

Research Interests – Prof. Dr. Andrea Musacchio

The main focus of Andrea Musacchio's laboratory is the study of the molecular mechanisms supporting chromosome inheritance. As carriers of the genetic information stored in DNA (deoxyribonucleic acid), chromosomes play a crucial role in cellular and organismal heredity. Collectively, the 23 pairs of chromosomes present in each human cell carry almost exact copies of the three billion nucleotides of the human genome. In addition to be DNA carriers, chromosomes provide a protein-based scaffold that allows the genetic information contained in DNA to be decoded. Furthermore, and equally importantly, chromosomes act as units for the replication of the DNA in a mother cell and for its subsequent segregation into its two daughters. This foundational process in genetic heredity, which repeats itself in our bodies billions of times every day, is astonishingly accurate, with essentially negligible natural rates of chromosome gain or loss. However, this process goes often awry in tumours, generating imbalances in chromosome number that have dire consequences for cell physiology. Defects in this process are also observed in sexual reproduction, especially as a consequence of organismal aging, and represent prominent causes of infertility, miscarriage and birth defects.

The series of events that allow a mother cell to replicate itself to generate two identical daughters is known as the cell cycle. This process is responsible for inter-generational propagation of organisms and for their development. In adult organisms, the cell cycle also promotes the continued, rapid renewal of many tissues, such as the intestine, the skin and the blood. In dividing cell, the chromosomes are typically first replicated and later transmitted to the daughter cells in a process called mitosis. Mitosis is probably the most scenic of all stages in the life of the cell, because it comes with a complete, dramatic reorganisation of cellular structures. A most prominent feature of mitotic cells is the condensation of the replicated chromosomes (sister chromatids) in their iconic "sausage-like" appearance. Another prominent feature of mitosis is the reorganisation of the cell's skeleton (the cytoskeleton) into a spindle-like structure, the mitotic spindle, which macroscopically appears to be mirror-symmetric. The essence of the mitotic programme is that the replicated chromosomes, as a pair, interact with the opposing halves of the spindle, in such a way that upon their separation they will be parted to opposite spindle poles, ensuring equal inheritance of the genetic material by the two daughter cells.

The micron-sized mitotic spindle is remarkably complex and reflects the nanoscale interactions of hundreds or thousands of different proteins. Essential ingredients of spindles are dynamic tubular structures named microtubules, together with various microtubule binding proteins and molecular motors that move directionally and exercise forces that slide microtubules. The goal of the spindle is to capture and divide the sister chromatids. Capture occurs on a specialised disk-like structure of chromosomes named the kinetochore. Each sister chromatid is endowed with a single kinetochore, and equal chromosome segregation requires that the two sister kinetochores interact with microtubules belonging to opposite spindle poles. It has been known for over 50 years now that the attainment of this configuration requires a force-sensing mechanism within kinetochores that allows to distinguish correct microtubule-kinetochore attachments from unattached or incorrectly attached kinetochores. The molecular underpinnings of this crucial force-sensing pathway, however, have remained unclear. Deciphering the molecular basis of chromosome alignment within the mitotic spindle is the “holy grail” of kinetochore biology and more generally of genetic inheritance. The Musacchio laboratory has been leading this quest for over twenty years. To make inroads into this problem, Musacchio established a highly interdisciplinary laboratory where methodologies from structural, cellular and chemical biology, biochemistry and biophysics were integrated seamlessly to support a progressive, comprehensive, quantitative molecular understanding of the basis of kinetochore function.

Understanding kinetochores represents a tremendous challenge, because kinetochores are very complex structures comprised of at least eighty different polypeptides, each in multiple copies and interacting in complex and highly regulated manners through dynamic post-translational modifications. To access this daunting complexity, Musacchio’s laboratory began a distinctive path where biochemical reconstitution was harnessed to assemble progressively larger kinetochore sub-structures and regulatory pathways in vitro. Inspired by physicist Richard Feynman’s motto “what I cannot create, I do not understand”, the approach taken by Musacchio’s laboratory was highly successful and led to fundamental insights into the structural organisation of kinetochores, for instance through the elucidation of the structure of machinery involved in microtubule binding (the so-called KMN network of proteins) or in the assembly of an interface between the kinetochore and the chromosome (the so-called constitutive centromere associated network, or CCAN). This information, in turn, inspired detailed biological investigations that probed the main functional implications of the structural work. In a parallel tour-de-force of biochemical reconstitution, Musacchio’s laboratory elucidated fundamental principles of the organisation of the spindle assembly checkpoint (SAC), a kinetochore-based signalling pathway that prevents premature separation of the sister chromatids

to preserve genome stability. Musacchio's current efforts aim to combine kinetochore and checkpoint reconstitutions to elucidate the molecular basis of force sensing within kinetochores, a goal that finally appears within reach.