Editorial

The middle and the end

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Welcome to ‘The Middle & The End’, an *EMBO Journal* focus review series on centromere and telomere biology. The molecular biology of DNA and chromosomes has always been a centre of attention for readers and contributors of *The EMBO Journal* alike since its inception 27 years ago. Those years have seen amazing progress in our understanding of these notable chromosomal regions, yet even in the light of most recent advances it is clear that a lot more is yet to be deciphered—figuratively speaking, we are still far from the ‘end’ in terms of learning and understanding them, but we may well be in the very ‘middle’ of things by now.

Having a middle and an end is a privilege of eukaryotic chromosomes, which—in contrast to the circular DNA of typical prokaryotes—are usually linear, a feature that endows them with characteristic properties as well as problems. For one, ends need to be protected and maintained, despite the intricacies of semi-conservative replication and in the face of DNA break surveillance mechanisms liable to attempt their repair. The middle, on the other hand, is commonly the place for spindle microtubule attachment and thus important for chromosome segregation. In light of these peculiarities, centromeres and telomeres have become highly specialized compared with the bulk of eukaryotic chromosomes, which fulfills the more intuitive (and most fundamental) role of DNA, to encode genes for proteins or RNAs and to regulate their expression. This specialization of centromeres and telomeres is reflected at numerous levels, starting with DNA sequence through chromatin structure to the recruitment and function of specialized structural and signalling proteins. Nine review articles, combined in this web focus series, ‘The Middle & The End’, and published in print over several upcoming issues of *The EMBO Journal*, will summarize our current understanding of these various aspects of chromosome biology, especially in the light of recent advances, and show parallels as well as differences in the function and organization of centres and ends.

At the basis of things is, once again, chromatin. Not surprisingly, both telomeric and centromeric regions show, to varying degrees in all eukaryotes, specialized chromatin structures, which have been the focus of many studies and intense investigations. Various aspects of the resulting increasingly complex picture of chromatin organization and function at both telomeres and centromeres are therefore covered in several reviews in this series. The importance of telomeric heterochromatin for protection of chromosome ends is now well understood in lower eukaryotes, such as yeast as well as in mammals, in which studies using transgenic mice have significantly broadened our horizon. This is

reviewed in the article by Stefan Schoeftner and María Blasco, who depict how the epigenetic regulation through histone and DNA modifications of (sub)telomeric regions impinges also on differentiation and cellular reprogramming in higher eukaryotes. Among unicellular fungi, the budding yeast *Saccharomyces cerevisiae* sports heterochromatin at the ‘end’ but not the ‘centre’, whereas fission yeast silences chromatin both in telomeric and peri-centromeric regions, and Marc Bühler and Susan Gasser discuss what these two model organisms have taught us about commonalities and differences in silencing mechanisms in the middle and at the end. At centromere proper, however, the formation of a specialized chromatin structure is also essential, as a basis for chromosome segregation during cell division. Here, the specialization in fact goes beyond histone modification down to the very core of the nucleosome, with the incorporation of a centromere-specific histone H3 variant being the key event for specifying centromere identity. The last few years have brought significant new insights into the peculiar nature of CenH3-containing nucleosome as well as into the mechanisms governing CenH3 incorporation and centromere specification, and this is reviewed by Mònica Torras-Llort, Olga Moreno-Moreno and Fernando Azorín.

As a consequence of the presence of heterochromatin in the middle and at the ends, centromeres and telomeres have long been considered to be transcriptionally silent—with RNA-dependent mechanisms, however, governing heterochromatin assembly, as outlined by Bühler and Gasser. The recent discovery of non-coding RNAs transcribed from telomeric regions has expanded our view, and how these telomeric RNAs may function in the regulation and maintenance of telomere length is the focus of the contribution by Brian Luke and Joachim Lingner. Less is known about the transcription at centromeres and the possible association and function of centromere-derived non-coding RNAs, but indications in this direction also exist, as Torras-Llort *et al.* discuss.

As mentioned earlier, the functional significance of centromeres lies primarily in their role in chromosome segregation, in which they provide the assembly platform for a complex proteinaceous structure mediating the attachment to opposite spindle poles through microtubule bundles. A comprehensive overview of this intricate multiprotein assembly, the kinetochore, is offered by Stefano Santaguida and Andrea Musacchio, who venture to integrate the multitude of newly available structural, biochemical and cell biological information into a unified picture of kinetochore function in microtubule attachment as well as in microtubule depolymer-

ization during anaphase. Given the importance of these processes, they are naturally subject to checkpoints controlling the orderly progression of attachment and segregation. For that reason, the centromere-assembled kinetochores also serve as signalling modules, initiating the so-called spindle assembly checkpoint that biochemically delays the onset of anaphase until the last kinetochore has been properly connected to spindle microtubules. The fact that not only qualitative, but also a considerable amount of quantitative experimental data on this process are now available, has made spindle assembly checkpoint signalling and its logics increasingly amenable to computational and theoretical approaches. Andrea Ciliberto and Jagesh Shah explain what we have already learnt, and what we may learn in the future, from such studies, and propose a view of spindle checkpoint dynamics from a systems biology perspective.

Another important cell cycle checkpoint comes into action at the ends of chromosomes—the DNA damage checkpoint, maybe not surprising considering that these ends very much resemble DNA double-strand breaks, known to trigger the damage checkpoint response anywhere else in the genome. However, as detailed in the review by David Lydall, this system provides a classical protective cell cycle arrest function only in the case of critical telomere shortening. Normal telomeres, however, have evolved mechanisms to not only prevent the DNA damage checkpoint proteins from arresting proliferation and erroneously ‘repairing’ chromosome ends, but at the same time even harnessing them for the assembly of the distinctive telomere protective structures. These higher order arrangements contain numerous proteins

as well as special DNA structures involving single stranded overhangs, and they also seem to be at the heart of a counting mechanism, feeding back into the regulation of telomere repeat length, as David Shore explains in his article. Adjusting and maintaining the appropriate length involves a tightly regulated interplay between replicative polymerases and telomerase, a specialized reverse transcriptase polymerizing telomeric repeat DNA, to deal with the end replication problem and to ensure that once we reach the end, this should not also spell ‘the end’ for chromosome duplication.

The latter also holds true in a physiological sense. Naturally, in light of the essential functions of telomeres and centromeres, there is a great potential for the occurrence of pathological dysfunction. Defects at the kinetochore and in the spindle assembly checkpoint, affecting accurate chromosome segregation, are linked to the generation of aneuploidy and thus tumourigenesis. Telomere length alterations, however, are implicated both in replicative senescence and in cancer. In his contribution, Peter Lansdorp provides a unique perspective on this, which integrates the known disease links of telomerase dysfunction to a concept explaining the apparent particular importance of telomerase in stem cell compartments and in relation to longevity.

On behalf of the editorial team at *The EMBO Journal*, we would like to thank all the advisors, reviewers, our publishers, and, most importantly, all the authors, who together have been instrumental in putting this collection together. We hope that as readers of the journal you will enjoy this focus series—ideally from the beginning to the ‘end’, but also feel free to start in the ‘middle’...