The Skin Zone

Our Two Skins

- Outer Skin
  - Makes you look younger
- Inner Skin
  - Makes you live longer

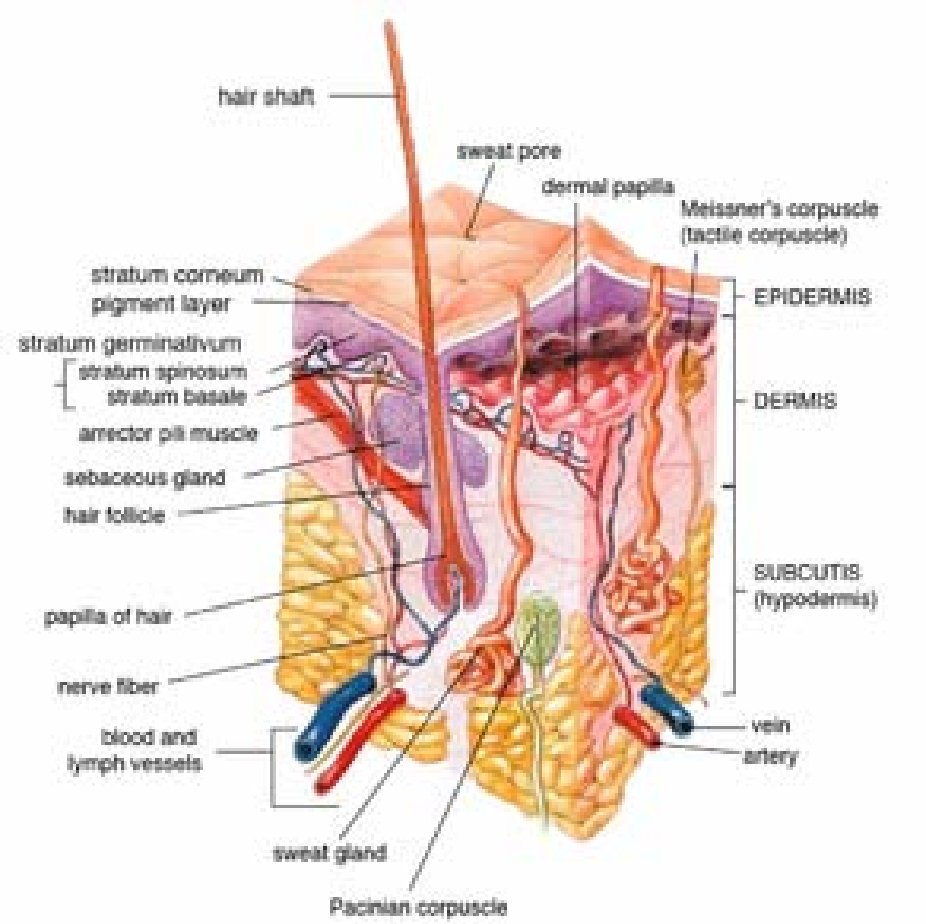
Major Problems with Aging Skin

- Loss of Dermal Fat
- Loss of Collagen and Elastin Structure
- Free Radical Damage

Molecular Drivers of Aging Skin

- Constant activation of innate immune system
- Insulin resistance in dermal fat cells
- Excess Reactive Oxygen Species (ROS)
- Increased activity of matrix metalloproteases (MMP)
- Increased production of Advanced Glycosylated End Products (AGE)

The Epidermis is a Difficult Barrier To Overcome



Skin Treatment Must Come From Within

- Controlling inflammation
  - Reduction of ongoing inflammation
  - Increasing resolution of inflammation

- Controlling gene transcription factors
  - NF-kB
  - PPARy
  - Nrf2

Insulin Resistance and Loss of Dermal Fat

- Insulin signal is not correctly transmitted
- Lack of inhibition of hormone-sensitive lipase
- Continuing release of stored fat
- Lipodystrophy is the extreme cause

Insulin Resistance and Cortisol

- Cortisol secreted in response to increased cellular inflammation
- Induces insulin resistance
- Excess cortisol thins the skin

Autologous Fat Grafting

- Fat source is liposuction of the patient
- Isolated adipose tissue contains stem cells
- If revascularization takes place, dermal filling may be permanent

Role of PPARγ

- Acceleration of loss of dermal fat in KO model
  - Wang et al PNAS 110 10856 (2013)
- Need for constant activation of PPARγ to maintain dermal fat content
- Controlling blood glucose levels to prevent insulin resistance

NF-kB and MMP

- MMP is one of inflammatory proteins expressed by consequence of NF-κB activation

- Stimulation by TNFα

AGE and RAGE

- Elevated glucose levels increase AGE formation
  - HbA1c levels
- Interaction of AGE with RAGE induces NF-κB activation
- NF-κB activation increases number of RAGE

ROS and Skin

- Causes
  - UVA and UVB radiation damage
  - Elevated levels of blood glucose
- Consequences
  - Excessive ROS induces oxidative stress
  - Oxidative stress activates NF-κB

A Drug Delivery Approach To Skin Aging

- Systematic and lifetime basis
- Requires an anti-inflammatory diet
  - Zone Diet
- Use of anti-inflammatory supplements
  - Inhibition of NF-κB
  - Activation of PPARγ
  - Activation of Nrf2

Useful Definitions For Skin Aging

- Pro-inflammation
  - Promotes initiation of inflammation
- Anti-inflammation
  - Inhibits initiation of inflammation
- Pro-resolution
  - Promotes resolution of inflammation

Nrf2

- Gene transcription factor for expression of SOD and GPx

- Activation by polyphenols

Scapagnini et al Mol Neurobiol 192 (2011)

Treating Aging Skin

- Reduce insulin resistance
  - Primarily by the Zone Diet
  - Measured by TG/HDL ratio
- Reduce blood glucose levels
  - Primarily by the Zone Diet
  - Secondarily by omega-3 fatty acids and polyphenols
  - Measured by HbA1c
- Reduce cellular inflammation
  - Primarily done by omega-3 fatty acids
  - Measured by AA/EPA ratio

Clinical Markers Of Healthy Skin

- Blood glucose control
  - HbA1c: 5.0%
- Insulin resistance
  - TG/HDL ratio: < 0.4 (mmol/l) or < 1 (mg/dl)
- Cellular inflammation
  - AA/EPA ratio: 1.5-3

Your Inner Skin

Some GI Track Facts

- Takes about 36 hours for meal to be fully digested and excreted
- Small intestine about 23 feet long
- Large intestine about 5 feet long
- Approximately 10x more bacteria in gut than cells in the body
- Without a healthy gut barrier, we are easy targets for microbial attack

Inner Skin Facts

- Far more complex than outer skin
  - Nutrients have to pass and let keep out microbes
- Only source of energy for cells in the colon is fermentable fiber
  - Only microbes can make the enzymes to break it down for energy
- 70% of our immune cells are located in the inner skin
  - Facing the barbarians at the gate

Inner Skin Defenses

- Mucus to trap the microbes
- A strong gut barrier
- Immune cells that line the gut

Mucus

- Need fermentable fiber to supply nutrients
- Short-chain fatty acids (SCFA) are products of fiber metabolism
- SCFA stimulate mucus production
- Without adequate levels of fermentable fiber, microbes begin to digest the mucus for energy

Leaky Gut Syndrome

- Tight junctions between cells break down
- Leakage of microbes and molecular fragments into the blood
- Enhanced by dietary fat
- Inhibited by omega-3 fatty acids

Metabolic Endotoxemia

- Bacterial fragments start inflammatory responses
- Makes gut even more leaky
- High levels of bacterial toxins in the blood cause sespsis
- Low levels of bacterial toxins in the blood cause metabolic inflammation
  - Obesity
  - Diabetes

Vagus Nerve Highway

- SCFA stimulate release of satiety hormones that go directly to the brain
  - Decrease hunger
- Direct path for bacterial fragments to enter the brain
  - Inflammation of the hypothalamus
  - Hunger increases

Vagus Nerve Is Bidirectional

- Stress hormones in the brain can go directly to gut

- “Gut-feelings”

Lifecycle of the Gut Microbiome

- Birth
  - Vaginal colonization
  - Fermentable fibers in breast milk
- 2 years
  - Changeover with increasing solid food
- Adult
  - Relatively constant

Diet and Gut Microbes

- Can rapidly change
- Fats
- Fermentable fiber

What Is Fermentable Fiber?

- 10-15% of total fiber

- Carbohydrate polymers that only microbes can break down
  - Fructose and galactose polymers (prebiotics)
  - Glucose polymers are only one that humans can break down

Common Sources of Fermentable Fiber

- Fruits
  - Apple (pectin)
- Vegetables
  - Onions, artichokes, garlic, asparagus
- Soluble fibers
  - Oatmeal and barley

Role of SCFA

- Increase mucus production
- Increase satiety
- Recruit Treg cells and decrease inflammation
- Epigenetic effects

Polyphenols And The Gut

- Only the gut can breakdown water-insoluble polyphenols to be absorbed
- Only 2-20% of metabolites are absorbed
- Higher the absorption, the greater the life extension
- Promote the growth of “good” bacteria
  - Roopchand et al. Diabetes 64:2847 (2015)

Key Components For Health Of Both Skins

- Anti-inflammatory diet
- Low in saturated fat
- High in omega-3 fatty acids
- High in polyphenols
- Rich in fermentable fiber