Stem Cell Therapy as An Antiaging Tool

Joy Kong, M.D.

Uplyft Longevity Center

American Academy of Integrative Cell Therapy (AAICT)

Seeking the Optimal

What Causes Our Decline ?

Root Cause:
the Aging process

Osteoarthritis

- Not a disease of “wear & tear”
- It is a systemic inflammatory condition
- implanted knee construct gets destroyed in an osteoarthritic knee
- lagging regenerative capacity prevents adequate repair

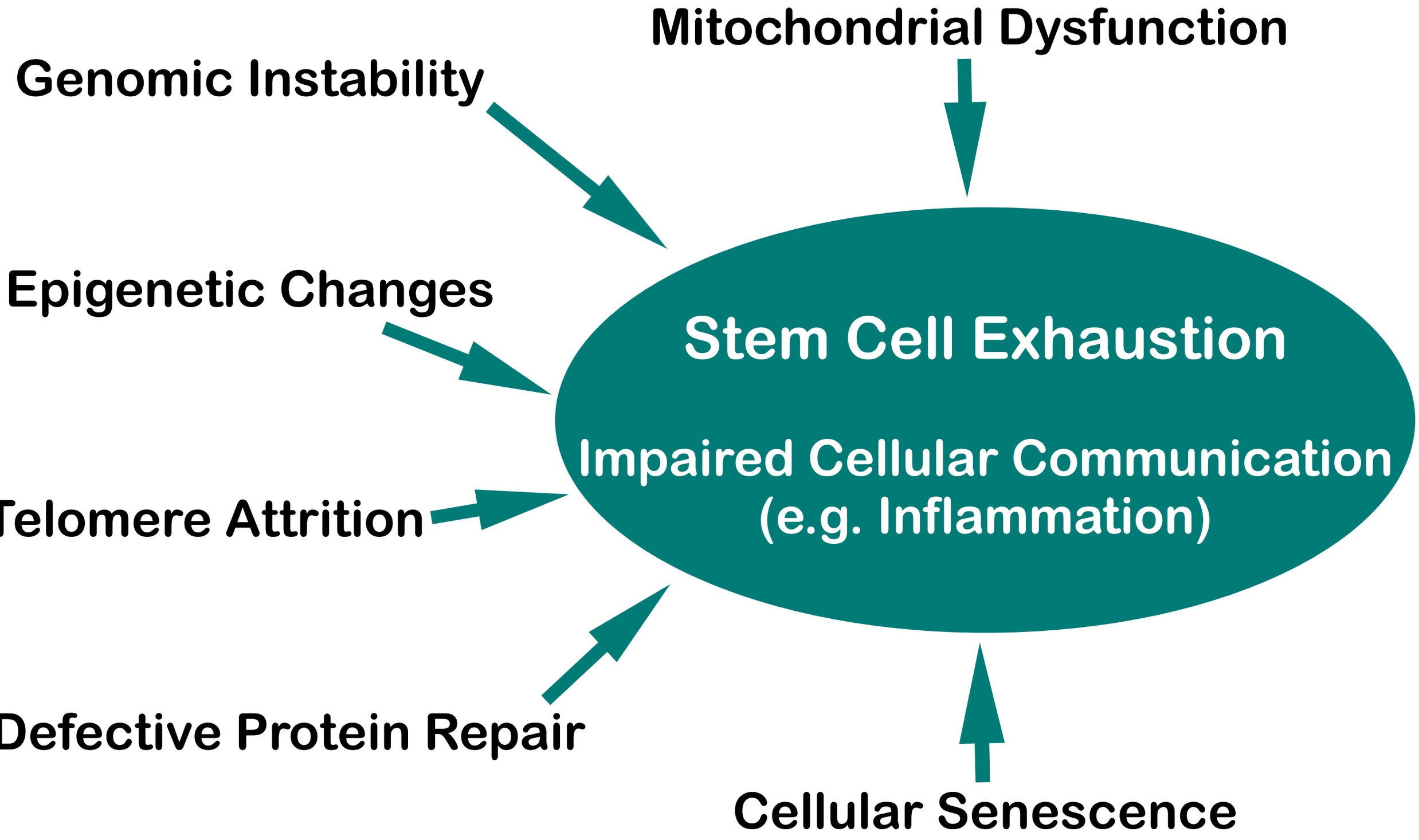
Damage → Repair

Supply

?

Demand

What Causes Aging?



The Hallmarks of Aging, C. Lopez-Otin et al, Cell, 2013

What's Disease? What's Aging?

“Inflammaging”

Markers of Aging

- even in apparently healthy elderlies, levels of inflammatory markers such as IL-6 and TNF-α are elevated, even in the absence of any infection. In younger people, such cytokines are tightly regulated.

  - inflammatory response is the main driver of tissue damage associated with almost ALL age-related diseases.
  - elevated levels of inflammatory markers can predict disease and disability in the aging population.
    - increased IL-6 and CRP levels are strongly linked to poor physical performance, decreased muscle strength, cognitive decline in the elderly, and early death.

Stem Cells as Anti-aging strategy by targeting inflammation

- R. Gonzalez et al, Cell & Tissue Transplantation & Therapy 2015

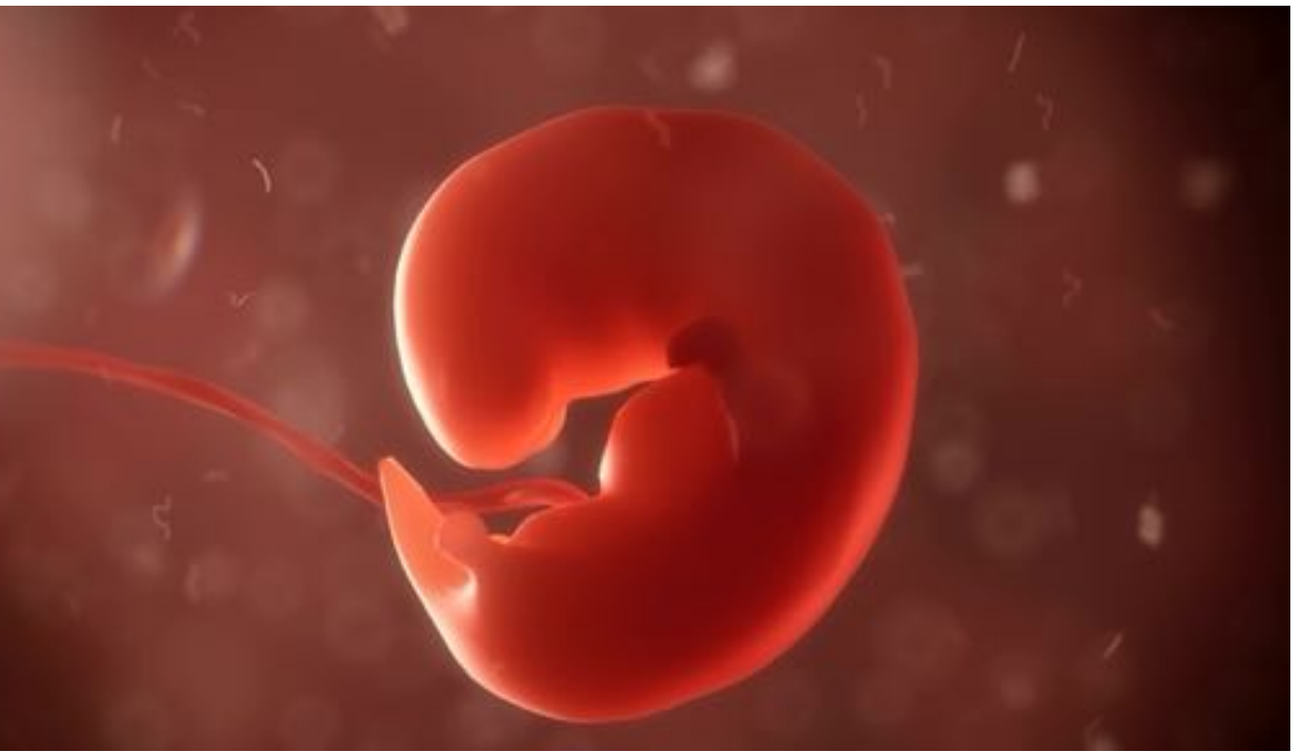
- In a rat traumatic brain injury model (TBI), intravenous infusion of MSCs decreased brain inflammatory cell infiltration, microglia, and apoptotic cell numbers

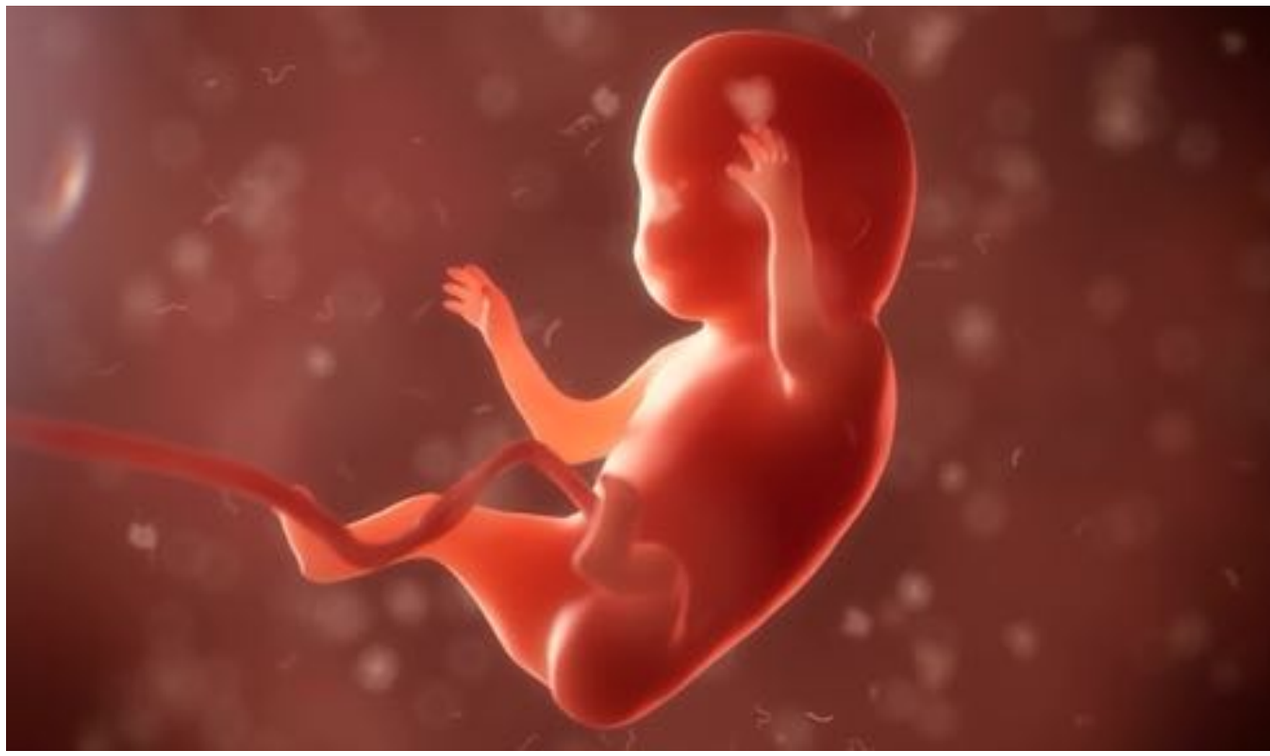
- in 172 rheumatoid arthritis (RA) and 16 systemic lupus erythematosus (SLE) patients, allogenic MSCs infusion helped reestablish balance in immune response from a pro-inflammatory to an anti-inflammatory state, with significant decreases in IL-6, TNF-α, and CRP levels.

- in patients with ankylosing spondylitis with high disease activity, infusing allogenic MSCs decreased CRP level and disease activity.

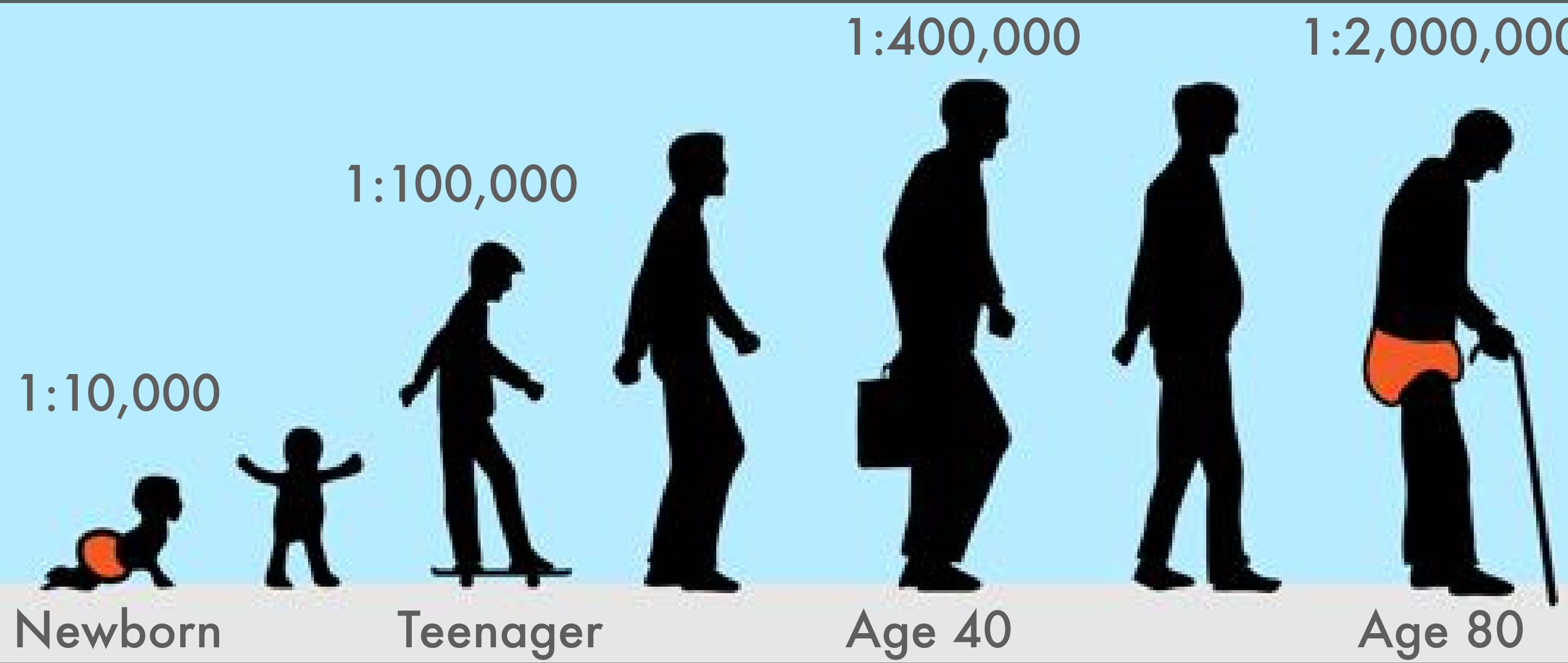
- in patients with Crohn's disease refractory to biologic therapy showed similar results — MSC therapy correlated with improved quality of life and improved CRP levels.

We are made from Stem Cells



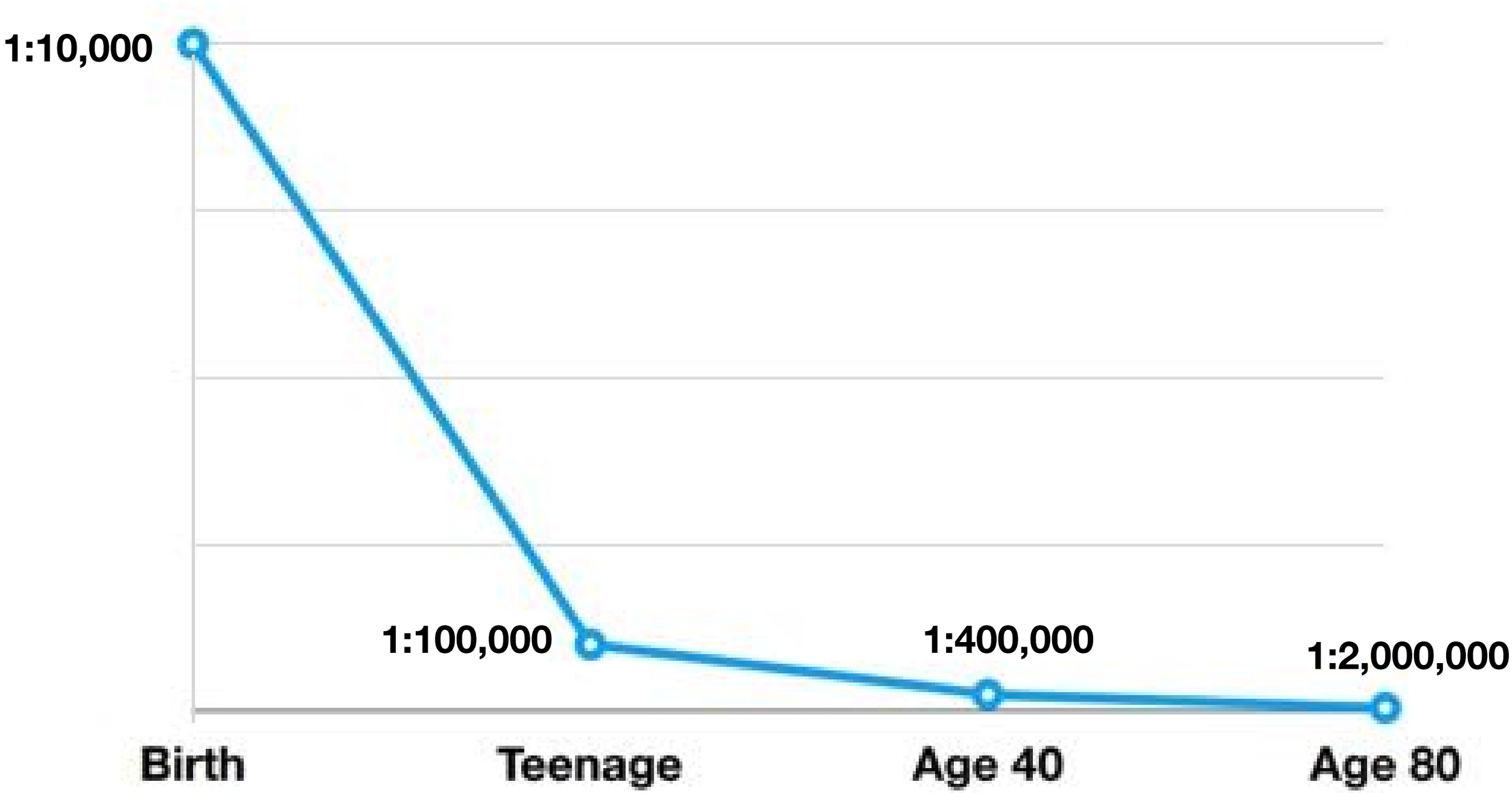


As we age…
some stem cells die
some go dormant



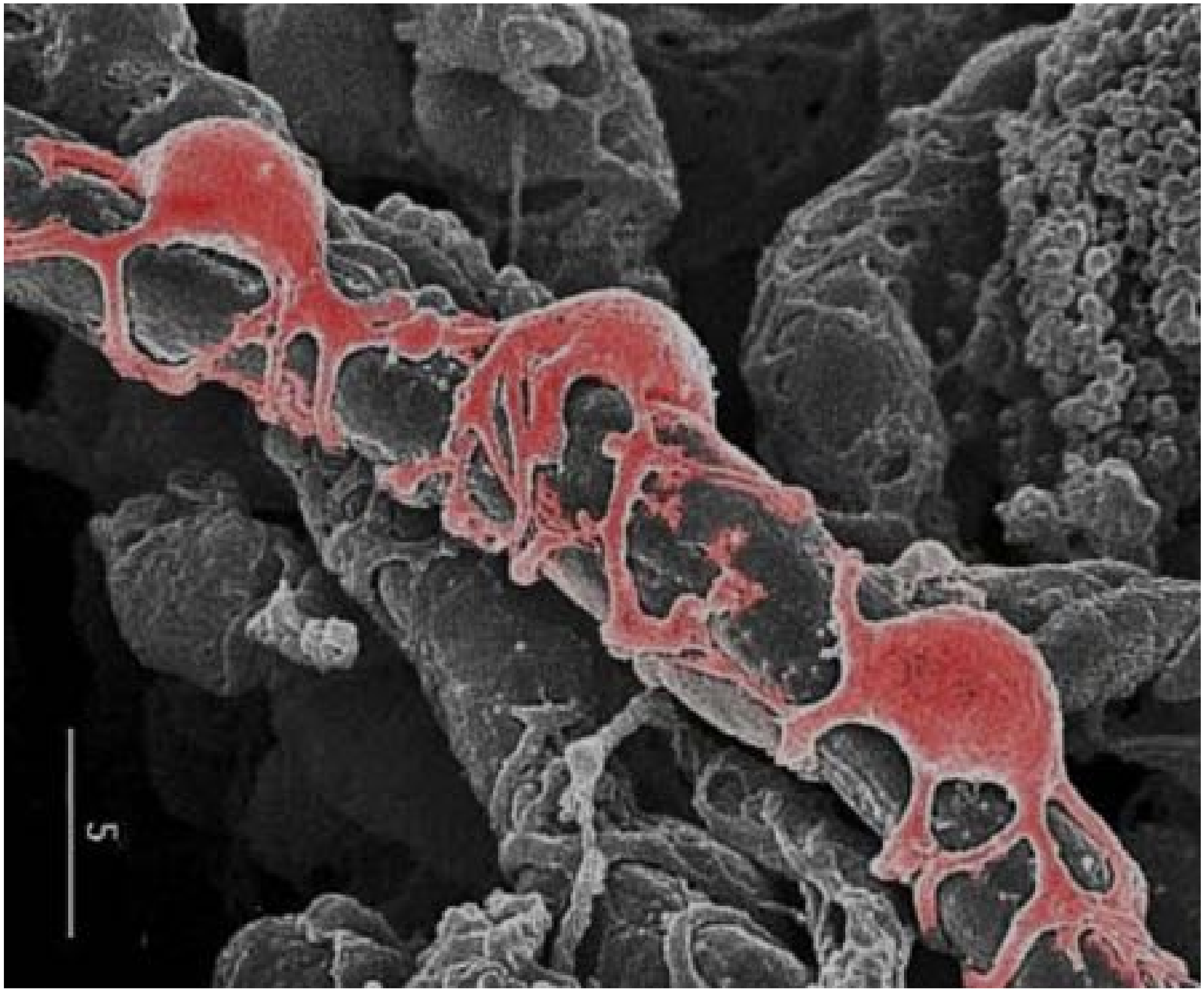
of MSCs : Total # of Cells in our body

Decline in MSC Supply as we age



Where Are **MSCs**?

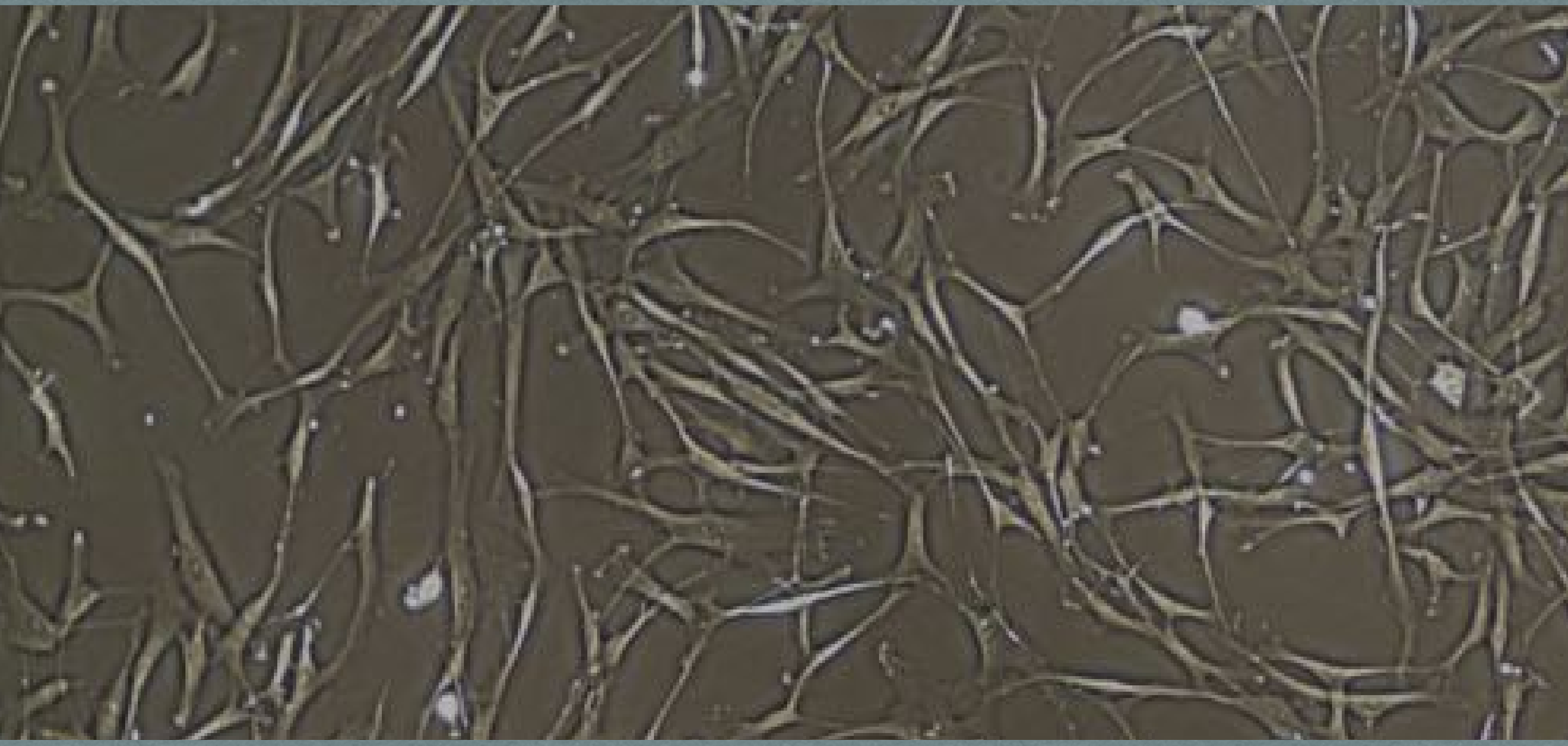
Pericytes



MSCs

Courtesy of Lipogem & Dr. Arnold Caplan

MSCs = Medicinal Signaling Cells?



Orchestration of Regeneration

How Do MSCs Help Us?

- Anti-inflammatory
- Anti-fibrotic
- Immunomodulatory
- Anti-apoptotic
- Regenerative
- Pro-apoptotic
- Angiogenic
- Anti-microbial
- Mitochondrial transfer

Young vs. Old MSCs

Does Age Matter?

- Lifelong perseverance of Adult MSC make them particularly susceptible to accumulation of cellular damage — which can lead to cell death, senescence, loss of regenerative function, and even neoplastic transformations

- Neonatal MSC (such as from Wharton's jelly) are spared of pro-aging factors

Age Matters Evidence

- Aged adipose derived MSCs are significantly compromised in their ability to support vascular network formation, unable to rescue age-associated impairments in cutaneous wound healing.

— K. Stenderup, "Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells," *Bone*, 2003

- Bone marrow derived MSCs have less myogenic potential and engraftment properties than developmentally early MSCs.

— C. H. Ting, "Age-related decreases of serum-response factor levels in human mesenchymal stem cells are involved in skeletal muscle differentiation and engraftment capacity," *Stem Cells and Development*, 2014

- BMSCs exhibit age-related decline in inflammatory response, cytokine/chemokine receptor expression important for MSC migration and activation, and immunomodulatory activities.

— M. L. Bustos, "Aging mesenchymal stem cells fail to protect because of impaired migration and antiinflammatory response," *The American Journal of Respiratory and Critical Care Medicine*, 2014.

Age Matters Evidence

- Genes related to senescence increase in ADSC with age.

— E. U. Alt, "Aging alters tissue resident mesenchymal stem cell properties," *Stem Cell Research*, 2012.

- Aging alters the availability of CD45-/CD34+/CD133+ ADSC and their angiogenic properties.

— R. Madonna, "Age-dependent impairment of number and angiogenic potential of adipose tissue-derived progenitor cells," *European Journal of Clinical Investigation*, 2011.

- Increased levels of ROS have been reported in aging BMSC.

— A. Stolzing, "Age-related changes in human bone marrow-derived mesenchymal stem cells: consequences for cell therapies," *Mechanisms of Ageing and Development*, 2008.

- Old ADSC are more sensitive to microenvironmental ROS, with impaired therapeutic effectiveness.

— L. Li, "Aging increases the susceptivity of MSCs to reactive oxygen species and impairs their therapeutic potency for myocardial infarction," *PLoS ONE*, 2014.

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Age Matters Evidence

- "Young" MSC (1-5 yrs of age) outperformed "older" MSC (50-70 yrs of age) in improving cardiac parameters after MI

— M. Fan, "The effect of age on the efficacy of human mesenchymal stem cell transplantation after a myocardial infarction," *Rejuvenation Research*, 2010.

- MSC from young individuals can undergo neuroectodermal differentiation in vitro, but BMSC from elderly patients cannot do so.

— A. Hermann, "Age-dependent neuroectodermal differentiation capacity of human mesenchy- mal stromal cells: limitations for autologous cell replacement strategies," *Cytotherapy*, 2010.

- Adult MSC are exposed to a lifetime of factors, e.g. NSAIDs — may inhibit MSC chondrogenic differentiation and disrupt endochondral bone formation.

— I. Pountos, "NSAIDS inhibit in vitro MSC chondrogenesis but not osteogenesis: implications for mechanism of bone formation inhibition in man," *Journal of Cellular and Molecular Medicine*, 2011.

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Age Matters Evidence

- Lifestyle affects quality of MSC — ADSC from high-fat fed mice showed higher adipogenic and lower endothelial differentiation potential in vitro compared to control group.

— V. Lamontagne, "High-fat diets-induced metabolic alterations alter the differentiation potential of adipose tissue-derived stem cells," *Open Journal of Endocrine and Metabolic Diseases*, 2013.

- Osteogenic potential from obese patients are impaired - mineralization nodules are fewer and smaller.

— M.Roldan, "Obesity short-circuits stemness gene network in human adipose multipotent stem cells," *The FASEB Journal*, 2011

- Metabolic diseases like diabetes alters ADSC milieu & diminishes the cells' ability to establish vascular network both in vitro & in vivo.

— R. C. Rennert, "Diabetes impairs the angiogenic potential of adipose-derived stem cells by selectively depleting cellular subpopulations," *Stem Cell Research & Therapy*, 2014.

35% of adults at age >20 are overweight, 11% obese, 8% with DM
(according to WHO)

Mesenchymal Stem Cell Aging: Mechanisms and Influences on Skeletal and Non-Skeletal Tissues

- H. Liu et al, Experimental Biology and Medicine 2015

- Aging leads to decreased bone marrow MSC pool, & biased differentiation into adipocyte at the cost of osteoblast - underlying the etiology of osteoporosis

- Transplanting young MSCs into the bone marrow of aged mice not only rescues bone loss, but also delays aging. Even subcutaneous implantation of MSCs suppresses aging-related degeneration of various organs!

- Aging of MSCs is also detrimental to non-skeletal tissues, including the hematopoietic system

- Aging compromises the therapeutic potentials of MSCs, including cells from aged individuals, or cells cultured for many passages

Transplantation of MSCs from Young Donors Delays Aging in Mice

- J. Shen et al, Scientific Reports, 2011

- Stem cells isolated from older donors have defective functions, such as impaired capacity to proliferate and differentiate when compared to those from young individuals

- Comparing function of BMSCs isolated from young (1–2 months old) vs. old (20-24 months old) mice — BMSCs from old animals had significantly less capability for differentiation (into bone, muscle, fat or neurons)

- transplantation of young BMSCs significantly delays the decrease of bone densities, while old BMSCs transplantation may actually accelerate the decline of bone density.

Antiaging Evidence

Health Span-Extending Activity of Human Amniotic Membrane- and Adipose Tissue-Derived Stem Cells in F344 Rats

- D. Kim et al, Stem Cell Translational Medicine, 2015

- Aging leads to progressive deterioration of cholinergic and dopaminergic systems.

- Concentrations of neurotrophins in the brain and muscles decline, leading to reduced neurogenesis and accelerated muscular atrophy, which lead to impairments of cognitive function and physical activity.

- Aging also leads to exhaustion of the stem cell population. Various stem cells exert neuroprotective effects and enhance functional recovery by secreting neurotrophic factors.

- Concentrations of TBARS (byproducts of lipid peroxidation) significantly increase in the brain, muscles, heart, liver, and lungs of aged rats, along with a low vessel density.

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Health Span-Extending Activity of Human Amniotic Membrane- and Adipose Tissue-Derived Stem Cells in F344 Rats

- D. Kim et al, Stem Cell Translational Medicine, 2015

- ADMSCs (adipose-derived MSCs) was shown to exert preventive and therapeutic effects on the memory deficit of AD (Alzheimer's disease) model mice, increased brain concentrations of ACh, BDNF, and NGF and improved cognitive and physical functions of aging mice
- ADMSCs secrete a very high concentration of vascular endothelial growth factor (VEGF), contributing to prolongation of life span in an amyotrophic lateral sclerosis (ALS) mouse model
- Muscle-derived Stem/Progenitor Cells (MSPCs) also extended health spans and life spans of progeria mice by restoring microvessels and muscle fibers through secreted factor(s)

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Health Span-Extending Activity of Human Amniotic Membrane- and Adipose Tissue-Derived Stem Cells in F344 Rats

- D. Kim et al, Stem Cell Translational Medicine, 2015

- This experiment: aged (10 month old) male F344 rats were divided into 3 groups: vehicle (n = 20), human amniotic membrane-derived mesenchymal stem cells (AMMSC)-transplant group (n = 20), and ADMSC-transplant group (n = 30)

- 1 million of either human AMMSCs or human ADMSCs (from 53 year old woman) were given per rat intravenously (via tail vein), once a month throughout the rest of their lives.

- AMMSCs and ADMSCs improved cognitive and physical functions of naturally aging rats, extending life span by 23.4% and 31.3% respectively.

Health Span-Extending Activity of Human Amniotic Membrane- and Adipose Tissue-Derived Stem Cells in F344 Rats

- D. Kim et al, Stem Cell Translational Medicine, 2015

- by the time rats reached 20 months of age, only 30% of control (vehicle-treated) rats survived, compared with 70% and 100% survival of AMMSC- and ADMSC-treated rats, respectively.

- By 23 months of age, all rats in the vehicle group died, whereas AMMSCs and ADMSCs groups had survival rates of 60% and 72% respectively

- The transplanted cells were found to differentiate into neurons, exhibiting differentiation rates of 62-76% in AMMSCs and 54-75% in ADMSCs, respectively

Health Span-Extending Activity of Human Amniotic Membrane- and Adipose Tissue-Derived Stem Cells in F344 Rats

- D. Kim et al, Stem Cell Translational Medicine, 2015

- Brain neurotrophic factors such as BDNF, NGF, GDNF, and VEGF markedly decreased in aged rat brain compared with young animals. These were upregulated by transplantation of AMMSCs or ADMSCs. VEGF that possesses angiogenic potential was greatly increased to levels higher than in young rats.

- Muscular neurotrophic factors such as BDNF, GDNF, VEGF, and IGF-1 that had decreased in aged rats were also restored by transplantation of AMMSCs or ADMSCs. GDNF and IGF-1 related to motor neuron development and muscular innervation and myogenesis were upregulated to levels higher than in young rats

- Transplantation of AMMSCs or ADMSCs significantly increased the number of blood vessels comparable to that of young rats, indicative of increased angiogenesis.

Health Span-Extending Activity of Human Amniotic Membrane- and Adipose Tissue-Derived Stem Cells in F344 Rats

- D. Kim et al, Stem Cell Translational Medicine, 2015

- Tissue injury was nearly fully attenuated by transplantation of AMMSCs and ADMSCs
- Monthly transplantation of AMMSCs or ADMSCs markedly increased the stamina and cognitive function of aged rats
- ACh concentrations in CSF and muscles of aged (21-month-old) rats were much lower than those of young (7-week-old) animals. These decreased ACh levels in CSF and muscles were significantly restored following transplantation of AMMSCs or ADMSCs
- Alteration in gene expressions of cholinergic nerve markers associated with aging were markedly restored after transplantation of AMMSCs or ADMSCs.

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Health Span-Extending Activity of Human Amniotic Membrane- and Adipose Tissue-Derived Stem Cells in F344 Rats

- D. Kim et al, Stem Cell Translational Medicine, 2015

- The number of host stem cells in aged rats is only 27.8% that of young rats. Transplantation of AMMSCs or ADMSCs increased the number of host stem cells to the level comparable to young rats, indicative of resumption of neurogenesis.

- expression of CCL11 (eotaxin), a chemokine suppressing neurogenesis, increases during aging, along with marked decrease in MAP2, a neuronal skeletal protein. These changes were fully reversed after transplantation of AMMSCs or ADMSCs.

- stem cell therapy increased the concentration of ACh and recovered neurotrophic factors in the brain and muscles, leading to restoration of cholinergic and dopaminergic nervous systems, microvessels, muscle mass, and antioxidative capacity.

Extension of Maximal Lifespan and High Bone Marrow Chimerism After Nonmyeloablative Syngeneic Transplantation of Bone Marrow From Young to Old Mice

- M. Kovina, et al, Frontiers in Genetics, 2019

- This experiment: beginning at the age of 15 months (equivalent to human age of 75 years), when about 50% of the mice have died, intravenous BM transplantation from young mice were given

- Dosing: 100 million nucleated cells from BM of young donors per injection through tail vein, and repeated 6 times within 3 months

- Mice aged 3-15 weeks from the same strain but heterozygous for the green fluorescent protein transgene were used as BM donors.

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Extension of Maximal Lifespan and High Bone Marrow Chimerism After Nonmyeloablative Syngeneic Transplantation of Bone Marrow From Young to Old Mice

- M. Kovina, et al, Frontiers in Genetics, 2019

- Results: maximum lifespan in transplanted mice increased by 31 ± 5%
- Survival time from the beginning of the experiment was increased by 3.2 fold
- At age 19.3 months: the last mouse of the control group died "sedentary, almost immobile, and hunchbacked with poor hair," the transplanted mice were active, had even spine, and shiny even hair
- The observed lifespan extension was accompanied by extension of an active and healthy life period
- The chimerism of the BM 6 months after the transplantation was 28%
- Result is highly encouraging for clinical applications for aged humans (70–80 years old)

Evaluation of Immune response to Intravenously Administered Human Cord Blood Stem Cells in the Treatment of Symptoms Related to Chronic Inflammation

- Mehling et al., Journal of Stem Cell Research & Therapy ***2015***

- 20 patients were treated for conditions associated with chronic inflammation (such as osteoarthritis, post-traumatic arthritis, inflammatory back pain, left shoulder bursitis and herniated disc), as well as for the purpose of anti-aging
- 1x IV infusion of 25 million HUCB stem cells in 100ml NS
- Patients did not demonstrate changes in inflammation markers in 3 mos, but:
- 10 patients showed significant improvement in CBC, CMP, AST/ALT, & Lipid panel
- Antiaging benefits are evaluated at 24 hrs, 2 wks and 3 mos after therapy. At 3 mos, there is significant improvement in skin, hair & nail growth, energy level, libido, mood, sleep, & pain level

Mesenchymal Stem Cell Therapy for Aging Frailty

- Hare et al, Frontiers in Nutrition, 2018

- Frailty syndrome is characterized by declines in lean body mass, strength, endurance, balance, gait speed, activity and energy levels, and organ physiologic reserve
- Frailty increases the risk of falls, hospitalizations, institutionalization, disability, and death
- Cardiovascular Health Study (CHS) Index defines frailty as having 3 out of 5 criteria indicating “compromised energetics”: weak grip strength, low energy levels or self-reported exhaustion, slow gait speed, low physical activity, and/or unintentional weight loss
- Prevalence of frailty in age > 65 in the US: 7–12%
- Prevalence of pre-frailty in age > 65 in the US: 35 - 50% (pre-frailty - when meeting 1-2 out of 5 criteria defined in CHS index)
- Comorbidities, esp. cardiovascular, pulmonary, musculoskeletal, neurologic, and psychiatric, are more prevalent in pre-frail compared to non-frail persons

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Mesenchymal Stem Cell Therapy for Aging Frailty

- Hare et al, Frontiers in Nutrition, 2018

- There is strong link between frailty, inflammation, & impaired ability to repair tissue injury due to decreases in endogenous stem cell production & function
- An individual's endogenous stem cell production/function decrease with age
- Aging induces a "quiescence-to-senescence switch" in stem cells, causing degradation in extracellular matrix and the stem cell niches in tissues — leading to reduced stem cell self-renewal, maintenance and regenerative potential
- Altered and dysfunctional stem cell niches have been implicated in frailty syndrome
- As MSCs undergo senescence, their multilineage differentiation, homing capacity, immunomodulatory and wound healing properties gradually disappear
- Intravenously delivered allogeneic MSCs are safe and produce significant improvements in physical performance measures and inflammatory biomarkers

Antiaging Stem Cell Therapy Protocol

Dosing Recommendation

- Minimally manipulated birth tissue-derived MSCs
- 2 million MSCs for every 60 lbs of body weight
- add 2 million for age >65-70
- add 2 million for severe/aggressive disease state
- Treatment intervals can range between 3-12 months based on individual needs

Live More Years with Vitality

Thank You!

Joy Kong, MD

Email: joykongmd@gmail.com

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