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Using synthetic chromosomes to study centromere epigenetics in human cells

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Human artificial chromosomes (HACs) recently became useful tools in cell biology, with the potential to rescue the loss of particular gene products in monogenic diseases, to produce huge proteins in human cells or to study chromosome stability and segregation mechanisms. Thanks to the use of a "bottom up" approach, which allows the construction of new HACs starting from synthetic DNA sequences transfected into human cells, we developed the first human artificial synthetic chromosome with a conditional centromere. This alphoidtetO-HAC was generated de novo using a 50 kb synthetic alphoid DNA array based on a repeating 340 bp dimeric unit, with one 170 bp monomer containing a tetracycline operator (tetO). By targeting specific proteins to the centromere of the HAC as tetracycline-repressor (tetR) fusion proteins, we can study the epigenetic landscape in this portion of the chromosome. Now a new generation of 2-domains HAC is under development. These two-domain HACs allow the simultaneous targeting of different chimeric proteins to both the centromere and the flanking pericentromeric heterochromatic region. These new two-domain HACs will allow workers to fully understand the differences in functional chromatin states that occur between the centromere and the heterochromatin that surrounds it, and in particular, how the centromere resists invasion by the heterochromatin. Overall, these chromosomes will help to define what makes centromeric chromatin so unique. Beyond these basic cell-biological properties, they may also provide improved tools for potential gene therapy applications and for screening for potential chemotherapeutic drugs that induce aneuploidy.

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