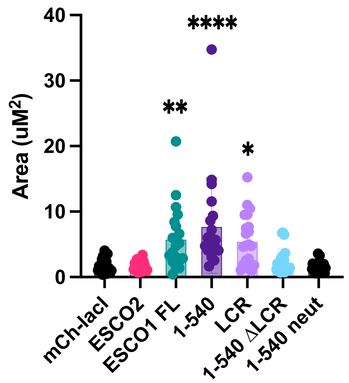


Fig 5: Mis-localization of GFP-ESCO1$^{\Delta DBD}$

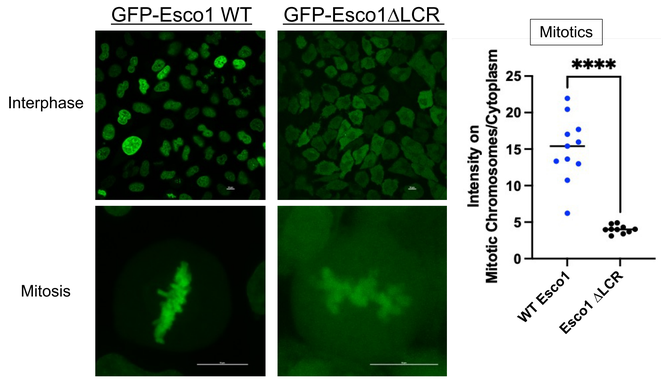
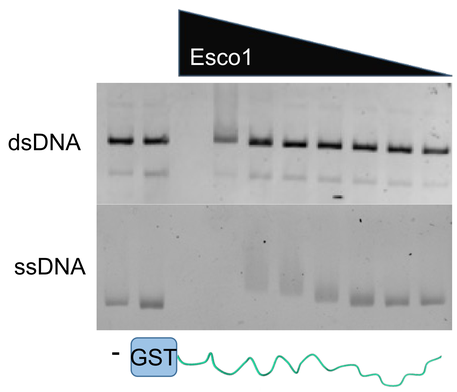
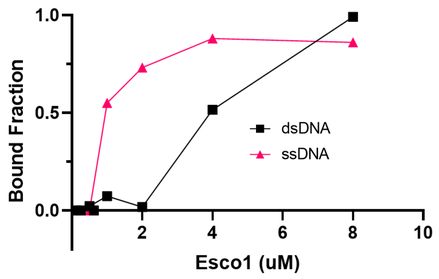
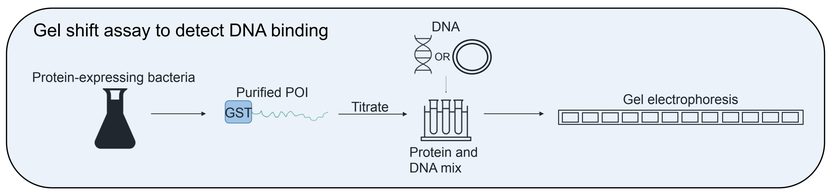


Fig 6: Purified ESCO1 peptide binds DNA in vitro

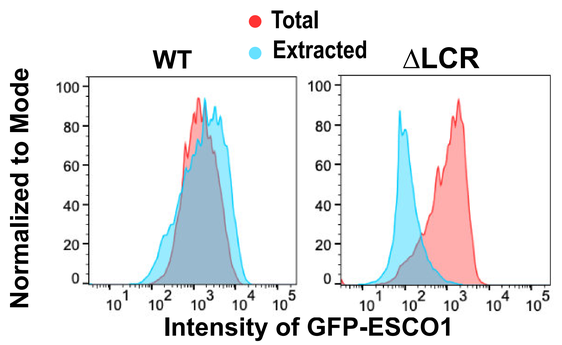






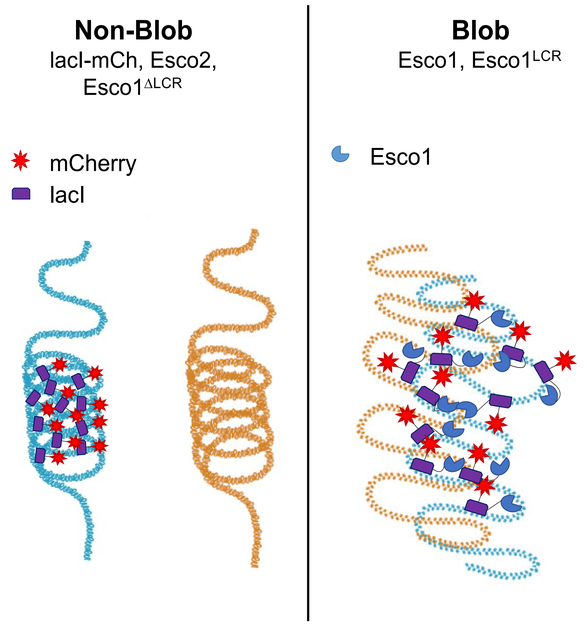
Unstructured peptide predicted by AlphaFold *J. Jumper et al.*, PMID: **34265844z**

Fig 7: ESCO1 needs this DBD to localize onto chromatin



Model

Fig 8: What is happening at the reorganized site?



- Esco1 can independently rearrange chromatin.

Acknowledgements

This work was supported by the National Institutes of Health (5R01GM101250-08, 3R01GM101250-08S1).

We are grateful to all members of the Cell Cycle and Cancer Biology program and the Cell Biology department for helpful discussions during the course of this work.