A sustainable mouse karyotype created by programmed chromosome fusion

CHEM-E8125 Synthetic biology
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Wang et al. (2022), A sustainable mouse karyotype created by programmed chromosome fusion. Science 377, 967-975.

img: Brandi Allred, 2022, Oldest mouse, az animals

Introduction

- A sustainable mouse karyotype:

  - Complete set: Size, number, shape

  - Rodents have 3,2 to 3,6 rearrangements per million years

  - Genetic engineering: Stable, balanced and persisting mutations

- What is programmed chromosome fusion?

  - Merging to form a larger chromosome: head-to-tail fusion method in sperm-like stem cells

  - New strains and traits, effect of rearrangements and genetic defects

The aim

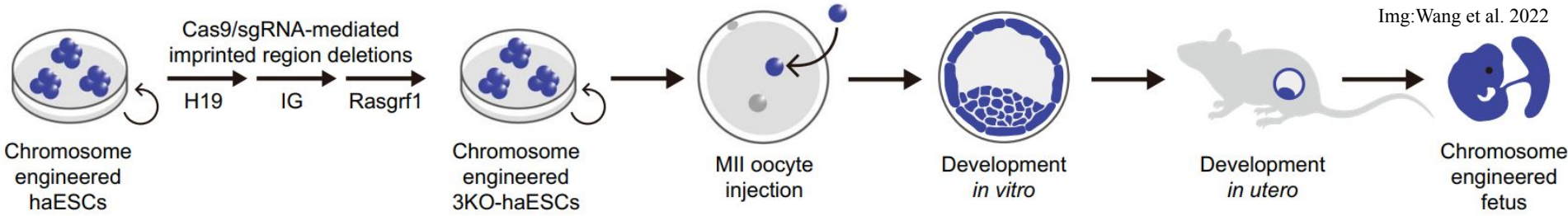
- The procedure was successful in yeast, not in mammals
  - Test the feasibility of chromosome engineering in mammals
- Living mice with new karyotypes that can produce a fertile offspring
  - Karyotype changes can fuel species evolution

"*We wished to address whether we could ligate chromosomes in mammalian cells. We also examined how it would affect stem cell differentiation and chromatin organization and to what extent it would affect mouse phenotypes*." Wang et al. 2022

Img: Cytogenetic gallery, Mouse karyotype

Methods and approaches

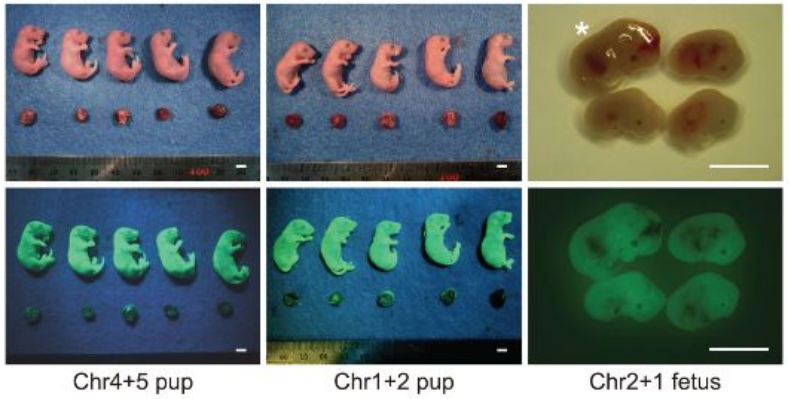
- CRISPR/Cas9 was used to program chromosome fusions in mouse embryonic stem cells (ESCs)
- For fusion, specific chromosome pairs were chosen based on their similar sizes and gene contents, as well as their relative positions in the karyotype.
- A selection system was developed to identify cells that have the desired chromosome fusions.
- By using methods such as karyotyping, chromosome painting, and RNA sequencing, the cells were validated and characterized.



Img:Wang et al. 2022

What was achieved?

- Successfully ligated mouse chromosomes 4 & 5 (Chr4+5) and chromosomes 1 & 2 (Chr1+2 and Chr2+1)
- Established new lines of haploid embryonic stem cells (haESC) with the ligated chromosomes
- Confirmed the successful transmission of the engineered chromosomes to the next generation for Chr4+5 and Chr1+2
- Chr4+5 succeeded to give birth to full-term pups carrying these ligated chromosomes



Img: Wang et al. 2022

What did not work?

- No viable pups were obtained carrying the ligated chromosomes in Chr 2+1
  - They showed abnormalities and died before embryonic day
- Chr1+2 mice exhibited overgrowth, had an high level of anxiety and moved significantly less and slower than normal mice, could not produce offspring

Why and how is this important?

- Previous researches engineered chromosomes successfully only in yeast now success also in mammals
- Insight into how chromosomal rearrangements may influence evolution

  → genetic understanding across millenia not just short-term knowledge

  → how to correct misaligned chromosomes

- showed that chromosome rearrangement
  - ➢ is the driving force behind the evolution of species → offers potential for large-scale modification of mammalian DNA.
  - ➢ is very important in the establishment of the reproductive isolation
    - ➢ abnormality in how chromosomes separated after alignment leads to weakened fertility
    - ➢ key evolutionary signal for the emergence of a new species

Img: How do geneticists indicate the location of a gene?: MedlinePlus Genetics