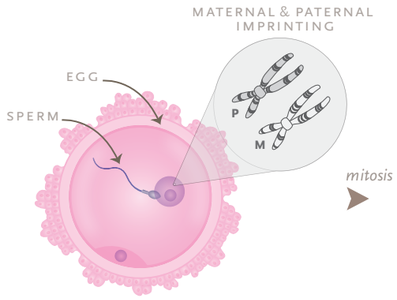
Nuclear Reprogramming . Human Development

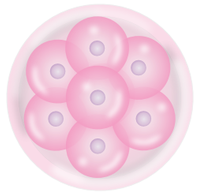
in vivo

FERTILIZATION



ZYGOTE
day 0

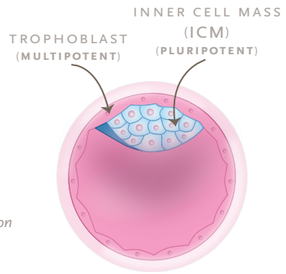
TOTIPOTENT *cells*



BLASTOMERE
day 3
8 cells

mitosis
&
differentiation

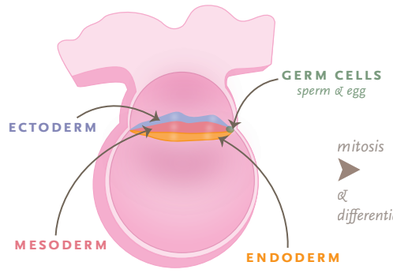
PLURIPOTENT & MULTIPOTENT *cells*



BLASTOCYST
day 5
~150 cells

mitosis
&
differentiation

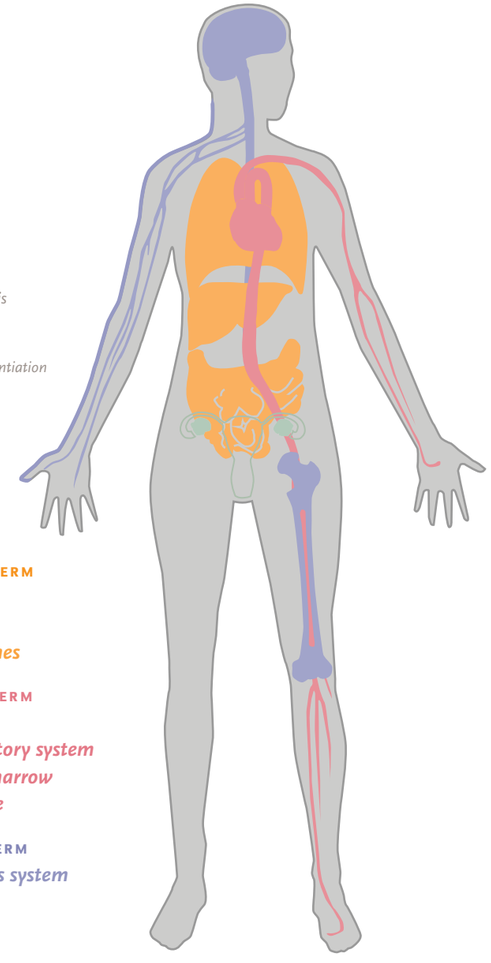
MULTIPOTENT *cells*



GASTRULA
day 14

mitosis
&
differentiation

mitosis
&
differentiation



ENDODERM
lungs
liver
intestines

MESODERM
heart
circulatory system
bone marrow
adipose

ECTODERM
nervous system
bone
skin

GERM CELLS
sperm & egg

Genomic Imprinting:

Humans have two copies of every gene in the genome, one from the father and one from the mother, but some genes code for products that are dosage sensitive. Humans have evolved to silence *one* copy of a gene in an effort to compensate for the "dose" of gene product made. This reprogramming is complementary, such that genes that are silenced on the paternal contribution of the genome are activated on the maternal contribution of the genome and vice versa. This kind of nuclear DNA reprogramming involves chemical modifications of the chromosomes such that some regions are physically compressed and inactive (imprinted). Maternal and paternal imprints result in complementary gene expression and ensure that humans reproduce sexually. Imprinting is a dynamic process. For example, during the generation of sperm and egg, complementary imprints are erased and replaced with either maternal (on eggs) or paternal (on sperm) imprints. When imprinting is not properly executed, embryogenesis is compromised. To date, 83 imprinted genes have been identified, though there may be over 1000 that undergo this DNA reprogramming process.

Cell Differentiation:

As embryogenesis continues, cells migrate in response to environmental cues. The position of the cells influences their exposure to a gradient of signals secreted by the womb, neighboring cells, and the extracellular matrix. This differential exposure ultimately influences which genes will be reprogrammed. Though each cell has a complete human genome, as cells differentiate they must activate some genes and silence others. Differential gene expression allows cells to exhibit different characteristics and determines how cells will respond to environmental cues in the future. Unlike imprinting, cell differentiation involves chemically modifying *both* maternal and paternal DNA sequences for a specific gene resulting in localized gene activation and silencing. Thus, the trophoblast cells express the genes necessary for placenta and umbilical cord function, while ICM cells silence that same set of genes and activate genes necessary for pluripotency ("Yamanaka iPSC factors" Oct4, Klf1, Sox2). Perturbations in nuclear reprogramming can compromise human development and human health; aberrant nuclear reprogramming is associated with the development of most cancers.

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