



Review

Diagnostic opportunities based on skin biomarkers

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ABSTRACT

Systemic as well as localized skin diseases modify the molecular composition of human skin. Changes in skin chemistry have been observed in diseases such as cancer, psoriasis, eczema, diabetes, and atherosclerosis. Skin chemistry, represented by an enormous wealth of disease biomarkers including lipids, structural proteins, inflammatory mediators, nucleic acids and small molecules, therefore, can serve as a “window to body’s health”. Various methods including tape-stripping, iontophoresis, microneedles and ultrasound, among others, are being developed to access skin biomarkers and understand skin’s detailed molecular composition. This information provides opportunities to diagnose various diseases and their response to therapeutic treatments. This review provides an overview of such diagnostic and theranostic opportunities.

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1. Introduction

Disease pathologies considerably modify the molecular composition of skin, which is otherwise maintained by a delicate balance be-

tween various biomolecules in healthy skin (Elias et al., 1999; Elias, 2004). In addition to skin-intrinsic diseases such as cancer, psoriasis and eczema, diseases associated with internal organs also induce alterations in the chemical composition of skin (Braverman, 1998).

Table 1
Diagnosis for local skin diseases.

Disease	Sampling method
Atopic dermatitis	Skin biopsy: histopathology and IgE level of 44 (normal 16) U/ml (Jansén et al., 1973) Suction blister: allergen induced IgE level of 6690 (serum 26,600) U/ml (Barnetson et al., 1981) Ultrasound: IgE level of 0.16 (normal 0.05) ng/cm ² (Paliwal et al., 2010) Microdialysis: histamine of 154 ng/ml induced by allergen 1 U/ml (Petersen et al., 1996), and high iron of 44.3 (normal 21.8) µg/l and low ascorbic acid of 46.7 (normal 176.8) µg/ml (Leveque et al., 2003), nerve growth factor of 184 (normal 236) pg/ml (Papoiu et al., 2011) Tape-stripping: nerve growth factor of 150 (normal 0) pg/µg (Yamaguchi et al., 2009), vascular endothelial growth factor of 138.6 (normal 29.3) pg/µg (Amarbayasgalan et al., 2012), and glucosyl ceramides 27 (normal trace) (Popa et al., 2012) Iontophoresis: histamine-induced itch and flare reaction (Heyer et al., 1998)
Melanoma	Skin biopsy: histopathology and immunoblotting (Welch et al., 2005) Tape-stripping: genomic detection (Wachsmann et al., 2011)
Skin infectious diseases	Skin biopsy: lyme disease with PCR (Schwartz et al., 1992), Ebola virus with immunohistochemistry (Zaki et al., 1999), mucormycosis (Gartenberg et al., 1978), leprosy (Yamamura et al., 1991), cat scratch disease (Adal et al., 1994), Mycobacterium ulcerans infection with PCR (Ross et al., 1997), and Streptococcal infections (Bisno and Stevens, 1996) Tape stripping: chromoblastomycosis, lobomycosis, paracoccidioidomycosis (Miranda and Silva, 2005), and dermatophytosis with PCR (Saunte et al., 2008) Iontophoresis: leprosy (Martinez Dominguez, 1962) Suction blister: erythema migrans by cytokines levels of 178.9 pg/ml (Salazar et al., 2003)
Other skin diseases	Skin biopsy: darier's disease by immunohistological of desmonomes (Burge and Garrod, 1991) Tape stripping: psoriasis mRNA RT-PCR (Benson et al., 2006) Iontophoresis: skin irritation by prostaglandin E2 of 11.5 ng/gel (Mize et al., 1997) Microdialysis: regional psoriasis by histamine of 3.10 nmol (Guihen et al., 2012) Suction blister: psoriasis by eosinophil cationic protein of median 18.1 µg/l (Lundin et al., 1990) and soluble intercellular adhesion molecule-1 and procollagen III peptide (Ameglio et al., 1994), urticaria by increased tryptase levels of over 50 (control 15) µg/l (Deleuran et al., 1991), pemphigus by soluble interleukin-2 receptor level of 2186 (control 1299) U/ml (Zillikens et al., 1993), vitiligo by basic fibroblast growth factor levels of 11.9 (control 4.7) pg/ml (Ozdemir et al., 2000), and scleroderma by N-terminal connective tissue growth factor of 83 (control 25) ng/ml (Dziadzio et al., 2005)

Table 2
Diagnosis for systemic and internal diseases.

Disease name	Diagnostic method
Alzheimer's disease	Skin biopsy: beta-amyloid (Joachim et al., 1989) Iontophoresis: skin vessel reactivity by administrated acetylcholine (Algotsson et al., 1995)
Breast carcinoma	Sentinel-node biopsy (Veronesi et al., 1997) Microdialysis: growth factors (Dabrosin, 2005), and overexpressed osteopontin of 34 (control 0) ng/ml (Xu et al., 2010)
Cardiovascular diseases	Skin biopsy: cholesterol and apoprotein B level (Bouissou et al., 1982) Palm test: FDA-approved cholesterol 1,2,3 TM level of 55–206 hue angle (Zawydiwski et al., 2001) Iontophoresis: laser Doppler after iontophoresis of acetylcholine and sodium nitroprusside (Ijerman et al., 2003) Tape stripping: both ceramide and free fatty acid up to 1 µg/ml (Weerheim and Ponc, 2001)
Diabetes	Skin biopsy: diabetes neuropathy by intraepidermal nerve fibers (Tsfaye et al., 2010) Suction blister: diabetes neuropathy by intraepidermal nerve fibers (Tsfaye et al., 2010) Iontophoresis: glucose monitoring of 100 µM for 2 h (Rao et al., 1993), and laser doppler imaging after acetylcholine and sodium nitroprusside administration (Veves et al., 1998) Microdialysis: glucose level of 10 mmol/l (Jansson et al., 1988) Microneedles: blood glucose level of 213.6 mg/dl (Smart and Subramanian, 2000) Tape stripping: SC glucose level of 360 ng/cm ² (Cunningham and Young, 2003) Electroporation: glucose level of 5–45 mg/dl (Murthy et al., 2008)
Drugs of abuse	Skin biopsy: methamphetamine, cocaine, and codeine of 2.5–100 ng/skin biopsy (Yang et al., 2006) Microdialysis: cocaine of 5–17 ng/10 µl (Inada et al., 1992) Tape stripping: cocaine (Paliwal et al., 2010) Ultrasound: cocaine of 5 × 10 ³ ng/cm ² (Paliwal et al., 2010)
Other diseases	Skin biopsy: Brill's disease (Mandelbaum and Hollander, 1947), Fabry's disease (Le Charpentier et al., 1980), Lafora disease (Carpenter and Karpati, 1981), neurologic metabolic disease (Carpenter, 1987), genetic skin disease (Holbrook et al., 1993), raft-versus-host disease (Grzanka et al., 2008), Parkinson's disease (Miki et al., 2010), neuronal intranuclear inclusion disease (Sone et al., 2011), Refsum's disease (Steinberg, 1983), and Lesch-Nyhan disease (Stanbury et al., 1983) Iontophoresis: cystic fibrosis by high concentrations of sweat electrolytes (Webster, 1983), phenylketonuria by elevated concentrations of phenylalanine of 3.4 nmol/cm ² (Longo et al., 2007), and chronic kidney disease by urea 20–230 mg/dl (Wascotte et al., 2008) Suction blister: peripheral nerve disease by epidermal nerve fibers 212 (biopsy 20) ENFs/mm ² (Kennedy et al., 1999), and severe sepsis by matrix metalloproteinases MMP-8 of 8.2–84.7 ng/ml (Gaddnas et al., 2010) Microneedles: lymphedema by fluorescence microlymphography (Bollinger and Amann-Vesti, 2007)

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