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Dis-solving the mechanisms of mitotic chromosome formation

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William C. Earnshaw completed his Ph.D. with Jonathan King at MIT in 1977. Postdoctoral training in Cambridge with Aaron Klug and Ron Laskey and in Geneva with Ulrich Laemmli was followed by 13 years at the Johns Hopkins School of Medicine in Tom Pollard's Department of Cell Biology and Anatomy. In 1996 he moved to Edinburgh as a Wellcome Trust Principal Research Fellow as part of the initiative to bring modern Cell Biology research to Edinburgh. He continues to hold that fellowship today. Bill is a Fellow of the Royal Society of London (2013), The Academy of Medical Sciences (2009), the Royal Society of Edinburgh (2002), the American Association for Advancement of Science (2007) and a member of EMBO (1999). He got many awards, sign about 370 publications cited more than 60,000 times (h index of 128). Bill Earnshaw's primary goal throughout his career has been to understand how chromosomes are compacted and segregated when cells divide.

Abstract

Attempts to understand how the DNA is packaged in mitotic chromosomes are confounded by the huge size of the DNA, the incredible chromatin density in mitotic chromosomes and the complexity of the machinery that does the DNA packaging. We study this problem by combining chemical genetics, Hi-C genomic analysis, polymer modelling, light and electron microscopy and proteomics. In our system, an entire cell population of chicken DT40 lymphocytes enters mitosis with near perfect synchrony within 2 to 3 minutes of release of a G_2 phase arrest. This allows us to "kinetically section" the process and perform biochemical and structural analyses with minute-by-minute resolution. The cells can be engineered so that chromosome formation is directed by single SMC complexes: cohesin, condensin I or condensin II. Our latest models suggest that chromosomes are a disorderly helix of loops created by the SMC complexes. Condensin II drives the formation of cylindrical chromosomes but is restrained from achieving its ideal state by residual cohesive cohesin. Our electron microscopy analysis in human cells reveals that nucleosomes achieve a near millimolar concentration in mitotic chromosomes. The data from our electron microscopy and modelling are most consistent with chromosome formation involving a combination of looping by SMC complexes and chromatin phase separation. However, the chromatin concentration in chromosomes is much higher than the concentration of nucleosomes in phase-separated droplets in vitro. The mechanism responsible for this compaction of the chromatin is unknown and we have recently obtained evidence inconsistent with all previous models for how the compaction is achieved. Preliminary evidence suggests that a preference of condensin I for G:C_rich DNA may drive a radial organisation where A:T-rich DNA is preferentially located towards the chromosome periphery. Despite over 140 years of study, the essential mysteries of mitotic chromosome formation remain elusive.

Selected publications

K. Samejima†, J.H. Gibcus†, S. Abraham‡, F. Cisneros-Soberanis‡, I. Samejima‡, A.J. Beckett, N. Pučeková, M. Alba Abad, C. Spanos, B. Medina-Pritchard, J.R. Paulson, L. Xie, A.A. Jeyaprakash, I.A. Prior, L.A. Mirny*, J. Dekker*, A. Goloborodko*, W.C. Earnshaw*. (2025). Rules of engagement for condensins and cohesins guide mitotic chromosome formation. Science 388, eadq1709.

Cisneros-Soberanis, F.†, E. Simpson†, A.J. Beckett, N, Pucekova, S. Corless, N.Y. Kochanova, I.A. Prior, D.G. Booth*, W.C. Earnshaw*. (2024). Near Millimolar Concentration of Nucleosomes in Mitotic Chromosomes from Late Prometaphase into Anaphase, J. Cell Biol. 223: e202403165

Samejima, I., C. Spanos, K. Samejima, J. Rappsilber, G. Kustatscher & W.C. Earnshaw. (2022). Mapping the invisible chromatin transactions of prophase chromosome remodelling. Mol. Cell 82:696-708;

Gibcus, J.H.*, K. Samejima*, A. Goloborodko*, I. Samejima, N. Naumova, J. Nuebler, M. Kanemaki, L. Xie, J.R. Paulson, W.C. Earnshaw†, L.A. Mirny†, J. Dekker†. (2018). A pathway for mitotic chromosome formation. Science 359: eaao6135. *equal first authors. †equal corresponding authors.