Umbilical Cord
Wharton’s Jelly
Mesenchymal Stem
Cells – The Next
Future

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• A Center for Stem Cell Therapeutics and Longevity/Regenerative Medicine
THE NEXT FUTURE OF HEALTHY AGING

FOCUS ON:

STEM CELLS – THE WHAT THE HOW THE KNOW THE USES

AGING - AUTOPHAGY SENESCENCE

THE NEXT FUTURE OF HEALTHY AGING
The Future of Medicine
Focus on:
• What are stem cells? (Birth Tissue and Cell Products)
• Types of stem cells.
• Theory of stem cells.
• Uses of stem cells.
The View of Stem Cells
THE NEXT WAVE OF MEDICINE

Stem cell therapy has been gaining support and popularity in the medical community and is the next level to soon become the standard of care.

Research is producing solid evidence regarding the benefits of stem cell therapy to not only control symptoms but to reverse the deleterious effects of certain diseases and disorders.

A paradigm shift in the way medicine is delivered is now underway.

Regenerative Medicine is using therapies that have the potential to fully heal damaged tissues and organs offering hope for patients who have exhausted their treatment options.
Stem Cell Theory

History
1868 - German biologist, Ernst Haeckel uses the phrase stem cell to describe a single celled organism that acted as the ancestor cell to all living things.

1909, Alexander Maximow introduces the idea of blood cells being multipotent.

1953 - Leroy Stevens performing cancer research in mice found scrotal tumors containing mixtures of differentiated and undifferentiated cells. These cells were pluripotent.

1968 - Robert Good of the University of Minnesota performs the first successful bone marrow transplant.

1981 - Martin Evans of the University of Cambridge and Gail Martin of the University of California, San Francisco, are the first to isolate embryonic stem cells.

1986, Andrew Lassar and Harold Weintraub of Seattle, Washington convert fibroblasts directly into myoblasts using a single gene (MyoD). This experiment of converting one type of adult cell into another was the first step towards regenerative medicine.

1998, scientists reported that they had successfully isolated and cultured human embryonic stem cells

2004 - Woo-Suk Hwang et al., used therapeutic cloning to create the first human stem cells.

2009, Geron Corporation obtains approval from the FDA for the first clinical trial for a therapy based on human embryonic stem cells.

2009 – The NIH (National Institute of Health) issues guidelines on federal funding for stem cell research. Any scientist wanting to conduct research on any of the 13 recognized line of human embryonic stem cells can now apply for federal funding.
Types of Stem Cells

- **Totipotent** – The only type of stem cell that can construct a complete, viable organism. These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent.

- **Pluripotent** - Stem cells are the descendants of totipotent cells and can differentiate into nearly all cells, i.e. cells derived from any of the three germ layers.

- **Multipotent** - Stem cells can differentiate into a number of cell types, but only those of a closely related family of cells.

- **Oligopotent** - Stem cells can differentiate into only a few cell types, such as lymphoid or myeloid stem cells.

- **Unipotent** - Stem cell can produce only one cell type, their own, but have the property of self-renewal, which distinguishes them from non-stem cells.
Stem Cell Theory

- Stem cells are undifferentiated biological cells that can differentiate into specialized cells and can divide (through mitosis) to produce more stem cells. Stem cells of a specific type are capable of evolving into many different types of specialized cells within the body.
Stem Cell Theory

- Stem cells are theorized to not only **replace** damaged or dysfunctional cells, but also **regenerate** new healthy tissues.

- Applications: Orthopedic, aesthetics, Multiple Sclerosis, Autoimmune Diseases, COPD, Rheumatoid Arthritis, Cardiovascular Diseases, Parkinson’s disease, Osteoarthritis, Alzheimer’s disease, Diabetes Type 1 & 2, Cerebral palsy, Autism, and more.
Stem Cell Theory

Characteristics of Embryonic Stem Cells

1. Origin:
   Derived from pre-implantation or peri-implantation embryo

2. Self-Renewal:
The cells can divide to make copies of themselves for a prolonged period of time without differentiating.

3. Pluripotency:
   Embryonic stem cells can give rise to cells from all three embryonic germ layers even after being grown in culture for a long time.

The three germ layers and one example of a cell type derived from each layer:

- **Ectoderm**
  - gives rise to: brain, spinal cord, nerves, cells, hair, skin, teeth, sensory cells of eyes, ears, nose, and mouth, and pigment cells.
  - Example: Neuron

- **Mesoderm**
  - gives rise to: muscles, blood, blood vessels, connective tissues, and the heart.
  - Example: Blood cells

- **Endoderm**
  - gives rise to: the gut (pancreas, stomach, liver, etc.), lungs, bladder, and germ cells (eggs or sperm)
  - Example: Liver cell

stemcellgurus.wordpress.com/2012/05/09/escposter
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Embryonic stem (ES) cells

- have an almost unlimited developmental potential - pluripotent
- unlimited self-renewal
- give rise to all cells of the organism
- ES cells that have proliferated in cell culture for six or more months without differentiating, are pluripotent, and appear genetically normal are referred to as an embryonic stem cell line. At any stage in the process, batches of cells can be frozen and shipped to other laboratories for further culture and experimentation.
• This is the most potent stage of the stem cell
• The ethics of using ES cells comes into question as harvesting of the ES cells sacrifices the blastocysts.
• The dilemma addresses two fundamental moralities that humans value:
  • 1) the duty to prevent or alleviate suffering
  • 2) to respect the sanctity of possible human life
• As the morality of this argument has not been resolved, ES cells are not used in the United States for regenerative therapies.
Stem Cell Theory
Stem Cell Theory

- **Hematopoietic stem cells**
  - Blood collected from venous draw prior to chemotherapy and radiation. Stem cells are separated by a process of apheresis.
  - Typical use: hematologic malignancies (e.g., leukemia, lymphoma, and myeloma), nonmalignant acquired bone marrow disorders (e.g., aplastic anemia), and genetic diseases associated with abnormal hematopoiesis and function (thalassemia, sickle cell anemia, and severe combined immunodeficiency).
  - Hematopoietic cell transplantation (HCT) is the intravenous infusion of hematopoietic stem and progenitor cells.
  - These mesenchymal stem cells give rise to all red and white blood cells and platelets.
• Sources of Stem Cells

Umbilical cord/amniotic fluid

Bone marrow

Mesenchymal stem cells

Adipose tissue

Improved wound healing
Mesenchymal Stem Cells
Mesenchymal Stem Cells

• Positive Expression of CD 73 CD 90 CD 105

• Negative Expression of CD 14 CD 34 CD 45 CD 19 HLA-DR

  CD -the cluster of differentiation (also known as cluster of designation or classification determinant and often abbreviated as CD) is a protocol used for the identification and investigation of cell surface molecules. In terms of physiology, CD molecules can act in numerous ways, often acting as receptors or ligands important to the cell i.e. cell-cell adhesion, etc.

• Plastic-adherent in Standard Cultures

• MSC must differentiate into chondroblasts(a), adipocytes (b), or osteoblasts(c)
Stem Cell Theory
Bone Marrow

- Stem cells collected from bone marrow aspiration. Cells are separated by centrifuge and injected directly into the joint.
- Requires a minor surgical procedure. Takes up to 1 – 2+ hours in an office or surgical setting.
- A paucity of MSCs with bone marrow aspirate, .001 - .02% 1 in 30,000 cells are MSC’s
- Bone Marrow Aspirate produces 30 – 300 MSC’s per 1cc
- Efficacy is age dependent as well as dependent on the host’s health
Stem Cell Theory
Stem Cell Theory

- **Adipose**
  - Stem cells collected through a lipoaspirate procedure. Cells are separated by centrifuge and injected directly into the joint.
  - Greater numbers of MSC’s observed than with bone-marrow derived (1 – 7% vs .001 - .02%)
  - Adipose-derived produces 4,500 – 450,000 MSC’s per 1cc
  - More accepted as the method to obtain MSCs autologously
  - Efficacy is age dependent and subject to environmental/nutritional damage
Stem Cell Theory
Umbilical Cord Mesenchymal Stem Cells and Amniotic Products

- Collected from donors after live cesarean birth or normal vaginal delivery. No ethical conflicts.
- Day 0 source of MSC’s. The most potent the cells can be.
- There is a growing body of evidence showing that mesenchymal stem cells from umbilical cords are more robust than mesenchymal stem cells from other sources such as fat.
Stem Cell Theory
Umbilical Cord Blood and Amniotic Membrane

Umbilical Cord Blood MSCs
• Blood is extracted from the umbilical cord vessels and is processed to isolate hematopoietic cells and mesenchymal stem cells
• The amniotic placenta/membrane is processed for cytokines
• The concentration of MSCs is therapeutically insignificant in amniotic tissue
• Increase risk of host-graft rejection
• Increased risk of infections and adverse events.
Wharton’s Jelly/Umbilical Cord MSCs
• the gelatinous substance of the umbilical cord consisting of high concentrations of mucopolysaccharides (heavy chain hyaluronic acid and chondroitin sulfate)
• Hyaluronic acid necessary for chondrocyte homeostasis
• 50 x more efficient than a chicken comb or synthetic HA
• Provides support and protection for the vein and artery of the umbilical cord
• Also an excellent source for stem cells

Stem Cell Theory

- Cryopreserved at -200° F
- The number of viable MSC varies from cord to cord (2 x10^6/ml to 200 x10^6/ml)
- Rich in hematopoietic stem cells (HSC’s) and MSC’s
- Negative for HLA Class II surface antigens, therefore immunoprivileged
Stem Cell Theory

• Amniotic Fluid Matrix
• Amniotic Fluid - Surrounds the fetus in utero providing protection against physical trauma and provides temperature regulation
• Also contains hyaluronic acids and stem cells
• Rich in growth factors, cytokines, proteins, and hyaluronic acid
• Biochemical match for synovial fluid in joints providing anti-scarring, anti-adhesive and anti-inflammatory properties
• Typically collected and stored at -80°C
Stem Cell Theory

In Summary

• Bone Marrow aspirate produces viable MSC’s in the lowest numbers
• Adipose-derived produces viable MSC’s greater than bone marrow but also in low numbers questions on sterility
• Umbilical Cord Stem Cells produces a high volume of viable MSC’s much greater than bone marrow or adipose
• Any product stored at less than approximately -200°C does not contain viable MSC’s

• The FDA is responsible for protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices

• On December 23, 2014, the FDA announced a new draft guidance document entitled “Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products”. The draft guidance document advises manufacturers of human cells, tissues, and cellular and tissue-based product (HCT/P) products and healthcare providers of the FDA’s current policy on the minimal manipulation criterion of 21 C.F.R. § 1271.10(a)(1).

• Minimally Manipulated

• (1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and

• (2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.
Whether an HCT/P is more than minimally manipulated is of utmost importance when assessing the regulatory status of an HCT/P product. Under 21 C.F.R. § 1271.10(a) Section 361, for an allogeneic HCT/P product to qualify as an HCT/P that does not require a biologics license application or new drug approval, the product must meet four criteria:

1. it must be minimally manipulated
2. it must be intended for homologous use
3. the manufacturing, with some exceptions, “does not involve the combination of the cells or tissues with another article”
4. the product “does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function”
How Stem Cells Work

1. Direct engraftment onto inactive or damaged host cells to effect a repair of the host cells

2. “Paracrine-Effect”
   Cell to cell communication to host cells through exosomarial activity and other processes
   (maybe bioelectric frequency communication)

USES OF STEM CELLS

• Orthopedic Procedures
  • Knees, Shoulders, Backs, Hips, Ankles, Neck, TMJ, Feet, Hands, any joint

Aesthetic Procedures
  Hair, Faces, Scars, Deformities, Wounds

Autoimmune Diseases and Other Systemic Diagnoses
  MS, Dementia, Crohn’s, RA, Autism and many more

Wellness and Longevity
Stem Cell Uses

• Speed up the length of time it takes for injuries or wounds to heal
• Reduce pain, even chronic joint pain, with less need for medications and can even eliminate pain medications
• Repairs osteoarthritic joints
• Increase functionality, the range of motion, flexibility and sleep quality
• Reduce muscle compensations and risk for future injuries
• Decrease nerve damage and can repair nerves
• Increase collagen
• Help generate new heart and blood vessel tissue angiogenesis
• Help heal skin wounds, prevent the formation of scar tissue and reduce hair loss (even stimulates hair growth)
• Return patients to their normal activities as quickly as possible
Stem Cell Uses

• Orthopedic injuries
• Autoimmune conditions - MS, diabetes, lupus, Parkinson’s disease, autism, kidney damage, dementia, RA, etc.
• Heart disease, lung disease, TBI
• Wound care
• TMJ
• Hair Restoration
• Aesthetic procedures
Benefits for Aesthetics

- Treatment of chronic wounds scar remodeling
- Nonsurgical treatment of scleroderma
- A long-lasting autologous alternative to synthetic fillers
- Scar reduction
- Hair restoration
- Skin care overall texture stops environmental damage
- Recovery from laser procedures
- Increase collagen production
Stem Cells and Hair

- Multipotent stem cells can regenerate hair follicles with sebaceous glands in the skin. Stem cells can be used to regenerate hair in several therapeutic strategies:

- Reversing the pathological mechanisms which contribute to hair loss (especially in androgenic alopecia)

- Regeneration of complete hair follicles from their parts (cells in the bulge can regenerate a whole hair)

- Neogenesis of hair follicles from a stem cell culture with isolated cells or tissue engineering
Combinations Of Procedures

- Add stem cells to:
  - PRP
  - Growth factors
  - Hyaluronic acid products
  - Dermal fillers
  - Neuromodulators
  - Laser treatments
  - Fat transfers
  - IPL/Radiofrequency treatments
  - Peptides
  - PEMF
  - Light Therapies
Delivery Options

- IV intravenous
- IM, SQ intra muscular, sub cutaneous, intrathecal
- Intra articular
- Micro-needling
- Subdermal injections
- Deep dermal injections filling and lifting
- Cosmeceutical
Intra-articular joint injections
Micro-needling
Injection
Hair restoration
Wharton’s Jelly MSC
Umbilical Cord extraction of MSCs
Wharton’s Jelly MSC

- Wharton’s Jelly has become a preferential source of stem cells due to its ready availability from a large pool of donors, noninvasive and painless acquisition, no risk to the donor, no ethical limitations, weak immunogenic potential, and high multipotential differentiation capability.

Wharton’s Jelly MSC

- substantia gelatinea funiculi umbilicalis) is a gelatinous substance within the umbilical cord largely made up of mucopolysaccharides (hyaluronic acid and chondroitin sulfate). It also contains some fibroblasts and macrophages
<table>
<thead>
<tr>
<th>Umbilical cord tissue provides an abundant supply of mesenchymal stem cells.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No need to collect stem cells through invasive procedures such as liposuction or bone marrow aspiration</td>
</tr>
<tr>
<td>There is a growing body of evidence showing that mesenchymal stem cells from umbilical cords are more robust than mesenchymal stem cells from other sources such as fat.</td>
</tr>
<tr>
<td>Over 440 known cytokines, collagen 3.6%, glycoprotein .3%, Hylauronin .31% and billions of exosomes</td>
</tr>
</tbody>
</table>

Process of MSCs

- Cords obtained using the American Tissue Bank Protocol
  - Donors mother and father screened for any history of communicable diseases and behavioral risk
  - Blood tests are required within 7 days before or after birth
- Cords collected and shipped overnight to the lab
- The tissue is sanitized and handled utilizing aseptic protocols
- Cord tissues are processed using specialized non-enzymatic procedures
- Cord MSC are stored at ≈ -200 degrees C with amniotic products stored at -80 degrees C
- A sample of each lot sent to third party for sterility testing and quarantine for 2 weeks
- Shipped overnight on dry ice (if stored at facility then a cryo-freezer is used)
- UC-MSCs showed very high differentiation capacity
- Change into **chondrocytes** (cartilage), **adipocytes** (fat cells), osteoblasts (bone), **odontoblast-like** cells (teeth), dermal fibroblasts (skin), **smooth muscle** cells, **skeletal muscle** cells, **cardiomyocytes** (heart muscle), **hepatocyte-like** cells (liver cells), **insulin-producing** cells (pancreas diabetes), **glucagon-producing** cells (prevent diabetes), and **somatostatin-producing** cells (adrenal gland hormones), **sweat gland** cells, **endothelial** cells (blood vessel cells), **neuroglia** cells (oligodendrocytes) (brain cells), and **dopaminergic neurons** (neurotransmitter cell).
Skin cell renewal controlled by mesenchymal stem cells (MSCs)

- Quiescent until stimulated after any injury
- Promote wound healing by modulating the inflammatory environment, promoting angiogenesis and vascularization, encouraging the migration of keratinocytes and contribute to re-epithelization and extracellular remodeling as well as inhibiting apoptosis of wound healing cells

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• Chemotactic proteins cause MSCs to migrate to sites of injury, a response that is mediated by the activation of matrix metalloproteinases

• MSCs possess antimicrobial properties and may help to prevent infections in the wound bed. MSCs can secrete bactericidal factors, such as LL-37 (cathelicidin peptides), directly into the local environment, and they can indirectly increase the amount of phagocytosis by activating immunomodulatory factors

How do they work

- Angiogenesis, anti-inflammation, and anti-apoptosis mostly through secreted cytokines and growth factors rather than their differentiation into various cell types.

- Cytokines and growth factors have the potential to be used in cell-based treatments in regenerative medicine due to their promotion of fibroblast proliferation and the differentiation to fibroblast.

- Increase collagen secretion hence collagen density

- Increase dermal/cartilage thickness

Not embryonic stem cells or adult stem cells but have properties of both

Wharton’s Jelly is a mature mucous tissue and the main component of the umbilical cord, connecting the umbilical vessels to the amniotic epithelium.

Since HUCT mesenchymal stem cells are immune system privileged, cell rejection is not an issue and Human Leukocyte Antigen (HLA) matching is not necessary.

The stem cells with the best anti-inflammatory activity, immune modulating capacity, and ability to stimulate regeneration can be screened and selected.

Allogeneic stem cells can be administered multiple times over the course of days in uniform dosages that contain high cell counts.
Wharton’s Jelly Mesenchymal Stem Cells
Birth Tissue Cells and Products

- Are more primary cells
- Easily isolated and without invasive procedures
- No ethical problem
- More cost-effective than other sources of MSCs
- Express stem cell mesenchymal markers (CD44, CD105), whereas they do not express the hematopoietic markers (CD34, CD45)
- Express major histocompatibility complex (MHC) class I molecules (such as human leukocyte antigen (HLA)-A, -B, -C), while they do not express MHC class II (HLA-DR) on their cell surface
Markers for MSC Identification

- PositiveCD9: CD9 molecule (CD9)
- PositiveCD10: Membrane metalloendopeptidase
- PositiveCD13: Alanyl aminopeptidase, membrane
- PositiveCD29: Integrin subunit beta 1
- PositiveCD44: CD44 molecule (Indian blood group)
- PositiveCD49f: Integrin subunit alpha 6
- PositiveCD54: Intercellular adhesion molecule 1
- PositiveCD71: Transferrin receptor
- PositiveCD73: 5-nucleotidase ecto
- PositiveCD90: Thy-1 cell surface antigen
- PositiveCD105: Endoglin
### Markers for MSC Identification

<table>
<thead>
<tr>
<th>Marker Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive CD106</td>
<td>Vascular cell adhesion molecule 1</td>
</tr>
<tr>
<td>Positive CD146</td>
<td>Melanoma cell adhesion molecule</td>
</tr>
<tr>
<td>Positive CD166</td>
<td>Activated leukocyte cell adhesion molecule</td>
</tr>
<tr>
<td>Positive CD200</td>
<td>CD200 molecule</td>
</tr>
<tr>
<td>Positive CD271</td>
<td>Nerve growth factor receptor</td>
</tr>
<tr>
<td>Positive CD349</td>
<td>Frizzled class receptor 9</td>
</tr>
<tr>
<td>Positive CD362</td>
<td>Syndecan 2</td>
</tr>
<tr>
<td>Positive</td>
<td>Ganglioside</td>
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<tr>
<td>Positive</td>
<td>G protein nucleolar 3</td>
</tr>
<tr>
<td>Positive</td>
<td>Heat shock protein family A (Hsp70) member 8</td>
</tr>
<tr>
<td>Positive —</td>
<td>Heat shock protein 90 beta family member 1</td>
</tr>
<tr>
<td>Positive</td>
<td>Stage-specific embryonic antigen-4</td>
</tr>
<tr>
<td>Positive —</td>
<td>Sushi domain containing 2</td>
</tr>
<tr>
<td>Positive —</td>
<td>Alkaline phosphatase, liver/bone/kidney</td>
</tr>
</tbody>
</table>
Markers for MSC Identification

• Negative CD11b  Integrin subunit alpha
• Negative CD14  CD14 molecule
• Negative CD19  CD19 molecule
• Negative CD34  CD34 molecule
• Negative CD45  Protein tyrosine phosphatase, receptor C
• Negative CD79a  CD79a molecule
• Negative (unless stimulated with IFN-γ)  Human leukocyte antigen
Functions of MSCs

Exosome


Loaded with nucleic acids, cytokines, bioactive compounds, enzymes, surface encoded protein, mRNA, miRNA

Signaling pathways transferring new genetic material
Mechanism of an Exosome

Endosomal membrane invagination - multivesicular bodies with intraluminal vesicles – released as exosomes when fused with plasma membranes – direct fusion or endocytosis

Functions of Exosomes and extracellular vesicles


**Osteoarthritis:**
- *In vitro*: enhances cartilage anabolism, reduces inflammation
- *In vivo* (mice): protects against cartilage degradation and osteoarthritis progression

**Joint inflammation:**
- *In vitro*: immunomodulatory and chondroprotective effects
- *In vivo* (mice): anti-inflammatory effects with reduced cartilage degradation

**Cartilage/osteochondral injury:**
- *In vivo* (rats, rabbits): significant defect repair with hyaline-like cartilage formation
Functions of Exosomes

Factors affecting secretion of exosomes
1. Hypoxia
2. Inflammatory stimuli
3. Stress
4. Intracellular calcium

Mesenchymal stem cells

Extracellular vesicles

Cardiovascular disease
1. Reduce infarct size
2. Enhance tissue repair
3. Increase angiogenesis

Acute kidney injury
1. Tubuloepithelial regeneration
2. Reduce tubular cell apoptosis
3. Reduce fibrosis
4. Reduce tubular atrophy

Liver injury
1. Hepatocyte regeneration
2. Inhibit liver fibrosis
3. Reduce hepatocyte apoptosis

Cutaneous wound healing
1. Increase re-epithelialization
2. Inhibit apoptosis of skin cells
3. Promote proliferation of skin cells

Lung injury
1. Reduce lung edema
2. Reduce inflammation
3. Improve pulmonary hypertension
4. Improve ventricular hypertrophy
5. Improve lung vascular remodelling
Advantages of Exosomes or Extracellular vesicles/microvesicles

- Stable small circulate readily
- Induce stronger signaling efficacious
- Produce higher concentrations
- Intrinsic homing ability
- No immune rejection no inherent toxicity

Disadvantages of Exosomes or Extracellular Vesicles/microvesicles

- Manufacturing is in its infancy
- Proof is efficacy not established maintained over time? Need repeated doses
- Exosomes may not alone be sufficient to exert complete therapeutic effect.
- Batch to batch variation, purity (contaminating materials), quality control, lability, delivery off target effects, pharmacokinetics, storage difficulties, failure to completely isolate EV fractions
- Vesicle shedding in certain pathologies can cause problems i.e. cancer
Advantages of Whole Cell

- Cells maybe more suited have physiological activities yet undiscovered can serve as a natural slow-release platform for exosomes and continue to process exosomes as needed and for different situations.

- The whole original cell maybe overall a better source of natural pure signaling processes.

- The whole cell has the ability to rapidly respond to injury microenvironment.


Growth Factors and Cytokines

• Growth factors (scientific name is cytokines) are regulatory peptides that participate in cell to cell signaling as well as intracellular signaling. These proteins can be produced by fibroblasts, platelets, keratinocytes, and immuno-modulatory cells.

• **Four** main categories of cytokines
  - General
  - Growth factor
  - Scaffolding
  - Homeostatic

• Aid in repair by inducing collagen proliferation, promoting angiogenesis, stimulating cell migration and division, and reducing local inflammation.

• Tiny cell-signaling protein molecules secreted by various cells.
• Growth factors bind to the cell membrane and start the cascade of DNA synthesis, mitosis, and cell repair. Some of these growth factors affect the stem cell environment or as it is sometimes called the “stem cell niche”.
• Function like:
  • **Endocrine** system factors may affect cells in a distant area
  • **Paracrine** system factors may affect neighboring cells
  • **Autocrine** action meaning that the factors affect the surrounding cells
• **Cytokines** are the architects of cell repair

Cytokines/Growth factors

- Brain derived growth factor
- Fetuin-A
- Interleukin 37
- Complement component 5a
- Serpin A4
- Glial derived growth factor
- Bone Morphogenic protein-7
- Syndecan-4

Growth Factors
Exosomes

Ageing

- Ageing is considered the decline or deterioration of physiological functions
  - accumulated alterations in the genome
  - decreased telomere length
  - protein and cellular damage
  - increased inflammation and cell senescence
  - exhaustion of endogenous stem cell populations
  - issues with intercellular communication
  - increased generation of free radicals in cells, tissues, and organs
Ageing

- By 40 years of age, most organs, tissues, and cells gradually become less efficient.
- The skin becomes thin, transparent, less elastic, and more lined and wrinkled. There is a loss of underlying fat on the face leading to hollowed cheeks and eye sockets.
- Hair gradually thins on the scalp, pubic area, and armpits.
- Melanocytes decline in number, grey hair growth increases.
- Nail plates gradually thin.

What is autophagy?

cell cannibalism

Maintenance process for recycling broken or unwanted cellular structures and proteins

It is a regulator of the immune pathway which is destroyed by pathogenic microorganisms, reactive oxygen species, mitochondrial damage and environmental irritants.

As we age this process decreases allowing the build up of damaged cells which lead to age related diseases.

Lee, D., et.al., *Autophagy as a Therapeutic Target to Enhance Aged Muscle Regeneration*, Cells, 2019, 8, 183. 
Rezus, E. et al., The Link Between Inflammaging and Degenerative Joint Diseases, International Journal of Molecular Sciences, 2019, 20, 614.
Autophagy

Rezuš, E. et al., The Link Between Inflammaging and Degenerative Joint Diseases, International Journal of Molecular Sciences, 2019, 20, 614.
Inflammaging

Rezus, E. et al., The Link Between Inflammaging and Degenerative Joint Diseases, International Journal of Molecular Sciences, 2019, 20, 614.
Senescence is irreversible, and a senescent cell is blocked from further replication.

All senescent cells are soon destroyed, either by their own programmed cell death mechanisms, or by the immune system.

Senescent cells are very metabolically active, secreting a potent mix of molecules that disrupts tissue structure, produces chronic inflammation, and encourages nearby cells to also become senescent.

Senescent cells secrete myriad pro-inflammatory cytokines and proteases which can adversely affect the surrounding microenvironment.

Paracrine senescence by induction of senescence in healthy neighboring cells.

A small but growing number of senescent cells remain alive, and their secretions continue, day in and day out, their presence becomes very harmful. They are one of the causes of aging and age-related disease.

Effects of Zombie Cells

Possible therapies

Farr, J. and Khosla, S. Cellular Senescence in Bone, Bone, 2019, 121, 121.
Sencescence
Zombie Cells

Senescence-associated secretory phenotype

- increased number of senescent cells
  - hyperproduction
  - incomplete clearance

- immunosenescence
  - genetic factors
  - environmental factors
  - immune factors

- systemic age-related disorders
  - osteoarthritis
  - atherosclerosis
  - cancer
  - frailty, sarcopenia
  - dementia, Alzheimer disease

Rezus, E. et.al., The Link Between Inflammaging and Degenerative Joint Diseases, International Journal of Molecular Sciences, 2019, 20, 614.
Senescence and Aging

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**EPITHELIAL CELL**

** Basement Membrane **

** STROMA **

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**OLD TISSUE**

**EPITHELIAL CELL**

** Basement Membrane **

** STROMA **

**Degradative enzymes, Inflammatory cytokines, etc.**

**Senescent Fibroblast**

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**YOUNG TISSUE**

**EPITHELIAL CELL**

** Basement Membrane **

** STROMA **

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**AGING ?**

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Chrondroesenesence - OA DJD

Rezus, E. et al., The Link Between Inflammaging and Degenerative Joint Diseases, International Journal of Molecular Sciences, 2019, 20, 614.
MECHANISMS CONTRIBUTION TO STEM CELL AGING AND DYSFUNCTION

Prevention of Zombie Cells

**Prevention of senescence triggers**

**SASP inhibition**
Agents interfering with SASP production or activity including:
- NFκB and p38 inhibitors
- IL1α blockers
- Rapamycin
- Metformin

**Senescent cell killing**
Senoptotic and/or senolytic compounds targeting:
- Survival pathways
- Anti-apoptotic mechanisms
Immune system-mediated clearance:
- Augmented native removal
- T cell targeting
- NK cells
- Antibodies
- Antibody-mediated drug delivery

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Childs, B., et al., Cellular senescence in aging and age-related disease: from mechanisms to therapy, Nat Med. 2015, 21, 12, 1424.
Lee, D. at.al., Autophagy as a Therapeutic Target to Enhance Aged Muscle Regeneration, Cells 2019, 8, 183
The Damage of Senescent Cells

Blagosklonny, M., Paradoxes of Senolytics, Aging, 2018, 10, 12, 4289.
“Turning back the aging clock through cellular reprogramming”
The Next Future of Healthy Aging!

• Longevity
  • There are many theories of aging. Which one is the holy grail - Who knows?

Focusing on:
Increasing cell cannibalism (autophagy) - calorie restriction, intermittent dieting, exercise, selective pharmaceuticals
Killing the Zombie Cells – focusing on senolytics nutraceuticals, calorie restriction
Utilizing peptides
Adding Wharton’s Jelly Mesenchymal Human Cell and Tissue Products to the body
FOLLOWUP is VITAL to any SUCCESS!

Enjoy everyday your life!

Add appropriate stem cells and peptides to maximize your health.

Add appropriate senolytics and calorie restriction mimetics to your daily routine.

Decrease inflammation in your body.

Maintain an exercise program.

Maintain an exercise program.

Need to continue on a healthy diet.

Need to continue on a healthy diet.
The Cure of the Future
It Starts NOW
Questions?

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801 797 5901

Regenerative Wellness Center