To maintain balance in genetic information the replicated chromosomes of the mother cell divide equally to create two daughter cells, each with a perfectly identical copy of the cellular genetic material. Delivery of chromosomes to each daughter cell during cell division is mediated by the centromere, the fundamental requisite for chromosome inheritance (Figure 1). Indeed, centromeres play a major role in chromosome segregation and cell division driving the assembly of the kinetochore, the protein complex at which the spindle attaches during mitosis and meiosis. Failure in these processes can lead to chromosome mis-segregation and, consequently, to numerical and structural alterations, which in turn can give rise to conditions such as aneuploidy and/or chromosome instability (CIN), both common features of cancer cells.

The Fachinetti lab is interested in understanding how chromosome inheritance is achieved with such high fidelity by identifying how centromeres are established, the mechanisms that drive centromere function, how their integrity is preserved across the cell cycle and the role that centromere failure plays in genome stability.
Although natural human centromeres are positioned within specific megabase chromosomal regions containing α-satellite DNA repeats, the centromere position is epigenetically specified (Nechemia-Arbely*, Fachinetti*, et al, ECR, 2012). Using gene targeting in human cells and fission yeast, we have previously demonstrated that chromatin containing the centromere-specific histone H3 variant CENP-A is the essential epigenetic mark that acts through a conserved two-step mechanism to identify, maintain and propagate centromere function indefinitely (Fachinetti et al., NCB, 2013). Additionally, we have established that centromere function is not all epigenetically derived; the binding of CENP-B, the only known mammalian centromeric DNA sequence-specific binding protein (present in all human centromeres except the Y chromosome), enhances the fidelity of human centromere function by reinforcing kinetochore formation (Fachinetti et al., Dev Cell, 2015). Our research program is based on an integrated approach that combines the use of engineered cell culture models to conditionally control the stability of endogenous proteins [with an auxin-inducible degron (AID) (Holland*, Fachinetti* et al., PNAS, 2012)] with cell imaging, cytogenetic analysis, proteomic approaches and genome-wide and single molecule technologies (Figure 2). In particular, we are currently studying the molecular mechanism for centromere identification and the importance of DNA sequences for the maintenance of centromere function and integrity. Additional work in the lab is aimed towards the characterization of components that are essential for successful kinetochore nucleation.

Figure 2: Overview of the strategies/techniques used to determine the mechanisms of chromosome segregation and integrity including genome editing, cell biology, cytogenetic and genome-wide techniques.

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Key publications

Year of publication 2019

The N-Terminal Domain of cGAS Determines Preferential Association with Centromeric DNA and Innate Immune Activation in the Nucleus.
Cell reports : 3798 : DOI : S2211-1247(19)30365-1

Viviana Barra, Glennis A Logsdon, Andrea Scelfo, Sebastian Hoffmann, Solène Hervé, Aaron Aslanian, Yael Nechemia-Arbel, Don W Cleveland, Ben E Black, Daniele Fachinetti (2019 Jan 13)
Phosphorylation of CENP-A on serine 7 does not control centromere function.
Nature communications : 175 : DOI : 10.1038/s41467-018-08073-1

Year of publication 2018

V Barra, D Fachinetti (2018 Oct 20)
The dark side of centromeres: types, causes and consequences of structural abnormalities implicating centromeric DNA.
Nature communications : 4340 : DOI : 10.1038/s41467-018-06545-y

Year of publication 2017

Fachinetti D, Logsdon GA, Abdullah A, Selzer EB, Cleveland DW, Black BE (2017 Jan 9)
CENP-A Modifications on Ser68 and Lys124 Are Dispensable for Establishment, Maintenance, and Long-Term Function of Human Centromeres.

Year of publication 2016

Sebastian Hoffmann, Marie Dumont, Viviana Barra, Peter Ly, Yael Nechemia-Arbel, Moira A McMahon, Solène Hervé, Don W Cleveland, Daniele Fachinetti (2016 Nov 24)
CENP-A Is Dispensable for Mitotic Centromere Function after Initial Centromere/Kinetochore Assembly.
Cell reports : 2394-2404 : DOI : 10.1016/j.celrep.2016.10.084

Year of publication 2015

Daniele Fachinetti, Joo Seok Han, Moira A McMahon, Peter Ly, Amira Abdullah, Alex J Wong, Don
W Cleveland (2015 May 4)

**DNA Sequence-Specific Binding of CENP-B Enhances the Fidelity of Human Centromere Function.**

*Developmental cell*: 314-27 : [DOI: 10.1016/j.devcel.2015.03.020]