Strategies and Prospects for Organ Regeneration in Aging

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Overview of Talk

• Background on aging and organ function: Statement of the Problem

• Senescence ↔ Aging-related diseases

• Definitions- emphasis on Stem Cells

• Strategies and limitations for organ regeneration

• Prospects/Future considerations
Decline in Organ Function with Aging

• Kidney
• Lung
• Brain
• Heart
• Liver
• Structural tissues (muscle, bone)

• TREATMENTS LARGELY DIRECTED AT SYMPTOMS
Decline in Lung Function

Normal values for FVC, FEV1 and FEV 25-75%

- Men
- Women

- FVC (L)
- FEV1 (L)
- FEF 25–75% (L/s)

Age (years)

Important Points

• Many organs have tremendous reserve (lung)

• Loss of cells that carry-out organ function (parenchymal)

• Replacement with non-functional tissue (scar)

• Disease vs. Senescence
Diseases of Aging

- COPD
- Kidney Failure
- Diastolic Heart Failure
- Alzheimer’s, Parkinson’s
- Osteoporosis
- Diabetes (type II)
- Cancer
Senescence

• Cellular

• Organ

• Organismal

• Theories: evolutionary pressure, oxidants, mutations, immunological, wear and tear, STEM CELLS
Stem Cell: Definition

• Self renewing cells that have capacity to give rise to defined repertoire of differentiated parenchymal cells (blood, skin, neural)

• Important in development, lower animals,

• Varying degree of potency: uni-potent, bi-potent, pluripotent etc.

• Somatic, germ, embryonic**

• Reside in specialized anatomic sites: niches
Embryonic Stem Cells

• Derived from inner cell mass of embryo

• Pluripotent—can give rise to all tissues of mammalian organism

• Therapeutic potential, immune problems, moral issues

• iPS cells—induced pluripotent state in a fully differentiated cell (viruses, *in vitro*)
iPS Cells

- Revolutionary, paradigm shifting
- Overcomes moral and immune limitations
- Basic Biology, Disease study, Drug optimization, Fix Genetic defects

(Takahashi and Yamanaka: Cell 2006)
iPS Pluri-potency

Adult tissues

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<th>Skin</th>
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<th>Liver</th>
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(Boland, Nature 2009)
Organ Regeneration in Humans

• Difficult to determine
• Liver, skin, and blood
• Age dependency
• Rodents, invertebrates (worms, zebra fish)
Goal of Organ Regeneration: Restore Function

• Single cells vs. Multi-cellular structure

• How to do it?

• Delivery

• Space
General Strategies for Organ Regeneration

• New organs

• New parenchymal cells

• New stem stems or more stem cells

• Deliver stimulatory or inhibitory signals
Whole Organs

• Transplantation

• Animal source

• De-cellularized organs

• Organoids-stem cells and supporting cells, self-organize in vitro (gut, brain, liver)

• Mechanical devices
Parenchymal Cells

• Deliver fully differentiated cells

• Deliver stem cells

• Deliver iPS cells

• Limitations
Deliver Signals

• Circulating Signals (normal)

• Developmental signals

• Signals used in lower animals

• Direct *in vivo* re-programming (heart)

• Inhibit causes of senescence (anti-oxidants, resveratol, rapamycin etc.)
Circulating Factors

(Loffredo et al, Cell 2014)
Prospects/Issues

• Early, applicability to humans
• Basic biology
• Many technical obstacles
• Toxicities
• Costs/Regulations- (Geron^R trial)
• Appropriate Priority
-continued-

- Simple
- Low toxicity
- Scalable
- Reality
- Basic research