MicroRNAs: novel regulators in skin research

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What are microRNAs?

- Small, ~21-mer RNAs

- 1993: The first miRNA discovered, Lin-4, regulated the developmental transitions in *Caenorhabditis elegans*

- The second microRNA was discovered 7 years later (2000)

- Today (October, 2008) we know more than **8000 miRNAs** (miRBase 12.0)

- The most abundant regulators of gene expression in the genome!

Lee et al., *Cell*, 1993
MicroRNAs: regulators of gene expression

- Regulate the expression of most protein-coding genes
- MicroRNAs inhibit gene expression at the post-transcriptional level
- Their function and importance can be compared to transcription factors
- Regulate basic biological processes
  - Apoptosis
  - Morphogenesis
  - Proliferation
  - Metabolism
  - Signal transduction
  - Determination of cell fate
  - Developmental timing
MicroRNA biogenesis and mode of action

- Encoded in the genome
- Transcribed from DNA as pri-microRNA
- Processed into pre-microRNA in the cell nucleus
- In the cytoplasm they are processed into the mature microRNA
- Mature microRNA form complexes with the 3’ UTR (untranslated region) of target mRNA and
- Suppress their translation/induce their degradation
The emergence of miRNAs will not make the understanding of regulatory networks easier...

• Each miRNA regulates more than one gene

• Each gene is regulated by more than one miRNA

• Many miRNA targets are transcription factors – miRNAs regulate the regulators

• MiRNA expression is regulated by transcription factors

• The potential regulatory effect of miRNAs is enormous

Modified from George Calin, MD PhD
Abnormal miRNA expression can cause diseases

- Altered miRNA expression was first implicated in cancers
- MiRNAs may act as
  - tumor suppressors (i.e. miR-16, let-7s)
  - oncogenes (i.e. miR-155, miR-21)
- MiRNAs regulate proliferation, apoptosis and angiogenesis
- In the past few years miRNAs have also been implicated in developmental and metabolic diseases
Why study the skin?

- The largest organ (Surface area 1.5 - 2 m²; ~9 kg)

- Common and severe diseases
  - Inflammatory diseases (psoriasis, atopic eczema)
  - Tumors (BCC, SCC)
  - Genetic disorders (Xeroderma pigmentosum, ichthyosis)
  - Bullosus

- A handy model for other diseases
  - Easily accessible
  - Skin Immune System (SIS) — Inflammation
  - Carcinogenesis
  - Morphogenesis
Do microRNAs have a role in psoriasis?

- Is there a set of microRNAs that distinguishes healthy skin from psoriasis skin?
- If yes, which are those microRNAs?
- Does microRNA deregulation play a role in psoriasis?
Psoriasis has a specific microRNA expression profile

- Genome-wide analysis of miRNA expression using an array with LNA probes showed that:
  - A set of microRNAs is expressed in human skin
  - Healthy skin, atopic eczema lesion and psoriatic lesions display distinct microRNA expression profiles

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<th>Psoriasis</th>
<th>Fold change</th>
<th>Atopic eczema</th>
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Sonkoly et al., PloS One, 2007
miR-203 is specifically overexpressed in psoriasis

- **miR-203** and miR-146a are overexpressed in psoriasis but not in atopic eczema
- **miR-21** is overexpressed and **miR-125b** is suppressed in both diseases
- **miR-146** and miR-125b was recently implicated in the regulation of TLR-signaling
- **miR-203**: potential functions - unknown

Sonkoly et al., PLoS ONE, 2007
miR-203 is a skin-specific microRNA

- Highest expression in the skin
- Also expressed in the esophagus
- A role in the differentiation of squamous epithelia?

Sonkoly et al., PLoS ONE, 2007
miR-203 is a keratinocyte-specific microRNA

- Keratinocyte-specific expression
- Higher expression in the upper, more differentiated cell layers
- Increased expression in the epidermis of psoriasis lesions

Sonkoly et al., PLoS ONE, 2007
miR-203 is regulated during differentiation
miR-203 targets Suppressor of Cytokine Signaling-3 (SOCS-3)

- Predicted binding site for miR-203 in the 3’UTR of SOCS-3 gene
- Suppression of SOCS-3 in psoriasis lesions
- Mutually exclusive staining pattern of miR-203 and SOCS-3 in the epidermis
- Significant repression of the reporter in a luciferase assay
- Suppression of SOCS-3 may result in elongated/increased inflammatory response

Sonkoly et al., PLoS ONE, 2007
What is the relevance to cosmetics?
- Potential applications

microRNA inhibitor

microRNA

microRNA mimic

DNA → Transcription → RNA → mRNA → Translation → Protein

Reduced skin inflammation?
• microRNA expression patterns distinguish psoriasis from healthy skin and atopic eczema

• miR-203 is a skin- and keratinocyte-specific microRNA

• Its up-regulation in psoriasis is concurrent with the down-regulation of its target, SOCS-3

• a new layer of regulatory mechanisms is involved in the pathogenesis of chronic inflammatory skin diseases
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