ISSN 2218-6190 (online)

World Journal of *Dermatology*

World J Dermatol 2013 November 2; 2(4): 27-50

Baishideng Publishing Group
www.wjgnet.com

WJD World Journal of Dermatology

A peer-reviewed, online, open-access journal of dermatology

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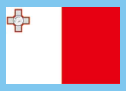

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WJD World Journal of Dermatology

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Quarterly Volume 2 Number 4 November 2, 2013

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WJD is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of dermatology. *WJD* covers fungal diseases, dermatitis and eczema, urticarial diseases, drug eruptions, pruritus, erythroderma desquamativum, connective tissue diseases, bullous skin diseases, vascular skin diseases, skin appendage diseases, pigmentary diseases, genetic diseases, nutritional and metabolic disorders, tumors, sexually transmitted diseases, AIDS, traditional medicine, integrated Chinese and Western medicine, evidence-based medicine, epidemiology and nursing. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to dermatology, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

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INDEXING/ABSTRACTING

World Journal of Dermatology is now indexed in Digital Object Identifier.

NAME OF JOURNAL
World Journal of Dermatology

ISSN
ISSN 2218-6190 (online)

LAUNCH DATE
June 2, 2012

FREQUENCY
Quarterly

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Santosh K Katiyar, PhD, Professor, Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL 35294, United States

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World Journal of Dermatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjdermatol@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F, Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
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Telephone: +852-6555-7188
Fax: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
November 2, 2013

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-6190/g_info_20100722173304.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Dermatology

Online Submissions: http://www.wjgnet.com/esps/
wjdermatol@wjgnet.com
doi:10.5314/wjd.v2.i4.27

World J Dermatol 2013 November 2; 2(4): 27-31
ISSN 2218-6190 (online)

EDITORIAL

Adipocytokines and psoriasis: Insights into mechanisms linking obesity and inflammation to psoriasis

Maria Dalamaga, Evangelia Papadavid

Maria Dalamaga, Department of Clinical Biochemistry, Medical School, University of Athens, "Attikon" General University Hospital, Chaidari, 12462 Athens, Greece
Evangelia Papadavid, Department of Dermatology, Medical School, University of Athens, "Attikon" General University Hospital, Chaidari, 12462 Athens, Greece
Author contributions: Dalamaga M designed the editorial and wrote the manuscript; Papadavid E reviewed the manuscript.
Correspondence to: Maria Dalamaga, MD, PhD, MS, MPH, Assistant Professor, Department of Clinical Biochemistry, Medical School, University of Athens, "Attikon" General University Hospital, Karyotaki 29, 15344 Athens, Greece. madalamaga@med.uoa.gr
Telephone: +30-210-5831915 Fax: +30-210-6082467
Received: June 1, 2013 Revised: June 26, 2013
Accepted: July 4, 2013
Published online: November 2, 2013

Abstract

Psoriasis has been lately seen as a potential systemic inflammatory disease associated with a range of co-morbidities exhibiting an overlapping pathology and presenting a great social health impact such as cardiovascular disease and metabolic diseases, including obesity. Adipose tissue is considered a genuine endocrine organ producing a variety of bioactive adipocytokines, like leptin, adiponectin, resistin and visfatin, participating in physiological and pathological processes, such as energy balance, insulin sensitivity and resistance, immunity, inflammation, hematopoiesis and angiogenesis. Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression, severity as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, progression, treatment outcome and risk of any co-morbidities. Interventions to decrease pro-inflammatory adipocytokine levels could offer preventive and therapeutic options for improving psoriasis severity and protecting against its co-morbidities. Candidate strategic interventions incorporate increased physical activity, weight control and pharmacologic approaches such as metformin. However, the mechanisms underlying the actions of adipocytokines in psoriasis as well as their potential diagnostic, prognostic and/or therapeutic utility require further investigation with larger prospective, longitudinal and mechanistic studies.

Key words: Psoriasis; Adipocytokine; Obesity; Leptin; Adiponectin; Omentin; Resistin; Visfatin

Core tip: Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression, severity as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, progression, treatment outcome and risk of any co-morbidities. Interventions to decrease pro-inflammatory adipocytokine levels could offer preventive and therapeutic options for improving psoriasis severity and protecting against its co-morbidities. Candidate strategic interventions may incorporate increased physical activity, weight control and pharmacologic approaches such as metformin.

Dalamaga M, Papadavid E. Adipocytokines and psoriasis: Insights into mechanisms linking obesity and inflammation to psoriasis. *World J Dermatol* 2013; 2(4): 27-31 Available from: URL: http://www.wjgnet.com/2218-6190/full/v2/i4/27.htm DOI: http://dx.doi.org/10.5314/wjd.v2.i4.27

PSORIASIS AND ADIPOSE TISSUE

Psoriasis represents a complex, chronic, systemic, T-cell immune-mediated inflammatory dermatopathy characterized by skin and joint manifestations, and presenting commonly with erythematous, scaly plaques on various surfaces of the body[1,2]. Its prevalence varies approximately from 0.1% to 3% worldwide, with a mean prevalence rate of 1.90% in Western countries and a lower one in Asia[3].

The etiology of psoriasis remains unknown but the disease is believed to result from an interaction between genetic susceptibility and exogenous environmental factors, such as infection, in particular with β-hemolytic streptococci, stress and trauma[1-2,4]. Several human leukocyte antigen (HLA) alleles including HLA-Cw*0602 are associated with psoriasis, with *PSORS1* being the major susceptibility gene mapped next to the HLA-Cw6 antigen[2,5]. Moreover, non-HLA related genes and loci have been identified and associated with psoriasis risk such as interleukin (IL)-12B and IL-23R[2].

Psoriasis has been lately seen as a potential systemic inflammatory disease associated with a range of co-morbidities exhibiting an overlapping pathology and presenting a great social health impact such as cardiovascular disease, metabolic diseases, autoimmune disease, malignancy, chronic obstructive pulmonary disease, sleep apnea and psychiatric disorders[1,2,6,7]. Overweight/obesity, metabolic syndrome (Mets), diabetes mellitus type 2 (t2DM) and dyslipidemia occur at a higher frequency in psoriasis patients than in general population[8]. Mets constitutes a constellation of cardiometabolic risk factors comprising central obesity, impaired glucose tolerance, elevated blood pressure and dyslipidemia[9]. Both psoriasis and Mets share common genetic predisposition; though their exact interplay remains enigmatic. Also, psoriasis and metabolic disorders share common risk factors such as smoking, obesity, physical inactivity and psychological stress[8]. Hence, all these cardio-metabolic risk factors, lifestyle parameters and the underlying chronic systemic psoriatic inflammation may all contribute to an increased risk for cardiovascular disease.

Apart from its fat storage function, adipose tissue constitutes an active endocrine organ secreting several bioactive adipocytokines regulating physiological and pathological processes, such as appetite, insulin sensitivity and resistance, immunity, inflammation, hematopoiesis and angiogenesis[10]. Increased adiposity following weight gain is associated with elevated levels of adipocytokines, comprising leptin, resistin and visfatin, and decreased levels of adiponectin and omentin, that may promote stimulation of monocytes and T cells, leading to both T-helper (Th)1 and Th17 immune responses and impairing the function of T regulatory cells[10-12]. Besides, the etiopathogenesis of Mets is attributed to hyperinsulinemia and insulin resistance mediated by adipocytokines, such as tumor necrosis factor-alpha (TNF-α), leptin, adiponectin and resistin[11]. It seems that obesity may potentiate the inflammation of psoriasis while, at the same time, it may help the development of Mets. Therefore, adipocytokines may represent a missing link in the association between psoriasis and metabolic co-morbidities, and could be used as potential biomarkers for assessing psoriasis severity, progression, treatment outcome, and risk of co-morbidities.

ADIPOCYTOKINES AND PSORIASIS

Leptin

Leptin is a 16-kDa, 167-amino acid adipocytokine that is primarily produced in adipose tissue. It is a pleiotropic molecule regulating food intake, appetite, energy expenditure, immunity, inflammation, hematopoiesis, cell differentiation and proliferation[12,13]. Leptin levels are directly proportional to the amount of body fat and fluctuate with acute changes in caloric intake, signaling the amount of energy stored in adipose tissue[12,13]. Although patients with hypoleptinemia and leptin deficiency are obese, common forms of obesity, insulin resistance and metabolic syndrome are accompanied by hyperleptinemia due to leptin resistance[12]. Leptin may be involved in the pathogenesis of psoriasis. It stimulates monocytes and macrophages, enhances the secretion of proinflammatory cytokines TNF-α, IL-6, IL-1, and IL-12, and shifts T-cell differentiation to Th1 phenotype[12,14]. Leptin stimulates also keratinocyte proliferation, angiogenesis and expression of adhesion molecules[14]. Despite the small size of epidemiologic studies and the lack of adjustment for body mass index (BMI) in analyses, the majority of studies examining the association between leptin and psoriasis has documented that psoriasis is associated with hyperleptinemia[14-17]. Also, elevated leptin levels characterize psoriatic arthritis and correlate with Psoriatic Arthritis Joint Activity Index[18]. In most studies, leptin correlated with Psoriasis Area Severity Index (PASI) score, representing, therefore, a biomarker of psoriasis severity and chronicity[19]. Indeed, severely affected psoriatic patients exhibit a significant increase in leptin levels compared to moderately affected patients[14]. Furthermore, leptin receptor and leptin expression in skin biopsies were found increased in severe psoriasis[19]. However, a possible association of psoriasis with leptin needs to be analyzed further with larger prospective, longitudinal and mechanistic studies in order to provide further insights into the paracrine and endocrine mechanisms underlying leptin's role in psoriasis.

Adiponectin and omentin

Adiponectin is a 30 kDa, 244-amino-acid protein produced predominantly by white adipose tissue, sharing a homology with TNF-α, collagen Ⅷ, X and complement factor C1q[10,11]. Adiponectin exhibits insulin-sensitizing, anti-inflammatory, anti-atherogenic, cardioprotective and anti-neoplastic effects as well as distinct actions in lipid metabolism[10,11]. The high molecular weight isoform is the biologically active configuration of adiponectin, being related with Mets, insulin resistance and cardiovascular

disease[11]. Hypoadiponectinemia is the common pathodenominator of the constellation of risk factors that compose Mets, such as hypertension, dyslipidemia, obesity, hyperglycemia and insulin resistance[11]. In contrast, hyperadiponectinemia is present in chronic inflammatory and autoimmune diseases not related to obesity such as rheumatoid arthritis and inflammatory bowel disease[10]. Adiponectin exhibits powerful anti-inflammatory properties by inhibiting the inflammatory cytokine network and down-regulating TNF-α-induced expression of endothelial adhesion molecules, TNF-α-expression in macrophages and adipose tissue, TNF-α-induced secretion of IL-6 in monocyte cells and keratinocytes *in vitro* as well as TNF-α, IL-6, IL-17, IL-22 and interferon-γ from T-lymphocytes[3,10,14]. Despite the fact that psoriasis is often associated with disease states characterized by hypoadiponectinemia such as Mets and obesity, controversial data exist in the literature regarding the association of adiponectinemia with psoriasis. A decrease, no change and even an increase in adiponectin levels have been reported in psoriasis patients[14,20-22]. Although not all results were adjusted for BMI, some studies have indicated a BMI independent change in adiponectin levels especially after treatment[21] as well as a negative correlation with PASI and pro-inflammatory cytokines such as TNF-α and IL-6[20,22].

Omentin, a newer 40-kDa adipocytokine, secreted mainly by stromal cells in the visceral fat, with similar properties to adiponectin, was found decreased in psoriatic patients in comparison to controls[23].

Resistin

Resistin is a 12 kDa cysteine-rich polypeptide which is produced in humans predominantly by stromal macrophages and monocytes of the visceral adipose tissue[24]. Elevated resistin levels are found in obesity and inflammation, and may play a significant role in the pathogenesis of insulin resistance, Mets and t2DM[24-27]. More importantly, resistin acts as a pro-inflammatory factor leading to an increased mRNA expression of twenty chemokines and cytokines including TNF-α, IL-1, IL-6, IL-12, chemokine ligand CXCL8, monocyte chemoattractant protein-1 and resistin itself *via* the nuclear factor-kappa B (NF-κB)[25]. In the majority of studies exploring the association of resistin with psoriasis, hyperrestinemia characterized untreated psoriatic patients and correlated with disease severity and nail psoriasis severity index[14,25-29].

Visfatin and other adipocytokines

Visfatin is a 52-kDa pleiotropic adipocytokine secreted by the macrophages of the visceral fat, acting as a cytokine, a growth factor and an enzyme, and playing a significant role in the cellular energy metabolism and in a variety of metabolic and stress responses[30-32]. Despite the conflicting association of visfatin with metabolic and anthropometric parameters, its concentrations are usually elevated in obese individuals, obese children and adolescents, in patients with coronary heart disease, t2DM, Mets and non-alcoholic fatty liver disease as well as in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease[31-34]. Visfatin enhances the production of IL-1α, IL-6, TNF-α, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 through the pro-inflammatory transcription factor NF-κB, and may contribute to the pathogenesis of vascular inflammation of obesity[31,32]. Visfatin may play a significant role in psoriasis pathophysiology. In a small size study, serum visfatin was significantly elevated in psoriasis patients than in healthy controls, correlating positively with disease chronicity and severity[23]. *In vivo*, the visfatin gene expression profile was increased in psoriasis while *in vitro* visfatin upregulated TNF-α-induced chemokine ligands: CXCL 8, 10 and CCl20 production and mRNA expression in human keratinocytes[35,36].

Data regarding newer and promising adipocytokines, such as vaspin, retinol-binding protein 4 and chemerin with respect to psoriasis are sparse and controversial[14,37].

The controversy of results in epidemiologic studies examining the association of adipocytokines with psoriasis may be attributed to the (1) retrospective study design; (2) small sample size; (3) non-adjustment of the results for BMI, waist circumference and metabolic parameters as well as for important confounders such as coronary disease; (4) different ethnic groups examined; (5) importance of measuring fasting samples *vs* non-fasting; and (6) different laboratory assays used.

In conclusion, adipocytokines such as leptin, adiponectin, resistin and visfatin represent key players in many physiologic processes including energy balance, immunity and inflammation. Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, treatment success and risk of any co-morbidities. We also speculate that interventions to decrease pro-inflammatory adipocytokine levels could represent a preventive and therapeutic option for improving disease severity and protecting against its co-morbidities. Candidate strategic interventions incorporate increased physical activity[38], weight control and pharmacologic approaches such as metformin[10,11]. However, the mechanisms underlying the actions of adipocytokines in psoriasis as well as their potential diagnostic, prognostic and/or therapeutic utility require further investigation with larger prospective, longitudinal and mechanistic studies.

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P- Reviewers Ayroldi E, Di Lernia DV
S- Editor Gou SX **L- Editor** A **E- Editor** Lu YJ

World Journal of Dermatology

Online Submissions: http://www.wjgnet.com/esps/
wjdermatol@wjgnet.com
doi:10.5314/wjd.v2.i4.32

World J Dermatol 2013 November 2; 2(4): 32-35
ISSN 2218-6190 (online)

EDITORIAL

Metabolic co-morbidities and psoriasis: The chicken or the egg?

Maria Dalamaga, Evangelia Papadavid

Maria Dalamaga, Department of Clinical Biochemistry, Medical School, University of Athens, "Attikon" General University Hospital, 12462 Athens, Greece
Evangelia Papadavid, Department of Dermatology, Medical School, University of Athens, "Attikon" General University Hospital, 12462 Athens, Greece
Author contributions: Dalamaga M designed the editorial and wrote the manuscript; Papadavid E reviewed the manuscript.
Correspondence to: Maria Dalamaga, MD, PhD, MS, MPH, Assistant Professor, Department of Clinical Biochemistry, Medical School, University of Athens, "Attikon" General University Hospital, 1 Rimini street, Karyotaki 29, 12462 Athens, Greece. madalamaga@med.uoa.gr
Telephone: +30-210-5831915 Fax: +30-210-6082467
Received: June 15, 2013 Revised: September 25, 2013
Accepted: October 17, 2013
Published online: November 2, 2013

Abstract

Accumulating evidence supports that psoriasis may be a potential multisystem inflammatory disease associated with a range of co-morbidities showing an overlapping pathology and an important health impact such as metabolic diseases. Psoriasis is associated with an increased risk of obesity, metabolic syndrome (Mets) and diabetes mellitus type 2, following a "dose-response" relationship from mild to severe psoriasis. Conversely, recent evidence from large prospective studies suggests that obesity constitutes a risk factor for psoriasis and psoriatic arthritis. Also, a dyslipidemic profile may precede psoriasis onset. Both obesity, Mets and psoriasis, characterized as chronic inflammatory states, stem from a shared underlying pathophysiology exhibiting common genetic predisposition and risk factors such as high caloric intake, physical inactivity and psychological stress. Excess weight may potentiate the inflammation of psoriasis through the deregulation of adipocytokines while, at the same time, it may help the development of Mets. Interestingly, recent translational data has shown that psoriasis, through increased T-helper inflammatory cytokines in skin and sera, may exert a plethora of effects on insulin regulation and lipid metabolism. Larger population-based prospective cohort and longitudinal studies are needed to unravel the association between psoriasis and metabolic co-morbidities. The recognition of the intricate complex interplay between psoriasis and metabolic co-morbidities may help dermatologists to be aware of associated metabolic co-morbidities in order to screen for metabolic diseases and manage holistically and effectively the psoriatic patient.

Key words: Psoriasis; Obesity; Metabolic syndrome; Metabolic co-morbidities; Diabetes mellitus; Insulin resistance

Core tip: Psoriasis is associated with an increased risk of obesity, metabolic syndrome (Mets) and diabetes mellitus type 2, following a "dose-response" relationship from mild to severe psoriasis. Conversely, recent evidence from large prospective studies suggests that obesity constitutes a risk factor for psoriasis and psoriatic arthritis. Both obesity, Mets and psoriasis, characterized as chronic inflammatory states, stem from a shared underlying pathophysiology exhibiting common genetic predisposition and risk factors such as high caloric intake, physical inactivity and psychological stress. Larger population-based prospective cohort and longitudinal studies are needed to unravel the association between psoriasis and metabolic co-morbidities.

Dalamaga M, Papadavid E. Metabolic co-morbidities and psoriasis: The chicken or the egg? *World J Dermatol* 2013; 2(4): 32-35 Available from: URL: http://www.wjgnet.com/2218-6190/full/v2/i4/32.htm DOI: http://dx.doi.org/10.5314/wjd.v2.i4.32

INTRODUCTION

Psoriasis is a chronic, systemic, T-cell immune-mediated inflammatory skin disorder characterized by dermal and

joint manifestations[1,2]. The prevalence of psoriasis varies approximately from 0.1% to 3.0% worldwide, with a mean prevalence rate of 1.90% in Western countries and a lower prevalence elsewhere[3].

Its etiology is unknown; however, the interplay between genetic susceptibility and exogenous environmental factors plays an important role[2]. Several human leukocyte antigen (HLA) alleles including HLA-Cw*0602 and non-HLA related genes such as interleukin (*IL*)-*12B* and *IL-23R* genes are associated with psoriasis risk[1,4].

PSORIASIS AS A CHRONIC INFLAMMATORY DISEASE

There is accumulating evidence that the characteristic T-helper (Th)-1 chronic inflammation seen in the psoriatic plaque may be connected with the systemic chronic inflammatory process seen in atherosclerosis and insulin resistance through various inflammatory mediators and cells[5]. The contribution of T cells to psoriasis pathophysiology shows the extent of its systemic involvement. Indeed, Th-1, Th-17 and Th-22 cell populations are expanded and enhanced to secrete inflammatory cytokines, comprising tumor necrosis factor-α (TNF-α), IL-17 and IL-22[1,2]. The psoriatic inflammatory pathology may play a role in immune and metabolic changes that contribute to the perpetuation of psoriasis and the development of co-morbidities[3,6]. In contrast to rheumatoid arthritis, psoriasis is not a systematic disease *per se* with multi-organ involvement (except joints); however, accumulating medical evidence supports the assertion that psoriasis may be a potential multisystem inflammatory disease associated with a range of co-morbidities exhibiting an overlapping pathology and an important health impact such as metabolic diseases, cardiovascular disease (CVD), autoimmune disease, psychiatric disorders, malignancy, chronic obstructive pulmonary disease and sleep apnea[2,7,8].

PSORIASIS AND THE RISK OF METABOLIC CO-MORBIDITIES

Metabolic diseases such as obesity, insulin resistance, metabolic syndrome (Mets), diabetes type 2 (t2DM) and dyslipidemia occur at a higher frequency in psoriatics than in general population[3,9-12]. Indeed, substantial evidence shows that psoriasis is associated with an increased risk of obesity[3,9]. Obesity is more common in psoriatic arthritis (PsA) than in rheumatoid arthritis[11]. Central or abdominal obesity represents an important component of Mets along with impaired glucose tolerance, elevated blood pressure and dyslipidemia. A recent meta-analysis has provided further evidence that psoriatic patients present a higher prevalence of Mets than the general population[13]. In particular, the prevalence of Mets in psoriatic patients is higher than that of the general population, being 40% in the United States and 27.4% in Japan[9]. Additionally, patients with PsA present significantly higher prevalence of Mets compared to the general population[3]. Whether the connection between Mets, obesity and psoriasis is valid for the full spectrum of psoriasis patients or only for those with more severe psoriasis remains controversial. Nonetheless, psoriasis was independently associated with Mets and followed a "dose-response" relationship from mild to severe psoriasis[10,11]. Also, obesity as expressed by the body mass index (BMI) was positively associated with psoriasis area and severity index (PASI) score[10-13]. The parameters defining Mets go hand in hand with an elevated risk for t2DM and CVD while emerging data indicate that psoriasis could be an independent risk factor for CVD[6]. Psoriasis patients demonstrate more frequently insulin resistance compared to healthy controls when challenged with oral glucose tolerance test and present an increased risk of t2DM, particularly female patients[6,12]. The adjusted risk ratios for t2DM risk following psoriasis vary between 1.08 and 3.61[12], being somewhat stronger in Asian than in European and American studies[12]. The risk of t2DM increases in patients with psoriasis and PsA with BMI, psoriasis severity and duration[11]. Finally, psoriasis patients are at increased risk for non-alcoholic fatty liver disease and liver fibrosis compared to healthy controls[10].

Both psoriasis and metabolic co-morbidities share common genetic predisposition. For example, the psoriasis genetic risk loci *PSORS* 2-4 and *CDKAL1* are associated with susceptibility of t2DM[12]. Furthermore, psoriasis and metabolic co-morbidities share common risk factors such as smoking, weight gain, physical inactivity and psychological stress[9]. Psoriatics are more likely to lead unhealthy lifestyles and to present psychological impairment suffering thus, from obesity, Mets, t2DM, anxiety and depression as a result. Moreover, severe psoriasis greatly affects patients and is associated with habits (*i.e.,* eating, smoking, alcohol) and states of mind (*i.e.,* depression) that may represent risk factors for metabolic co-morbidities[8]. Hence, all these genetic, lifestyle parameters and the underlying chronic systemic psoriatic inflammation may contribute in tandem to an increased risk for metabolic co-morbidities and CVD.

METABOLIC DISEASES AND THE RISK OF PSORIASIS

Although there is a strong association between psoriasis and metabolic diseases, the etiology of this link remains enigmatic. Whether excess weight is a predisposing factor or a manifestation of psoriasis is still controversial. Recent evidence from large prospective studies suggests that obesity constitutes a risk factor for psoriasis and PsA development[6,11,14]. Additional data have revealed that a dyslipidemic profile characterized by elevated triglycerides, total and low-density lipoprotein cholesterol as well as decreased high-density lipoprotein levels precedes psoriasis onset[9,15]. Whether obesity and its metabolic complications are the causes or the effects of psoriasis,

the obese state may exacerbate the severity of psoriasis as confirmed in a number of cross-sectional studies whereas increased BMI correlates positively with PASI and psoriasis area[6].

Both obesity, Mets and psoriasis, characterized as chronic inflammatory states, stem from a shared underlying pathophysiology. Apart from its energy storage function, adipose tissue is a genuine endocrine organ secreting several bioactive adipocytokines regulating physiological and pathological processes, including appetite, insulin sensitivity and resistance, immunity, and inflammation[16-19]. Increased adiposity following weight gain is associated with elevated levels of adipocytokines, comprising TNF-α, IL-6, leptin, resistin and visfatin, and decreased levels of adiponectin, that may promote immune stimulation, leading to both Th1 and Th17 immune responses and impairing the function of T regulatory cells[16-18]. In parallel, the etiopathogenesis of Mets is attributed to hyperinsulinemia and insulin resistance mediated by adipocytokines, such as TNF-α, leptin, adiponectin and resistin[9,18-20]. It seems that obesity may potentiate the inflammation of psoriasis while, at the same time, it may help the development of Mets. Hence, adipocytokines may be a missing link in the association between metabolic co-morbidities and psoriasis, and could be used as potential biomarkers for assessing disease severity and risk of co-morbidities[20]. Conversely, it is now recognized from translational data that psoriasis, as a chronic inflammatory systemic disease through TNF-α and T-helper inflammatory cytokines that are increased in skin and sera, may exert a plethora of effects on insulin regulation and lipid metabolism which are important in the pathophysiology of metabolic co-morbidities[9-11].

UNRAVELING THE VICIOUS CYCLE OF PSORIASIS AND METABOLIC CO-MORBIDITIES

A vicious cycle is established whereby weight gain and Mets may play a pivotal role in psoriasis, and, as psoriasis progresses in severity and chronicity, obesity and metabolic co-morbidities may be more pronounced due to enhanced caloric intake, physical inactivity and unhealthy habits caused by psychological factors in psoriasis and PsA[21,22].

In order to unmask the association between psoriasis and metabolic co-morbidities, evidence is needed from adequately powered, large, long-term, population-based prospective cohort and longitudinal studies taking into account in multivariable statistical analyses important parameters such as anthropometric variables (*i.e.*, BMI, waist circumference), metabolic factors (*i.e.*, glucose, insulin, homeostasis model assessment scores), habits (*i.e.*, smoking, alcohol) and psoriasis systematic treatment.

The recognition of the intricate complex interplay between psoriasis and metabolic co-morbidities may help dermatologists to be aware of associated metabolic co-morbidities in order to screen for metabolic diseases and manage holistically and effectively the psoriatic patient. Lifestyle interventions, diet, physical activity and management of metabolic co-morbidities may be beneficial for psoriasis patients by improving both their physical and psychological well being and prolonging their lifespan. More studies are also needed to study the effect of psoriasis systemic therapies on metabolic co-morbidities and to unravel the mechanisms of the underlying association between psoriasis and metabolic co-morbidities.

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P- Reviewers Buechler C, Sakata N
S- Editor Gou SX **L- Editor** A **E- Editor** Lu YJ

World Journal of Dermatology

Online Submissions: http://www.wjgnet.com/esps/
wjdermatol@wjgnet.com
doi:10.5314/wjd.v2.i4.36

World J Dermatol 2013 November 2; 2(4): 36-43
ISSN 2218-6190 (online)

EDITORIAL

Molecular mimicry in cutaneous autoimmune diseases

Fabrizio Guarneri, Claudio Guarneri

Fabrizio Guarneri, Claudio Guarneri, Department of Clinical and Experimental Medicine, University of Messina, 98125 Messina, Italy
Author contributions: Guarneri F designed the editorial and wrote the manuscript; Guarneri C reviewed the manuscript.
Correspondence to: Fabrizio Guarneri, MD, Professor, Department of Clinical and Experimental Medicine, University of Messina, AOU Policlinico "G. Martino", Via Consolare Valeria 1, 98125 Messina, Italy. f.guarneri@tiscali.it
Telephone: +39-90-357070 Fax: +39-90-2927691
Received: August 12, 2013 Revised: September 2, 2013
Accepted: September 14, 2013
Published online: November 2, 2013

Abstract

The emulation of characteristics of a different organism to gain biological advantage is a common phenomenon in nature, described and defined with the term "mimicry" in the second half of the 19th century. In the last decades, mimicry at molecular level has been evidenced as a method used by several pathogen microrganisms to control metabolic functions of infected cells and elude host's immune system. Because of molecular mimicry, immune reactions against microbial molecules can turn against the mimicked self-molecules in predisposed subjects, leading to autoimmunity. This pathogenic mechanism, which gives a possible explanation for the specific epidemiological and chronological association between some infections and some autoimmune diseases, is well known and verified in many fields of medicine, but not adequately studied in dermatology: experimental data are available only for leprosy, atopic dermatitis, Behçet's disease, Vogt-Koyanagi-Harada syndrome and systemic erythematous lupus, while for few other diseases its role is hypothetical or suggested on the basis of single, small experiments or anecdotal reports. An overview of available data and hypotheses about the role of molecular mimicry in autoimmune cutaneous diseases is presented here, together with the perspectives offered by the use of bioinformatics and the personal experience of the author in this field.

Key words: Molecular mimicry; Dermatology; Autoimmunity; Bioinformatics; Amino acid sequence homology

Core tip: Molecular mimicry between microbial and human proteins is often used by pathogens to control biosynthetic/regulatory pathways of infected cells and elude immune reaction of host. In predisposed subjects, immune response against non-self molecules can, because of molecular mimicry, turn against self antigens and trigger autoimmune diseases. This mechanism, which explains the specific epidemiological link between some infections and some autoimmune diseases, is known and experimentally confirmed in several disciplines, but much less studied in dermatology. Bioinformatics can greatly help and boost research by quickly and almost inexpensively identifying molecules most probably involved in triggering autoimmunity *via* molecular mimicry.

Guarneri F, Guarneri C. Molecular mimicry in cutaneous autoimmune diseases. *World J Dermatol* 2013; 2(4): 36-43 Available from: URL: http://www.wjgnet.com/2218-6190/full/v2/i4/36.htm DOI: http://dx.doi.org/10.5314/wjd.v2.i4.36

MIMICRY IN NATURE

The first use of the term "mimicry" in biology dates back to 1862, when Henry Walter Bates[1] published the results of his studies on some species of the order *Lepidoptera* living in the Amazon valley. He reported that some species, belonging to different families, show unexpected similarities of the appearance of wings, and suggested a possible correlation between this phenomenon and natural selection. Indeed, some color patterns of wings allow predators to visually distinguish edible

from not edible preys. Based on this mechanism, Bates suggested that an edible prey showing the color pattern of a not edible species can significantly reduce the probabilities of being attacked, thus increasing the chances of survival.

The development of similar morphological characteristics in different organisms had been already noticed about one century earlier by Carl Nilsson Linnaeus, during his complex work of classification of known living species, and had been explained as a consequence of physical or biochemical interactions with the surrounding environment. The revolutionary element introduced by Bates was the demonstration that some prey-predator interactions occur exclusively through transmission of visual information, and that survival strategies of an organism can include transmission of deliberately false information about its identity or characteristics (the term used by Bates was actually "deception"). Subsequent studies have shown also the existence of acoustic, olfactory and behavioral mimicry in nature.

The so-called "Batesian mimicry" was only the beginning of a fascinating journey that led scientist to better understand the complexity of the interactions between living beings. Soon after his first discoveries, Bates found that some unrelated species, equally not edible for predators, also shared the same color pattern. This apparent contradiction was explained in 1878 by Müller[2] (hence, this kind of mimicry was defined "Mullerian mimicry"). Müller pointed out that predators learn that a prey is not edible by trial and error, and suggested that, in this case, mimicry is useful to equally split over many species, instead of only one, the number of individuals sacrificed for such learning process[2]. In 1968 Wolfang Wickler, concluding a work started by previous researchers, reported another type of mimicry, defined as "emsleyan" (in honor of M. G. Emsley[3], who first proposed it) or "mertensian" (in honor to R. Mertens)[4]. Mimicry is not used only for defensive purposes: some predators can mimic features of different species to deceive preys and capture them more easily ("aggressive mimicry")[5]. A particular type of Batesian mimicry has been defined as "automimicry": in this case, an individual shows characteristics of different individuals of the same species which are more often avoided by predators (a typical example is that of many bees and wasps, whose males, devoid of defensive systems, take the color pattern of females, which are dangerous for predators because of their sting)[6].

MOLECULAR MIMICRY

Relatively recently, the progress of biology and laboratory techniques allowed to discover that mimicry is present in living organisms also at a molecular level, probably even more than at a macroscopic level. Circumscribing discussion only to human diseases, it must be pointed out that molecular mimicry has several peculiarities, because of the intrinsic complexity of host-pathogen interactions. During an infection, a pathogen is at the same time a "predator" of its host, but also a "prey" of the host's immune system; consequently, molecular mimicry between pathogens and hosts could be classified as aggressive mimicry (although atypical, because the mimicked model is also the prey) and, at the same time, as Batesian mimicry. Moreover, pathogens use hosts' resources to live and replicate, and molecular mimicry is used to control such resources rather than just killing the host.

Typically, microrganisms are able to synthesize proteins similar to those that are involved, in humans, in the regulation of fundamental processes such as apoptosis, cell proliferation, inflammation and immune response. In this way, they can "hijack" and modulate these mechanisms to their advantage.

In the dermatologic field, one of the most studied examples is that of HHV8 (human herpesvirus 8), which is notoriously linked to Kaposi's sarcoma. This virus extensively exploits molecular mimicry and can interact with cells at multiple levels. The viral genetic loci ORFK12 and ORFK72 produce v-FLIP and v-cyc-D, viral homologs of the human proteins FLIP and cyclin D, respectively. FLIP (FLICE Inhibiting Protein) prevents cell apoptosis mediated by tumor necrosis factor α and Fas-ligand, by inhibiting FLICE (Fas-associated death domain-like interleukin 1 beta-converting enzyme), while cyclin D activates kinases cdk4 and cdk6, thus inducing phosphorilation and inactivation of pRb, a protein which is able to stop the G1 phase of the cell cycle in case of DNA damage[7,8]. Additionally, HHV8 produces a homolog of human Bcl-2 (a protein which inhibits Bax-induced apoptosis) and human IRF (Interferon Regulating Factor), and can also switch immune response from Th1 to Th2 type through homologs of human interleukin 6 and macrophage inhibiting protein Ⅰ, Ⅱ and Ⅲ[8].

MOLECULAR MIMICRY AND AUTOIMMUNITY

The frequent and specific epidemiological association between some infections and some autoimmune diseases was already highlighted several decades ago: the most famous examples are probably diabetes, autoimmune thyroiditis, multiple sclerosis and, in dermatology, systemic erythematous lupus, vitiligo, scleroderma, lichen sclerosus, chronic atrophic acrodermatitis[9]. The hypothesis that similarities between molecules of different nature could be a cause of autoimmunity was proposed in 1976 by Shapiro *et al*[10], who also created and introduced, in the same paper, the term "molecular mimicry". With rare exceptions, technical limits prevented almost completely experimental tests on this theory for about 20 years. Starting from mid-1990s, thanks to the simultaneous "coming of age" of new laboratory techniques for production and analysis of biomolecules, high-power and low-cost computers and worldwide informatic networks, a significant increase of research on molecular mimicry has become possible, and produced several

confirmations of the hypothesis proposed by Shapiro and colleagues, explaining its pathogenic mechanism.

It is well known that mounting a specific immune response requires antigen presentation by APCs (Antigen Presenting Cells) to T cells. More in detail, an antigen fragment is presented in the context of an MHC (Major Histocompatibility Complex) molecule present on APC surface, and the MHC-antigen fragment complex is recognized by a TCR (T-Cell Receptor) molecule on T cell surface. Physical and biochemical complementarity of the above three components (MHC, antigen fragment, TCR) is necessary for immune activation, and this guarantees the specificity of the response. However, the number of possible antigen fragments is between 10^{12} and 10^{15}, while the size of the human T cell repertoire is around 10^{8}. Thus, the antigen recognition mechanism has a certain degree of flexibility: a T cell clone can recognize several antigens which share some characteristics. This makes the system efficient even in case of many possible mutations of microbial antigens, and allows response not only against a single pathogen, but against all pathogens which possess similar antigens[11].

On the other hand, the flexibility of the antigen recognition system is the basis for possible development of autoimmunity *via* molecular mimicry. When a sufficiently high degree of similarity exists between a microbial and a human protein, the immune system of certain subjects can be unable to distinguish them, and an immune response mounted against the microbial antigen for defensive purposes can turn against the self antigen, and persist indefinitely even after resolution of the initial infectious process.

The frequency of autoimmune diseases in epidemiological studies is much lower than that expected on the basis of the aforementioned figures, suggesting the existence of control systems which decrease the risk of autoimmune reactions. Deletion of autoreactive T cell clones has been considered for a long time the main control mechanism, but modern studies suggest that its importance is limited: only the most dangerous clones are actually deleted, leaving many potential autoreactive ones in the available T cell repertoire. Other, quantitatively more important mechanisms are peripheral induction of T cell apoptosis, induction of anergy, action of regulatory T cells. Immunological cross-reactivity between two molecules is clearly not sufficient for the induction of autoimmune diseases: a simultaneous dysregulation of control mechanisms is necessary. This can occur because of complex and not yet completely understood combinations of genetic and environmental factors, including the immune system alterations induced by infectious microrganisms (directly and/or, again, *via* molecular mimicry).

MOLECULAR MIMICRY IN DERMATOLOGY

Commonly accepted as a trigger of autoimmunity in many fields of medicine[12-30], molecular mimicry is less known in dermatology, and only few experimental studies on its role in autoimmune cutaneous diseases are available. Indeed, when mentioned, molecular mimicry is often only postulated as a possible explanation for the onset of autoimmunity after some infections, without any *in vivo*, *in vitro*, computational or even theoretical data about the molecules possibly involved.

In a search on the PubMed database (http://www.pubmed.gov), the first paper of dermatological interest on molecular mimicry dates back to 1992, when Muryoi *et al*[31] studying anti-topoisomerase I antibodies from scleroderma patients, demonstrated homology between the human autoantigen and the UL70 protein of cytomegalovirus and suggested in their conclusions that "activation of autoreactive B cell clones by molecular mimicry is possible". After that paper, attention was focused on several skin diseases, but often anecdotally and with contrasting results.

Leprosy

Experimental data of "molecular mimicry reactions between cytoskeletal proteins, host stress proteins and *Mycobacterium leprae* antigens or stress proteins" were presented by Kroumpouzos *et al*[32] about 20 years ago. More recently, Singh and collaborators have confirmed those results, and, thanks to the progress in laboratory techniques, have been able to specify the molecules involved, *i.e.*, heat shock protein 65 (hsp65) of *Mycobacterium leprae* and human cytokeratin-10, which share seven epitopes[33]. This may not be the only cross-reactivity relevant for this disease: indeed, Rambukkana *et al*[34], in 1992, identified an epitope common to mycobacterial hsp65 and human cytokeratin 1/2.

Psoriasis

Mainly because of the striking association of certain forms of the disease with streptococcal infection, many of the dermatological studies on molecular mimicry have focused on psoriasis, but with controversial results. As described in a paper by Noah *et al*[35] the skin basement membrane zone is a depository for at least one circulating streptococcal antigen, which is largely present there in lesional skin and, to a lesser extent, in non lesional skin of psoriatic patients, but absent in the skin of healthy subjects. It is also known that *Streptococcus pyogenes* DNA can be detected in tissues of patients affected by plaque psoriasis[36], and T cells able to recognize determinants common to streptococcal M-protein and keratin can be found in patients' blood[37], but this is not sufficient to explain disease onset in the majority of cases[38,39]. Other microrganisms postulated as possible triggers of psoriasis *via* molecular mimicry are cytomegalovirus and human herpesviruses 6 and 7, but the only experimental study on them, performed on a small sample of 10 patients, did not show sufficient evidence to confirm such hypothesis[40].

Atopic dermatitis

At the end of 1990s, Valenta *et al*[41] introduced the idea of autoallergy, *i.e.*, IgE-mediated reactivity against self antigens, as a pathogenic factor in atopic dermatitis. Suc-

cessive studies by that and other workgroups not only confirmed the correctness of the original idea, but also showed that in some cases autoallergy can be induced by molecular mimicry between autoallergens and allergens produced by fungal species living on human skin and particularly abundant in atopic subjects[42].

Urticaria

The discovery of histamine-releasing autoantibodies against Fc epsilon receptor 1 or IgE in a remarkable percentage of patients affected by chronic idiopathic urticaria led some researchers to hypothesize a possible role of molecular mimicry in this condition[43]. Many microrganisms have been suspected as potential triggers, but only anecdotal reports exist to date, and, from an evidence-based viewpoint, arguments in favor of this theory are weak[44]. This does not rule out the possibility of a link, but suggests the need for further studies on this topic.

Behçet's disease

Multisystem inflammatory disorder which is epidemiologically associated to microbial infections, Behçet's disease appears as an ideal candidate to demonstrate the role of molecular mimicry in the pathogenesis of cutaneous autoimmune diseases. As suggested in a recent review, known potential triggers include *Saccharomyces cerevisiae*, mycobacteria, *Borrelia burgdorferi*, *Helicobacter pylori*, *Escherichia coli*, *Staphylococcus aureus*, *Mycoplasma fermentans*, *Streptococcus sanguinis*, herpes simplex virus-1, hepatitis C virus, parvovirus B19, cytomegalovirus, Epstein-Barr virus and varicella zoster virus[45]. However, no experimental evidence of molecular mimicry with human autoantigens is currently available. In 1997, Sakane *et al*[46] postulated that the autoantigen targeted by autoreactive T-cells cross-reacting with microbial antigens could be heat shock protein 60 (hsp60). Recently, Ghasemi *et al*[47] showed that human hsp60 shares significant homology, in particular for which concerns some segments known as epitopes, with hsp60 proteins produced by many bacteria epidemiologically associated to Behçet's disease: this provides a theoretical basis for the above hypothesis and suggests a path for future *in vitro* and *in vivo* research.

Systemic lupus erythematosus

The involvement of molecular mimicry in the pathogenesis of this systemic disease with cutaneous manifestations is experimentally and clinically well studied. As outlined in a 2008 review by Doria *et al*[48], "molecular mimicry, especially between Sm or Ro autoantigens and EBV Nuclear Antigen-1 response, as well as the overexpression of type 1 INF genes are among the major contributors to SLE development".

Other autoimmune cutaneous diseases

Some experimental data show the involvement of molecular mimicry in Vogt-Koyanagi-Harada syndrome, graft-versus-host disease and pemphigus. As discovered by Sugita, T cells specific for tyrosinase can also recognize the cytomegalovirus envelope glycoprotein H, and this can explain the reported association between cytomegalovirus infection and Vogt-Koyanagi-Harada syndrome[49]. Another product of the same virus, namely the protein UL94, is cross-reactive with the cell surface tetraspanin transmembrane 4 superfamily member 7 (TM4SF7 or NAG-2) human molecule and can constitute the trigger for the onset of scleroderma-like skin lesions in chronic graft-versus-host disease in allogeneic stem-cell transplant patients[50]. The case of pemphigus is rather peculiar, because the molecular homology found by Gilbert *et al*[51] is not between a self and a non-self antigen, but between the human monoclonal antibody F12 and the adhesion molecules desmoglein 1 and bullous pemphigoid antigen 2.

Molecular mimicry has also been postulated as a possible cause of herpes simplex virus-associated erythema multiforme, by Aurelian *et al*[52], sarcoidosis, by Tchernev *et al*[53], and -on the basis of single case reports- alopecia areata associated with gastric *Helicobacter pylori* infection[54], and vitiligo developing around nodular lesions of Kaposi's sarcoma in a patient with acquired immunodeficiency syndrome[55].

BIOINFORMATICS AND MOLECULAR MIMICRY

As previously mentioned in this article, the remarkable progress in research on molecular mimicry is the result of the simultaneous development and the interaction between two disciplines traditionally considered "distant", such as biology and informatics. After many years of pilot studies, bioinformatics has finally become an integral part of the modern set of research tools, particularly in some fields.

The high level of complexity of living organisms, determined by multiple, multifactorial and only partially known concurring events, can not be currently emulated or represented by any software or mathematical model; consequently, *in vivo* and/or *in vitro* experiments are still the essential part of research in any field of biology. However, when studying molecular mimicry, bioinformatic techniques allow quick and almost inexpensive analysis of a large number of microbial and self antigens, identifying the most probably cross-reactive ones and, in some cases, even the epitopes possibly involved. Such data are useful to better focus time and resources when performing traditional experiments.

One of the first bioinformatic techniques in this field, and still among the most used ones, is the analysis of homologies between amino acid sequences. A complete definition of the statistical methods needed for such analysis was published in 1997 by Altschul *et al*[56], authors of the software BLAST (Basic Local Alignment Search Tool). Originally created for the study of "evolutionary distance" between organisms, BLAST has been successfully used to define the probable function

of newly discovered proteins and to identify potential cross-reactive segments of different proteins.

Less common, but very interesting, are the softwares able to detect the presence, in the sequence of a protein, of amino acid "motifs" that determine the binding of a peptide to a specific MHC (Major Histocompatibility Complex) molecule for presentation to the immune system. When such motifs are contained in homologous segments of microbial and self antigens, higher probability exists that such homology is pathogenically relevant; this could also explain, at least in part, the increased risk for certain autoimmune diseases in subjects who possess specific HLA (Human Leukocyte Antigen) genes.

Last in chronological order of development, but certainly not in importance, are some more sophisticated softwares able to predict secondary and tertiary structure of molecules, as well as their reciprocal interactions. These softwares can improve our understanding of immune phenomena, and, in the field of molecular mimicry, allow identification of cross-reactivity due to non-linear epitopes (epitopes formed by parts of a protein which are distant in the linear sequence, but close to each other in the actual three-dimensional structure). Mainly because of the high computational resources needed, this kind of bioinformatic analysis has been used only by some Centers, but the continuous progress of informatic technology should allow a larger diffusion in relatively short times[11].

Use of bioinformatic tools could be a relatively easy way to boost research on molecular mimicry in dermatology. Studies performed and published by our workgroup in this field concern: (1) the possible correlation of lichen sclerosus, borreliosis and Hashimoto's thyroiditis; (2) autoimmune diseases characterized by anti-Ku autoantibodies; and (3) atopic dermatitis.

The idea of a possible correlation of lichen sclerosus, borreliosis and Hashimoto's thyroiditis originated by our observation of a woman affected by lichen sclerosus and seropositive (IgG and IgM) for *Borrelia burgdorferi*, who developed Hashimoto's thyroiditis three months after the onset of the autoimmune cutaneous disease[57]. Based on that hypothesis, we initially used BLAST to search for amino acid sequence homologies of the four known thyroid autoantigens -thyroid stimulating hormone receptor (TSH-R), thyroid peroxidase (TPO), thyroglobulin (Tg) and sodium-iodide symporter (NIS)- with the 6606 proteins of *Borrelia* known at that time. We found 16 significant homologies, of which 5 for TSH-R, 2 for Tg, 3 for TPO and 6 for NIS; all of them concerned protein sequences known as autoepitopes[29]. Successively, we found that human thyroid autoantigens and proteins of Yersinia and Borrelia share amino acid sequence homology that includes binding motifs to HLA-DR molecules and T-cell receptor[30]. In that occasion, to find HLA binding motifs we developed the first version of our program MotiFinder, which was later improved to become a general purpose pattern search software[58]. In the last phase of our study, we evaluated the similarity between *Borrelia* proteins and the human ECM-1 protein (Extra Cellular Matrix protein 1), which is the autoantigen involved in lichen sclerosus: in this case, 18 bacterial proteins with significant primary sequence homology were identified. We also searched the potentially cross-reactive microbial and human proteins found in all the above researches for the binding motif of MHC molecules encoded by the HLA-DQ7 allele, which is reported in literature as a risk factor for both Hashimoto's thyroiditis and lichen sclerosus: this motif was present in all but one of the proteins examined, thus supporting the idea that, in some genetically predisposed subjects, *Borrelia* infection can be the trigger of Hashimoto's thyroiditis and/or lichen sclerosus[59].

The Ku protein is a heterodimer made of two subunits, p70 and p80, is part of a group of DNA-associated nuclear proteins and plays a key role in fundamental processes like DNA repair, maintaining of chromosomal stability and regulation of transcription and V(D)J recombination, particularly in conditions of cell stress. Anti-Ku autoantibodies are found in some patients with systemic erythematous lupus and related diseases and in about 5% of scleroderma patients; in this latter case, they are strongly suggestive of a systemic sclerosis/polymyositis overlap syndrome[9]. In 1992, Reeves suggested the possible role of molecular mimicry in the etiopathogenesis of anti-Ku autoimmunity[60]. Using *in silico* techniques, we verified the potential cross-reactivity of the two Ku subunits with bacterial (n = 5229868 at the time of our search), viral (n = 629582) and fungal (n = 511126) proteins. The results are an excellent example of the possibilities of bioinformatics: in few minutes of elaboration, we found that only 14 proteins out of the more than 6300000 examined have significant homology with the p70 subunit and 12 with the p80 subunit of Ku. These proteins, all belonging to fungal species which are known as human pathogens, should be considered primary targets of experimental research in this field. Additionally, we found that homologous segments overlapped totally or, in one case, partially, with at least one of the sequences of p70/p80 that contain T-cell autoepitopes[61].

Concerning atopic dermatitis, the role played by molecular mimicry in determining the so-called "autoallergy", *i.e.*, IgE-mediated autoimmunity, has been demonstrated in 2005 by Schmid-Grendelmeier *et al*[42]. These researchers showed that the fungal allergen Mala s 11 of *Malassezia sympodialis*, a common component of the cutaneous flora, can trigger IgE response against the highly similar human protein manganese superoxide dismutase, and a similar response can be induced by allergen Asp f 6 of *Aspergillus fumigatus*. We used bioinformatic tools to verify whether other allergens could play a role similar to that of Mala s 11 and Asp f 6 *via* molecular mimicry. A BLAST analysis allowed us to discover a single allergen, in addition to the aforementioned ones, significantly homologous to human manganese superoxide dismutase,

namely Hev b 10 of *Hevea brasiliensis* (better known as "latex tree")[62]. Indeed, the level of homology to the autoallergen is in this case even higher than that of Mala s 11 and Asp f 6, and a three-dimensional model of the proteins, created with the software SWISS-MODEL[63], confirmed that this is true even for which concerns solvent-exposed residues[62]. Experimental studies are currently in progress to verify whether such homology is pathogenically relevant for atopic dermatitis.

CONCLUSION

The full understanding of the mechanisms underlying the development of autoimmunity is a fundamental target of basic and clinical research, not only for its scientific relevance, but also for its possible therapeutic applications: indeed, knowledge and control of the key points of the pathway which leads to autoimmune diseases could allow a really "etiological" treatment of such diseases, with significant progress also in the treatment of immunodeficiency syndromes and tumors.

Induction of autoimmunity is a complex and largely unknown process, which requires a precisely synchronized multi-step interaction of several predisposing and environmental factors. In such contest, it would be obviously rather simplistic to think of molecular mimicry as the only cause of all autoimmune diseases: indeed, infections are a trigger in a small number of cases, and possession of specific HLA haplotypes is not a sufficient explanation. However, research in this field is worth to be performed, because it could shed a new light on our understanding of autoimmunity: molecular mimicry certainly plays its role at the initial stages of the pathway(s) leading to autoimmunity, and could be at least one of the key elements/events which break the equilibrium of the immune system, somehow maintained by the organism until a given moment, and, interacting with genetic factors, transform predisposition into actual disease.

Bioinformatic tools can be particularly useful to promote, improve and accelerate research on molecular mimicry, particularly in disciplines like dermatology, where it has not yet been adequately studied: such tools can quickly and almost inexpensively identify molecules worth of further investigation with laboratory and clinical techniques, and, in a next future, could help to design therapeutic and/or preventive strategies aimed to the real causes of autoimmune diseases.

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P- Reviewers Katiyar SK, Kimyai-Asadi A, Negosanti L
S- Editor Qi Y **L- Editor** A **E- Editor** Liu XM

World Journal of Dermatology

Online Submissions: http://www.wjgnet.com/esps/
wjdermatol@wjgnet.com
doi:10.5314/wjd.v2.i4.44

World J Dermatol 2013 November 2; 2(4): 44-50
ISSN 2218-6190 (online)

MINIREVIEWS

Potential biomarkers for malignant melanoma

Ye-Nan Wang, Yuki Yamamoto, Fukumi Furukawa

Ye-Nan Wang, Yuki Yamamoto, Fukumi Furukawa, Department of Dermatology, Wakayama Medical University, Wakayama 641-0012, Japan

Author contributions: Wang YN wrote this manuscript and made the figure; Yamamoto Y contributed to the writing of this manuscript; Furukawa F critically revised this manuscript.

Correspondence to: Ye-Nan Wang, MD, Department of Dermatology, Wakayama Medical University, 811-1, Kimiidera, Wakayama City, Wakayama 641-0012, Japan. wangyenan1112@live.cn

Telephone: +81-73-4472300 Fax: +81-73-4481908

Received: July 7, 2013 Revised: August 14, 2013
Accepted: September 3, 2013
Published online: November 2, 2013

Abstract

Melanoma is one of the most aggressive cancers and its high metastatic potential has a large impact on the number of melanoma deaths. The pathological diagnosis is still the gold standard for melanoma and immunohistochemistry plays an important role in discriminating between melanomas. Recently, emerging molecular knowledge may lead to further identification of clinically relevant biomarkers, such as S100B, MIA, TA-90IC,5-S-CD, SPARC, CSPG4, HSP105, IMP3, KI-F2A, miR-221, YKL-40, some cancer stem cells (CD133, Nestin, CD166, CD20, CD271) and some monoclonal antibodies (KBA62, PNL2), for malignant melanoma detection, risk stratification and prediction/prognosis. However, all of the current main markers have some shortcomings. For example, all markers have limitations in sensitivity and specificity, even the first-line marker, S100 protein. So, sometimes, many of the classification criteria that have been proposed show considerable overlap, making it difficult to categorize cases reproducibly, based on histopathological criteria alone. Besides that, the increased expression of some proteins in melanomas suggests that there are abnormal proteins synthesized due to the genetic pathway. Therefore, we expect that there will be more instrumental breakthroughs in the abnormal gene field, especially with respect to gene mutation. Ultimately, novel melanoma biomarkers could be found and gradually become targeted treatment strategies for a poor prognosis in advanced melanoma in the near future.

Key words: Melanoma; Prognosis; Survival; Biological marker; Immunohistochemistry

Core tip: Melanoma is one of the most common cancers and its high metastatic potential has a large impact on the number of melanoma deaths. Emerging molecular knowledge may lead to further identification of clinically relevant biomarkers, such as S100B, MIA, TA-90IC, 5-S-CD, SPARC, CSPG4, HSP105, IMP3, KI-F2A, miR-221, YKL-40, some cancer stem cells (CD133, Nestin, CD166, CD20, CD271) and some monoclonal antibodies (KBA62, PNL2), for malignant melanoma detection, risk stratification and prediction/prognosis. However, all current markers have some shortcomings and thus we expect there will be more novel melanoma biomarkers discovered as supplementary diagnostic criteria in the near future.

Wang YN, Yamamoto Y, Furukawa F. Potential biomarkers for malignant melanoma. *World J Dermatol* 2013; 2(4): 44-50 Available from: URL: http://www.wjgnet.com/2218-6190/full/v2/i4/44.htm DOI: http://dx.doi.org/10.5314/wjd.v2.i4.44

INTRODUCTION

Melanoma is a malignancy characterized by a high potential to metastasize at a relatively small size of the primary tumor[1]. A nationwide survey of Japanese patients with malignant skin tumors from 1987 to 2001 showed that the most prevalent skin tumor was basal cell carcinoma, which increased year by year, followed by squamous cell carcinoma, and then malignant melanoma[2]. Furthermore, the number of patients with malignant

skin tumors has increased year by year. The prognosis of patients with advanced malignant melanoma remains extremely poor but that of patients in stage Ⅲ has shown some improvement[2].

A pathological diagnosis is still the gold standard for melanoma. Immunohistochemistry plays an important role in discriminating between melanomas, but all markers have limitations in sensitivity and specificity; even the first-line marker, S100 protein, is not expressed in all melanomas[3]. In the quest to reduce cancer mortality and morbidity, there is a continued effort to identify novel biomarkers to aid in the early detection and accurate prediction of tumor behavior[4]. The following discussion reviews some potentially novel and adjuvant biomarkers to help to diagnose melanoma.

S100B

The S100 proteins are a multi-gene calcium-binding family comprising of 20 known human members, each coded by a separate gene[4]. S100B is a homodimer of the S100b chain originally identified as "S100" by Moore *et al*[5] in 1965. Serum levels of S100B have been evaluated in patients with melanoma at different stages and have been shown to increase in a stage-dependent manner[6]. S100B expression levels are the highest in grade Ⅵ melanoma[6-8] and have been associated with the presence of metastases[9,10]. Increased expression levels of serum S100B also correlate with reduced survival[8,11], have been shown to reflect the tumor load, stage and prognosis[7,12-14], and are an independent prognostic factor for a poor outcome in melanoma[11].

This allows S100B to be used as a diagnostic marker and in the staging of malignant melanomas in a clinical setting. S100B has also proven to be a valuable marker in assessing a patient's response to treatment[15]. Decreased levels of S100B following treatment correlates with a good response to therapy and with increased survival[10].

MELANOMA INHIBITORY ACTIVITY

Melanoma inhibitory activity (MIA) is an 11 kDa protein secreted by malignant melanomas, is strongly expressed in melanoma cells but not in melanocytes, and is likely to represent a key molecule regulating melanoma progression[16]. Purified MIA causes a significant alteration of cell morphology as melanoma cells round up[17]. MIA protein is a clinically-valuable marker in patients with malignant melanomas as elevated values can diagnose metastatic melanoma stages Ⅲ and Ⅳ[18]. MIA expression *in vivo* correlates with progressive malignancy and is now widely-recognized as a novel serum marker for the malignant progression of metastasizing melanoma[19,20].

INSULIN-LIKE GROWTH FACTOR-Ⅱ MESSENGER RNA-BINDING PROTEIN-3

Recently, an immunohistochemical marker, insulin-like growth factor-Ⅱ messenger RNA (mRNA)-binding protein-3 (IMP3), has been reported to differentiate between melanomas and benign nevi[21]. IMP3, also known as K homology domain-containing protein overexpressed in cancer or L523S, promotes tumor cell proliferation by enhancing insulin-like growth factor-Ⅱ protein expression[22].

In the research from Pryor *et al*[21], fifty-six melanocytic neoplasms from 48 subjects were immunohistochemically studied using a monoclonal antibody against L523S/IMP-3. Their study demonstrated that IMP-3 is expressed in malignant melanomas but not in benign nevi, even when dysplastic features are present. Furthermore, IMP-3 is expressed in a significantly higher proportion of melanomas than Spitz nevi and IMP-3 is expressed in metastatic melanomas significantly more than in thin melanomas[21].

In conclusion, IMP-3 appears to be involved in the progression of malignant melanomas and may play an important role in the regulation of the biological behavior of these tumors. Additionally, IMP-3 may have diagnostic utility in distinguishing melanoma cells from benign nevic cells, dysplastic nevi and Spitz nevi[21].

KINESIN FAMILY MEMBER 20A

Kinesin family member 20A (KIF20A) belongs to a large family of proteins that share a conserved motor domain which binds to microtubules and couples ATP hydrolysis to generate mechanical force[23].

In research by Yamashita *et al*[24], KIF20A expression was detected in 59% of melanomas and 12% of nevi by immunohistochemistry, and 64% of melanomas and 60% of nevi by quantitative reverse transcript PCR. The primary melanomas that were immunopositive for KIF20A showed a significantly greater thickness than those that were immunonegative and patients with KIF20A+ melanomas tended to develop recurrence earlier. These results suggest that immunotherapy with KIF20A may be a novel treatment option for advanced melanoma[24].

KBA62, PNL2

KBA62 recognizes an unknown determinant expressed in melanoma cells[25] and is a monoclonal antibody raised to a melanoma cell line recognizing yet another unidentified epitope[26]. PNL2 monoclonal antibody was raised against the somatostatin receptor but was found to be nonreactive to the intended target protein[3].

In the study by Aung *et al*[3], KBA62 and PNL2 were sensitive markers for metastatic melanomas and were expressed in a great majority of cases (86% and 89%, respectively, for KBA62 and PNL2) by examining a large number of metastatic melanomas and other melanocytic neoplasms and their mimics. Moreover, KBA62 and PNL2 also recognized S100 protein-negative metastatic melanomas (KBA62, 4 out of 7 and PNL2, 6 out of 7), indicating that these new markers are useful diagnostic

complements for this rare subgroup (2% of all metastatic melanomas)[3].

HEAT SHOCK PROTEIN 105

Heat shock protein-105 (HSP105), identified by the serological identification of antigens by recombinant expression cloning (SEREX), is overexpressed in a variety of human cancers. The amino acid sequences and expression patterns of HSP105 are also very similar in humans and mice.

Miyazaki *et al*[27] found that HSP105 was highly immunogenic in mice and that HSP105 DNA vaccination induced antitumor immunity without causing autoimmunity. Therefore, HSP105 is an ideal tumor antigen that could be useful for immunotherapy or the prevention of various human tumors that overexpress HSP105, including colorectal cancer and melanoma. Whether HSP105 is an ideal target for immunotherapy in human cancers, which are at a high risk of melanoma, will continue to be investigated in their laboratory[27].

5-*S*-CYSTEINYLDOPA

5-*S*-cysteinyldopa (5-*S*-CD) has been used as a biochemical marker of melanoma progression. In one study by Wakamatsu *et al*[28], serum levels of 5-*S*-CD were assayed in 2648 samples taken from 218 patients in order to evaluate the usefulness of this parameter in following melanoma progression and prognosis.

5-*S*-CD levels were significantly elevated above the upper limit of the normal range (10 nmol/L) in stage Ⅳ melanoma patients. The sensitivity of the elevated serum 5-*S*-CD levels in detecting distant metastasis was 73%, whereas the specificity was 98% and the positive predictive value 94%. Patients without metastases had elevated 5-*S*-CD values in 5% of the 1480 serum samples. In 33% of the patients, an elevation in serum 5-*S*-CD levels preceded the clinical detection of visceral metastases and in 37%, an elevation of 5-*S*-CD levels occurred at the same time as visceral metastasis. Patients with elevated 5-*S*-CD levels before or after surgical treatment had significantly shorter survival times than those with normal levels[28].

These results show that the serum level of 5-*S*-CD is a sensitive and specific marker for predicting distant metastases. Elevated serum levels of 5-*S*-CD, before or after surgical treatment, are associated with a poor prognosis[28].

However, the serum levels of 5-*S*-CD, which is a common tumor marker for malignant melanoma, sometimes remain within the normal limit, especially in the early stages. Therefore, it is inadequate to use 5-*S*-CD for the early detection of malignant melanoma[29,30].

TA-90 IMMUNE COMPLEX

Urine tumor-associated antigen (U-TAA) is a high molecular-weight glycoprotein identified in the urine of patients with metastatic melanoma[31]. It comprises of multiple subunits, including an immunogenic 90-kD subunit designated TA-90[32]. TA-90 is expressed by 71% of melanoma cell lines and tumor biopsies and up to 70% of breast, colon and lung carcinomas and soft tissue sarcomas[33,34]. The study of Kelley *et al*[34] showed that an enzyme-linked immunosorbent assay for TA-90 in circulating immune complexes (TA90-IC) can detect subclinical metastasis before the surgical treatment of early-stage melanoma and thus they assayed the TA90-IC levels in the postoperative sera from patients with melanomas and evaluated their relationship to recurrence and survival.

SECRETED PROTEIN ACIDIC AND RICH IN CYSTEINE OR ITS COMBINATION WITH GLYPICAN-3

Secreted protein acidic and rich in cysteine (SPARC), also called osteonectin or BM-40, is a glycoprotein that modulates cellular interactions with the extracellular matrix during tissue remodeling[35]. SPARC was overexpressed in primary and metastatic melanomas and an overexpression of SPARC by melanoma cells was associated with an invasive phenotype *in vivo*[36,37].

Ikuta *et al*[30] recently identified glypican-3 (GPC3) as a novel tumor marker but it could only diagnose 40% of melanomas. Therefore, we focused our attention on SPARC overexpressed in melanomas as another candidate tumor marker. Secreted SPARC protein was quantified using ELISA in the sera from 109 melanoma patients, five patients with large congenital melanocytic nevus, 61 age-matched healthy donors and 13 disease-free patients after undergoing surgical removal. Surprisingly, 19 of the 36 patients showing increased SPARC levels were in stages 0 to Ⅱ. The serum SPARC levels decreased below the cutoff level in 10 out of 13 patients after surgical removal. Using SPARC plus GPC3 in combination enabled us to diagnose 47 out of 75 (66.2%) melanoma patients at an early stage (0-Ⅱ). Thus, SPARC or its combination with GPC3 is considered a potentially useful tumor marker, especially for melanoma at an early stage[30].

CHONDROITIN SULPHATE PROTEOGLYCAN 4

Chondroitin sulphate proteoglycan 4 (CSPG4) consists of a N-linked glycoprotein of 280 kDa and a proteoglycan component of about 450 kDa[38] and plays an important role in melanoma cell proliferation, migration and metastasis[39].

This transmembrane proteoglycan was originally identified as a highly immunogenic tumor antigen on the surface of melanoma cells and is associated with melanoma tumor formation and a poor prognosis in certain melanomas and several other tumor types. CSPG4 is essential to the growth of melanoma tumors through its

modulation of integrin function and enhanced growth factor receptor-regulated pathways, including the sustained activation of ERK 1, 2. CSPG4 expression has further been correlated to the resistance of melanomas against conventional chemotherapeutics[40].

YKL-40

YKL-40, a 40-kDa secreted glycoprotein, is produced by cancer cells and inflammatory cells and plays a role in inflammation, cell proliferation, differentiation, protection against apoptosis, the stimulation of angiogenesis and the regulation of extracellular tissue remodeling[41].

Elevated plasma YKL-40 levels are an independent prognostic biomarker of shortened survival. There is still insufficient evidence to support its value outside of clinical trials as a screening tool, prognosticator of survival, predictor of treatment response and as a monitoring tool in the routine management of individual patients with cancer or diseases characterized by inflammation. Large, prospective, longitudinal clinical cancer studies are needed to determine if plasma YKL-40 levels represent a new cancer biomarker or are mainly a biomarker of inflammation[42].

PROTEINS RELATED TO CANCER STEM CELLS

Cancer stem cells, derived from the clonal expansion of atypical cells, exist in a wide array of tumors and are becoming increasingly important to the understanding of the molecular mechanisms that regulate self-renewal, differentiation and progression of metastasis[43,44]. The identification of cancer stem cells can potentially help to refine the classification, diagnosis and treatment of cancers, including malignant melanomas[45]. Recently, cancer stem cell markers, which are also expressed on melanocytes, have been described[45].

CD133 (human prominin-1/AC133) is a transmembrane glycoprotein that is expressed on hematopoietic stem cells, endothelial progenitors and dermal-derived stem cells capable of differentiating into neural cells[46,47]. CD133 (Prominin-1) is considered the most important cancer stem cell associated marker identified thus far and its increased expression is observed in the cancer stem cell fraction of a large variety of human malignancies, including malignant melanoma[48].

Some studies by Al Dhaybi *et al*[49] have shown that CD133+ cancer stem cell expression in childhood malignant melanoma might correlate with lymph node metastasis and, in fact, some studies showed that all malignant melanoma patients who had associated metastases had a positive expression of CD133. Moreover, they found stronger CD133 expression in metastatic/or visceral metastases[49].

CD133 expression might be associated with an increased risk of metastasis and a worse outcome in childhood malignant melanoma. However, it is sometimes difficult to distinguish a Spitz nevus from a malignant melanoma and many investigators are searching for tools and techniques that may help enhance diagnostic accuracy[50]. CD133 expression might be a useful tool to suggest malignant behavior[49].

Nestin is an intermediate filament expressed in the cytoplasm of neuroepithelial stem cells[51,52]. Its expression has also been found in metastatic melanomas[53]. In Klein's[45] research, nestin expression was identified in 35/64 banal nevi, 44/63 primary melanomas and 69/80 metastatic melanomas and thus its expression seems to correlate with the high proliferative and migrational activity of these tumors[45].

Activated leukocyte adhesion molecule (CD166) is a member of the immunoglobulin super family and is a type 1 transmembrane protein. CD166 is expressed on the surface of mesenchymal stem cells and has been found on human melanoma cell lines[54]. In addition, its expression correlates with tumor thickness in primary melanomas[55].

In analogy with other groups, Fang *et al*[56] used *in vitro* sphere culture conditions to enrich for cells with stem cell features. Surprisingly, cells within the spheres expressed the B cell marker CD20 (also known as MS4A1). Extending their CD20 experiments into the clinical setting, they used rituximab (an anti-CD20 antibody) treatment in a group of nine patients with metastatic melanomas at clinical stage Ⅳ. After a treatment period of 2 years and a subsequent median follow-up time of 42 mo, two thirds of the patients included in this study were recurrence-free, without any signs of major side effects or toxicity[57].

The low-affinity neurotrophin receptor p75 (p75NTR, CD271) has recently been identified as a surface marker for tumor-initiating cells in melanomas[58,59]. As shown by Boiko *et al*[58], CD271 (p75NTR)-expressing melanoma cells had a higher tumor-initiation capacity than CD271-negative cells and, moreover, gave rise to metastases upon transplantation, unlike CD271-negative cells.

CIRCULATING MELANOMA CELLS

Circulating melanoma cells are thought to be valuable for improving prognostic measures in melanoma patients. Research by Freeman *et al*[60] demonstrated that a combination of markers should be targeted for the optimal isolation of circulating melanoma cells. In addition, there are significantly more circulating melanoma cells in metastatic patients compared with non-metastatic patients and therefore the quantification of circulating melanoma cells may prove to be a useful marker of disease progression[60].

MIR-221

Growing evidence has supported the use of micro-RNAs (miRNAs) expression profiles to clearly distinguish between normal and neoplastic tissues, thus leading to the

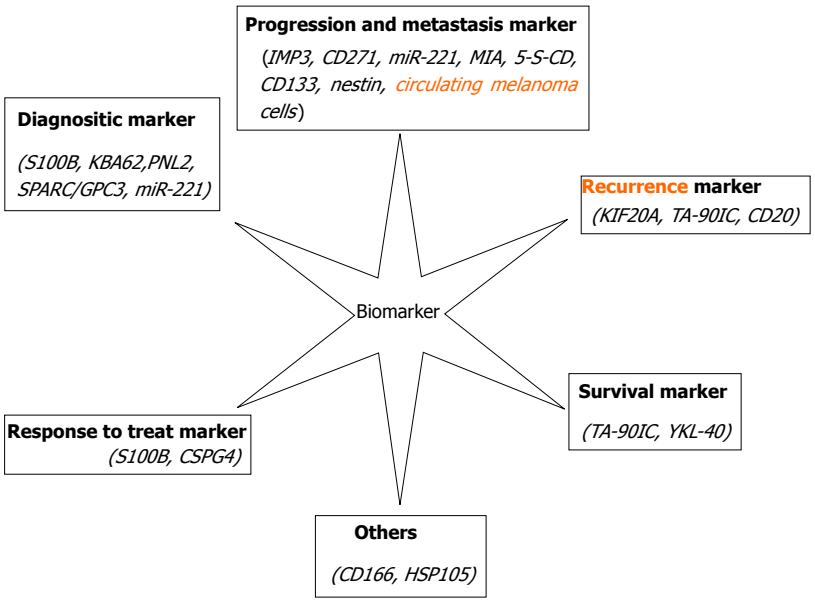

Figure 1 Many biological markers are related to different aspects (such as diagnosis, progression, increased risk of metastasis, recurrence, survival, response to treatment and even tumor thickness) of malignant melanomas.

identification of new diagnostic and/or prognostic markers[61].

For example, miR-221, encoded on the X chromosome, is one of these miRNAs[61] and microRNA-221 (miR-221) is known to be abnormally expressed in malignant melanoma cells. To evaluate the possibility that serum miR-221 levels can be a marker for malignant melanoma, serum samples were obtained by Kanemaru *et al*[61] from 94 malignant melanoma patients and 20 healthy controls. MicroRNAs were purified from the serum and the miR-221 levels were measured by quantitative real-time PCR. Malignant melanoma patients had significantly higher miR-221 levels than healthy controls. Among the malignant melanoma patients, the miR-221 levels were significantly increased in patients with stages I -IV malignant melanoma compared to those with malignant melanoma *in situ* and the levels were correlated with tumor thickness. Moreover, a longitudinal study revealed a tendency for the miR-221 levels to decrease after the surgical removal of the primary tumor and to increase again at recurrence. The serum levels of miR-221 were significantly increased and were correlated with the tumor thickness in malignant melanoma patients; thus, it may be useful not only for the diagnosis and prognosis of malignant melanomas, but also for differentiating in situ from stage I -IV malignant melanomas and for evaluating tumor progression and monitoring patients[61].

LOOKING FORWARD

In the end, the increased expression of some proteins in melanomas suggests that there are abnormal proteins synthesized due to the genetic pathway. Moreover, all of the current main markers have some shortcomings. Therefore, we expect that there will be more instrumental breakthroughs in the abnormal gene field, especially with respect to gene mutation. Ultimately, potential melanoma biomarkers (Figure 1) could be found and gradually become targeted treatment strategies for a poor prognosis in advanced melanoma.

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World Journal of Dermatology

Online Submissions: http://www.wjgnet.com/esps/
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World J Dermatol 2013 November 2; 2(4): I-V
ISSN 2218-6190 (online)

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World Journal of Dermatology

ISSN

ISSN 2218-6190 (online)

Launch date

June 2, 2012

Frequency
Quarterly

Editor-in-Chief
Santosh K Katiyar, PhD, Professor, Department of Dermatology, University of Alabama at Birmingham, Birmingham, AL 35294, United States

Editorial office
World Journal of Dermatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
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Hong Kong, China
Telephone: +852-6555-7188
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E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

Production center
Beijing Baishideng BioMed Scientific Co., Limited
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
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Instructions to authors
Full instructions are available online at http://www.wjgnet.com/2218-6190/g_info_20100723184812.htm.

Indexed and Abstracted in
Digital Object Identifier.

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