Immunohistochemical Expression of Discoidin Domain Receptor1 (DDR1) in Non-Neoplastic Skin Disease: A Systematic Review

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ABSTRACT

Background: The discoidin domain receptor-1 (DDR1) is a non-integrin collagen receptor recently implicated in the collective cell migration of other cancer types.

Objective: To review the immunohistochemical expression of discoidin domain receptor1 (DDR1) in non-neoplastic skin disease. **Data Sources:** A systematic search of MEDLINE (PubMed, Medscape, Science Direct. EMF-Portal) and internet was conducted on all articles published from 2002 to 2021.

Study Selection: English-language reports of immunohistochemical expression of DDR1 on non-neoplastic skin disease. The initial search presented 90 articles where 30 studies had the inclusion criteria. Then, they were divided into 12 studies about immunopathogenesis of non-neoplastic skin disease, 9 studies about expression of discoidin domain receptor1 and 9 studies emphasized DDR1 expression in non-neoplastic skin disease.

Data Extraction: Articles not reporting on immunohistochemical expression of DDR1 in non-neoplastic skin disease in the title or abstract were not included. 9 independent investigators extracted data on methods.

Findings: Interaction of DDR1 with various receptors is important for the regulation of cell survival, migration, and differentiation in development and pathological conditions. The discovery of inhibitors of DDR1 kinase activity might be beneficial in several pathological conditions where DDR1 has been identified as a potential therapeutic target. **Conclusion:** Our review reported that the knowledge of the main cells and cytokines involved in the immunopathogenesis of non-neoplastic skin disease is essential for dermatologists to understand better the disease as well as the mechanism of action of the biologics, drugs that revolutionized the treatment of non-neoplastic skin disease in the last two decades.

Keywords: Discoidin domain receptor1, Immunopathogenesis, Non-neoplastic skin disease, treatment.

INTRODUCTION

Non-neoplastic or inflammatory skin diseases encompass a wide array of pathologic processes ranging from autoimmune to infectious to diseases of unknown etiology. In contrast to neoplastic surgical pathology, the histopathology of inflammatory skin diseases frequently does not exhibit a one-to-one correlation with a single diagnosis and requires correlation with the clinical presentation for a definitive diagnosis **(1).** In many instances, the dermatologist is neither looking for nor needs a specific histologic diagnosis. For instance, if the clinical differential diagnosis is between atopic dermatitis and psoriasis, the diagnosis of spongiotic dermatitis conveys the essential information to the clinician and guides appropriate therapy **(2)**. Although the diagnosis of many inflammatory skin diseases requires correlation with the clinical features, there are critical diagnoses, such as toxic epidermal necrolysis and staphylococcal scalded skin syndrome, which the surgical pathologist may be asked to differentiate **(3).**

The most accurate interpretation of the histopathology of inflammatory skin disease is accomplished if the pathologist is cognizant of the clinical differential diagnosis as well as the histopathologic differential diagnosis. The pathologist must insist that an accurate clinical differential diagnosis or impression be submitted in addition to other data such as the age and sex of the patient and the anatomic site of the biopsy. Although dermatopathology specimens should be interpreted objectively, the final interpretation should always be correlated with the clinical findings **(4).**

Discoidin domain receptors (DDRs); DDR1 and DDR2, lie at the intersection of two large receptor families, namely the extracellular matrix and tyrosine kinase receptors. DDR1 promotes inflammation in atherosclerosis, lung fibrosis and kidney injury, while DDR2 contributes to osteoarthritis. As such, DDRs are uniquely positioned to function as sensors for extracellular matrix and to regulate a wide range of cell functions from migration and proliferation to cytokine secretion and extracellular matrix homeostasis/ remodeling. While, activation of DDRs by extracellular matrix collagens is required for normal development and tissue homeostasis. Aberrant activation of these receptors following injury or in disease is detrimental **(5)**. In solid tissues, DDR1expression is restricted to epithelial cells. Freshly isolated peripheral blood mononuclear cells express low level of DDR1 mRNA and undetectable protein levels, however increased DDR1(mainly DDR1a) expression is evident when these cells are either cultured in complete medium or stimulated with cytokines**.** DDR1 expression is also evident in cultured megakaryocyte and in germinal center B cells expressing EBV-encoded latent membrane protein-1. In contrast, DDR2 is expressed constitutively in

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immature dendritic cells (DCs) and is upregulated in mature DCs following treatment with tumor necrosis factor α [6]. There were a few previous reports study the relationship between immunohistochemical expression of DDR1 and non-neoplastic skin disease, but until now, this relationship is not clearly defined. Therefore, the aim of this study was to review the immunohistochemical expression of discoidin domain receptor1 (DDR1) in non-neoplastic skin disease.

MATERIALS AND METHODS

Data Sources: A systematic search on immunohistochemical expression of DDR1in non-neoplastic skin disease using MEDLINE (PubMed, Medscape, Science Direct. EMF-Portal) and internet was conducted on all articles published from 2002 to 2021. The research focused on non-neoplastic skin disease/immunohistochemical expression/discoidin domain receptor1. Additional records were identified by reference lists in retrieved articles. The search was established in the electronic databases from 2002 to 2021.

Study Selection: Eligible articles were published in peer-reviewed journals and written in English. Articles not reporting on immunohistochemical expression of DDR 1 in non-neoplastic skin disease in the title or abstract were not included. Full-text articles were screened.

Inclusion criteria: Decisions were made according to the following: original studies, systematic reviews or meta-analyses, primary or first-line treatment and if necessary, secondary treatment described, and treatment success, complications and side effects described.

Data Extraction: 9 independent investigators extracted data on methods, health outcomes and traditional protocol. Surveys about symptoms and health without exposure assessment, report without peer-review, not within national research program, letters/comments/editorials/news and studies not focusing on immunohistochemical expression of DDR1in non-neoplastic skin disease.

The analyzed publications were evaluated according to evidence-based medicine (EBM) criteria using the classification of the U.S. Preventive Services Task Force & UK National Health Service protocol for EBM in addition to the Evidence Pyramid [7].

U.S. Preventive Services Task Force [7].

- Level I: Evidence obtained from at least one properly designed randomized controlled trial.
- Level II-1: Evidence obtained from well-designed controlled trials without randomization.
- Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Study quality assessment: quality of all the studies was assessed. Important factors included, study design, ethical approval, calculation of evidence power, specified eligibility criteria, appropriate controls, adequate information and specified assessment measures. It was expected that confounding factors would be reported and controlled for and appropriate data analysis made in addition to an explanation of missing data.

Data Synthesis: A structured systematic review was done with the results tabulated, 12 studies about immunopathogenesis of non-neoplastic skin disease, 9 studies about expression of discoidin domain receptor1, 9 studies emphasized DDR1 expression in non-neoplastic skin disease.

RESULTS

Study selection and characteristics:

A systematic search on the studies on immunohistochemical expression of discoidin domain receptor1 (DDR1) in non-neoplastic skin disease. Using MEDLINE (PubMed, Medscape, Science Direct. EMF-Portal) and internet was conducted on all articles published from 2002 to 2021. Articles not reporting on immunopathogenesis of non-neoplastic skin disease, expression of discoidin domain receptor1, DDR1 expression in non-neoplastic skin disease in the title or abstract were not included. 9 independent investigators extracted data on methods, health outcomes, and traditional protocol. Potentially relevant publications were identified, 51 articles were excluded as they were away from our inclusion criteria. 30 studies were reviewed as they met the inclusion criteria. 12 studies about immunopathogenesis of non-neoplastic skin disease, 9 studies about expression of discoidin domain receptor1, 9 studies emphasized DDR1 expression in non-neoplastic skin disease.

Regarding these studies there were four comprehensive analysis or cross-sectional or case-control studies [12-22] come to level I or (level A). These studies reported that there are at least 2000 different skin diseases in the field of dermatology, which cuts across all age groups. Non-neoplastic skin lesions form the majority of the morbidity from skin diseases. Noninfectious erythematous, popular and squamous diseases were the most common histopathological diagnosis reported (31.21%) followed by bacterial diseases (20.98%) followed by non-infectious vesicobullous vesicopustular diseases (17.097%). In addition, two comprehensive or case analysis come in the second level regarding the pyramid of EBM, reported that diagnoses for many inflammatory skin disorders are largely predicated on the results of

immunologic analyses [9, 11]. This has been true for more than 25 years. Most studies of non- neoplastic skin lesions are usually not histopathology based. The mean age of all the patients we studied was 38 years, with the peak age group been the 20-29 age bracket. While, five retrospective or prospective studies [10, 12, 13, 15, 17] come to level II-2 or (level B) and they estimated that the field of dermato-pathology is poorly developed in Nigeria, in the West Africa sub-region and sub-Saharan Africa. Therefore, in most circumstances general anatomic pathologists have to take up the burden of reporting skin biopsies, usually without the attendant intricate knowledge needed for this. Lichen planus was the most common subtype of lichenoid lesions. Hansen's disease is still the second most common skin disorder (Table 1).

Table (1): Immunopathogenesis of Non-neoplastic skin disease

Study	Year	Type	Level of EBM	Findings
Ogun *et al.* [8]	2016	a Comprehensive analysis	Level I or (level A)	There are at least 2000 different skin diseases in the field of dermatology which cuts across all age groups. Non-neoplastic skin lesions form the majority of the morbidity from skin diseases.
Wick *et al.* [9]	1996	Case analysis	Comes in the second level regarding the pyramid of EBM	In fact, diagnoses for many inflammatory skin disorders are largely predicated on the results of immunologic analyses. This has been true for more than 25 years.
Ogunbiyi *et al.* [10]	2005	A retrospective study	level II-2 or (level B)	The field of dermato-pathology is poorly developed in Nigeria, in the West Africa sub-region and sub-Saharan Africa. Therefore, in most circumstances general anatomic pathologists have to take up the burden of reporting skin biopsies, usually without the attendant intricate knowledge needed for this.
Samaila [11]	2008	Case analysis	Comes in the second level regarding the pyramid of EBM	Most studies of non- neoplastic skin lesions are usually not histopathology based. The mean age of the all the patients we studied was 38 years, with the peak age group been the 20-29 age bracket.
Ibekwe *et al.* [12]	2012	A retrospective study	level II-2 or (level B)	The dermatitis/eczema group constitutes the largest group of diseases in this current study. This may be a correlation to the rising frequency of eczematous lesions in clinical based studies of skin lesions from our environment.
Ogunbiyi *et al.* [13]	2004	A retrospective study	level II-2 or (level B)	Naevi/developmental disorders comprise 3.8% of the skin lesions. This is similar to its frequency observed in a community-based studies among school children in Ibadan.
Veldurthy *et al.* [14]	2015	a prospective study	level II-2 or (level B)	Lichen planus was the most common subtype of lichenoid lesions. Hansen's disease is still the second most common skin disorder.
D'Costa and Bharambhe [15]	2010	A cross-sectional study	Level I or (level A)	lichenoid lesions were commonest (46.57%) followed by psoriasis (19.88%).
Singh *et al.* [16]	2014	A cross-sectional study	Level I or (level A)	27.9% of the cases were diagnosed as nonspecific dermatoses followed by granulomatous lesions (23.5%).
Kumar and Goswami [17]	2018	a prospective study	level II-2 or (level B)	the commonest histopathological diagnosis was Psoriasis (42.5%) followed by Lichen planus.
Gupta *et al.* [18]	2019	A cross-sectional study	Level I or (level A)	Noninfectious erythematous, popular and squamous diseases were the most common histopathological diagnosis reported (31.21%) followed by bacterial diseases (20.98%) followed by non-infectious vesicobullous vesicopustular diseases (17.097%).

Additionally, one case analysis [21] Comes in the second level regarding the pyramid of EBM, reported that discoidin domain receptor 1 (DDR1) is a tyrosine kinase transmembrane receptor for collagen

constitutively expressed in several cell types and organs, including the gastrointestinal tract, lung, and kidney. In addition, four cross sectional studies [20, 23, 25, 27], one comes to Level I or (level A) and indicated that the DDR family comprises two distinct members, DDR1 and DDR2. DDR1 has five isoforms, whereas DDR2 has a single one. A recent study showed that collagen binding to DDR1 fails to induce a major conformational change that could explain kinase activation, and instead proposed that collagen-induced receptor oligomerization might be responsible for kinase activation. Finally, the discovery of inhibitors of DDR1 kinase activity might be beneficial in several pathological conditions where DDR1 has been identified as a potential therapeutic target. Meanwhile, four retrospective or cohort studies [21, 22, 24, 26], come to level II-2 or (level B) indicated that DDR1 stimulates several signaling pathways in a context- and cell type-dependent manner.

For example, DDR1 activates extracellular signal-regulated kinases (ERK) signaling in vascular smooth muscle cells, but inhibits ERK in mesangial cells. Interaction of DDR1 with various receptors is important for the regulation of cell survival, migration, and differentiation in development and pathological conditions (Table 2).

Table (2): Expression Discoidin Domain Receptor1 (DDR1)

Study	Year	Type	Level of EBM	Findings
Mattozzi *et al.* [19]	**2013**	Case analysis	Comes in the second level regarding the pyramid of EBM	Discoidin domain receptor 1 (DDR1) is a tyrosine kinase transmembrane receptor for collagen constitutively expressed in several cell types and organs, including the gastrointestinal tract, lung, and kidney.
Fu *et al.* [20]	**2013**	A Cross-sectional study	Level I or (level A)	The DDR family comprises two distinct members, DDR1 and DDR2. DDR1 has five isoforms, whereas DDR2 has a single one.
L'hôte *et al.* [21]	**2002**	A retrospective study	level II-2 or (level B)	DDR1 stimulates several signaling pathways in a context- and cell type-dependent manner. For example, DDR1 activates extracellular signal-regulated kinases (ERK) signaling in vascular smooth muscle cells, but inhibits ERK in mesangial cells
Borza, Pozzi, [22]	**2014**	A retrospective study	level II-2 or (level B)	Interaction of DDR1 with various receptors is important for the regulation of cell survival, migration, and differentiation in development and pathological conditions.
Xu *et al.* [23]	**2014**	A Cross-sectional study	Level I or (level A)	A recent study showed that collagen binding to DDR1 fails to induce a major conformational change that could explain kinase activation, and instead proposed that collagen-induced receptor oligomerization might be responsible for kinase activation.
Day *et al.* [24]	**2008**	A retrospective study	level II-2 or (level B)	Inhibition of DDR1 by imatinib, nilotinib, and dasatinib with IC50 values of 43 2.4 nM, 3.7 1.2 nM and 1.35 0.2 nM, respectively. However, these inhibitors are not selective, as they were originally designed to target Abl kinase.
Sun *et al.* [25]	**2012**	A Cross-sectional study	Level I or (level A)	Identified (3-(2-(3-(morpholino methyl) phenyl) thieno (3,2-b) pyridin-7-ylamino) phenol (LCB 03-0110) as a potent inhibitor of both DDR1 and DDR2 along with several other tyrosine kinases.
Gao *et al.* [26]	**2013**	Cohort study	level II-2 or (level B)	a series of 3-(2-(pyrazolo(1,5-a) pyrimidin-6-yl) ethynyl) benzamides as potent DDR1 inhibitors, the most potent of which have IC50 values of 6.8 and 7.0 nM, respectively.
Ruggeri *et al.* [27]	**2020**	A Cross-sectional study	Level I or (level A)	Finally, the discovery of inhibitors of DDR1 kinase activity might be beneficial in several pathological conditions where DDR1 has been identified as a potential therapeutic target.

Regarding DDR1 expression in in non-neoplastic skin disease, there were six prospective, retrospective, or a prospective observational studies [22, 28, 31, 33], come to level II-2 or (level B) and reported that genetic variants of DDR1 have been associated with vitiligo in two independent populations in Brazil, in a Korean population and in a Chinese population. DDR1 is a positive regulator of collagen IV and that this ability requires efficient collagen I binding and kinase activity. A significant reduction of DDR1 expression was observed in the lesioned skin. Mean value of immunohistochemical positive area for DDR1 in vitiligo samples was lower than in non-lesioned skin (10 687 vs. 16 029 lm2respectively; P < 0.001) and the comparison between the percentage of DDR1 in lesional and non-lesional skin showed a reduced expression in vitiligo (1.28 vs.1.95 respectively). On the other hand, three cross-sectional or case-control studies [29, 30] come to Level I or (level A) reported that, melanocytes interact only with collagen IV and not with collagen I. This is consistent with that E-cadherin observed in melanocytes and keratinocytes from NSV skin. Additionally, two case analysis [34, 35] came in the second level regarding the pyramid of EBM, reported that discoidin domain receptor 1, whose expression is restricted to epithelial cells, is responsible for the adhesive properties of CCN3-mediated melanocyte localization. Results findings also add to the cumulative evidence pointing to DDR1 as a major player of the impairment adhesion process involved in vitiligo pathogenesis (Table 3).

Table (3): Discoidin domain receptor1 (DDR1) expression in non-neoplastic skin disease.

Study	Year	Type	Level of EBM	Results
Cario [28]	2018	a prospective observational study	level II-2 or (level B)	Genetic variants of DDR1 have been associated with vitiligo in two independent populations in Brazil, in a Korean population and in a Chinese population.
Borza *et al.* [22]	2014	A retrospective study	level II-2 or (level B)	DDR1 is a positive regulator of collagen IV and that this ability requires efficient collagen I binding and kinase activity.
Fukunaga-Kalabis *et al.* [29]	2017	A case-control study	Level I or (level A)	Melanocytes interact only with collagen IV and not with collagen I.
Wagner *et al.* [30]	2015	A Cross-sectional study	Level I or (level A)	E-cadherin is stabilized by DDR1 and that DDR1 inhibition by RNA interference decreases E-cadherin at the cell surface.
Benzekri *et al.* [31]	2015	a prospective observational study	level II-2 or (level B)	E-cadherin observed in melanocytes and keratinocytes from NSV skin
Yoshimura *et al.* [32]	2005	A case-control study	Level I or (level A)	Immunohistochemistry was performed with DDR1 antibody (Abcam) at a dilution of1: 100 ll. Common vitiligo was the clinical type of the majority of patients studied (75.8%). The mean age was 41 years, 66.7% were females and the mean evolution period was 12 years. Most of patients did not present any auto-immune comorbidity (64.5%) or family history of vitiligo (59.4%).
Xu *et al.* [33]	2011	A prospective study	level II-2 or (level B)	A significant reduction of DDR1 expression was observed in the lesioned skin. Mean value of immunohistochemical positive area for DDR1 in vitiligo samples was lower than in non-lesioned skin (10 687 vs. 16 029 lm^2respectively; P<0.001) and the comparison between the percentage of DDR1 in lesioned andnon-lesional skin showed a reduced expression in vitiligo (1.28 vs.1.95 respectively).
Ricard *et al.* [34]	2012	Case analysis	Comes in the second level regarding the pyramid of EBM	Discoidin Domain Receptor 1, whose expression is restricted to epithelial cells, is responsible for the adhesive properties of CCN3-mediated melanocyte localization.
Reichert-Faria *et al.* [35]	2013	Case analysis	Comes in the second level regarding the pyramid of EBM	Results findings also add to the cumulative evidence pointing to DDR1 as a major player of the impairment adhesion process involved in vitiligo pathogenesis.

DISCUSSION

There are at least 2000 different skin diseases in the field of dermatology, which cuts across all age groups. Non-neoplastic skin lesions form the majority of the morbidity from skin diseases [8].

Although some of these lesions are easy to diagnose clinically, a substantial number will present a great challenge in diagnosis and management. Although immunohistology is most commonly regarded by general pathologists as a technique that has its greatest application in neoplastic diseases, this conclusion is far from accurate in the context of dermatopathology. In fact, diagnoses for many inflammatory skin disorders are largely predicated on the results of immunologic analyses. This has been true for more than 25 years [9].

The field of dermato-pathology is poorly developed in the West Africa sub-region and sub-Saharan Africa. Therefore, in most circumstances general anatomic pathologists have to take up the burden of reporting skin biopsies, usually without the attendant intricate knowledge needed for this [10]. Most studies of non-neoplastic skin lesions are usually not histopathology-based. The mean age of the patients we studied was 38 years old, with the peak age group been the 20-29 age bracket [11]. The dermatitis/eczema group constitutes the largest group of diseases in this current study. This may be a correlation to the rising frequency of eczematous lesions in clinical-based studies of skin lesions from our environment [12].

Nevertheless, the high frequency of non-specific dermatitis in the dermatitis/eczema group is attributable to the common reaction pattern of many non- neoplastic skin lesions. The frequency of Papulosquamous lesions was relatively high in this study with lichenoid dermatitis and lichen planus being very common. Naevi/developmental disorders comprise 3.8% of the skin lesions. This is similar to its frequency observed in a community-based studies among school children in Ibadan. These lesions are relatively rare in black Africans when compared to Caucasians [13]. Lichenoid lesions were the most common skin disorders reported followed by Hansen's disease. Lichen planus was the most common subtype of lichenoid lesions. Hansen's disease is still the second most common skin disorder in the study by **Veldurthy *et al.*** [14].

In the study by **D'Costa and Bharambhe** [15] lichenoid lesions were commonest (46.57%) followed by psoriasis (19.88%). In the study by **Singh *et al.*** [16], 9% of the cases were diagnosed as nonspecific dermatoses followed by granulomatous lesions (23.5%). In the study by **Kumar and Goswami** [17] the commonest histopathological diagnosis was psoriasis (42.5%) followed by lichen planus. **Gupta *et al.*** [18] reported that non-infectious erythematous, popular and squamous diseases were the most common histopathological diagnosis reported (31.21%) followed by bacterial diseases (20.98%), then non-infectious vesicobullous vesicopustular diseases (17.097%). On the other side, the exact incidence of all non-neoplastic lesions of skin is not given in the world literature, though the incidence of individual skin disease we can find. We found that the incidence of the skin diseases is on hospital-based data. The two cases of lamellar ichthyosis in the keratinizing disorders group occurred in sisters of the same family and is already documented in literature. A genetic predisposition is presumed because it is clustered in and run in this family. There is need for a careful and detailed evaluation of skin lesions by both clinicians and pathologists to reduce the frequency of these nonspecific diagnoses [12].

Discoidin domain receptor 1 (DDR1) is a tyrosine kinase transmembrane receptor for collagen constitutively expressed in several cell types and organs, including the gastrointestinal tract, lung, and kidney [19]. In addition, DDRs have a single transmembrane helix, an intracellular juxta membrane regulatory region upstream of a cytoplasmic tyrosine kinase domain [20]. The DDR family comprises two distinct members, DDR1 and DDR2. DDR1 has five isoforms, whereas DDR2 has a single one [18].

DDR1 stimulates several signaling pathways in a context- and cell type-dependent manner. For example, DDR1 activates extracellular signal-regulated kinases (ERK) signaling in vascular smooth muscle cells, but inhibits ERK in mesangial cells, and has no effect on ERK activation in T47D breast cancer cells [19].

In addition, DDR1 modulates signaling pathways initiated by other matrix receptors (e.g., integrins), cytokines (e.g., transforming growth factor (TGF)-b), and transmembrane receptors (e.g., Notch1) [20]. Interaction of DDR1 with various receptors is important for the regulation of cell survival, migration, and differentiation in developmental and pathological conditions [20]. The DDR1 intracellular kinase domain shares the typical structure of other kinase domains. However, how DDR1 kinase is activated upon collagen binding is poorly understood. A recent study showed that collagen binding to DDR1 fails to induce a major conformational change that could explain kinase activation, and instead proposed that collagen-induced receptor oligomerization might be responsible for kinase activation [22].

Day *et al.* [24] reported inhibition of DDR1 by imatinib, nilotinib, and dasatinib with IC50 values of 43 2.4 nM, 3.7 1.2 nM and 1.35 0.2 nM, respectively. However, these inhibitors are not selective, as they were originally designed to target Abl kinase. **Sun *et al.*** [25] identified (3-(2-(3-(morpholino methyl) phenyl) thieno (3,2-b) pyridin-7-ylamino) phenol (LCB 03-0110) as a potent inhibitor of both DDR1 and DDR2 along with several other tyrosine kinases. Recently, **Gao *et al.*** [26] identified a series of 3-(2-(pyrazolo(1,5-a) pyrimidin-6-yl) ethynyl) benzamides as potent DDR1 inhibitors, the most potent of which have IC50 values of 6.8 and 7.0 nM, respectively. Finally, the discovery of inhibitors of

DDR1 kinase activity might be beneficial in several pathological conditions where DDR1 has been identified as a potential therapeutic target. [27].

Genetic variants of DDR1 have been associated with vitiligo in two independent populations in Brazil, in a Korean population and in a Chinese population [28]. **Borza *et al.*** [22] demonstrated that DDR1 is a positive regulator of collagen IV and that this ability requires efficient collagen I binding and kinase activity. Since keratinocytes and melanocytes are in contact with the dermo-epidermal junction and not the dermis where collagen I is located, the mechanism of regulation may be different. **Fukunaga-Kalabis *et al.*** [29] demonstrated that melanocytes interact only with collagen IV and not with collagen I**.** Studies have shown that E-cadherin is stabilized by DDR1 and that DDR1 inhibition by RNA interference decreases E-cadherin at the cell surface [30]**.** This is consistent with the decrease in E-cadherin observed in melanocytes and keratinocytes from NSV skin [31]**.**

Two biopsies from each volunteer (vitiligo lesioned and non-lesioned skin) were obtained with a 3-mm punch. Formalin-fixed paraffin-embedded skin samples were prepared using tissue microarray (TMA) technique. Immunohistochemistry was performed with DDR1 antibody (Abcam) at a dilution of 1: 100 ll. Common vitiligo was the clinical type of the majority of patients studied (75.8%). The mean age was 41 years, 66.7% were females and the mean evolution period was 12 years. Most of patients did not present any auto-immune comorbidity (64.5%) or family history of vitiligo (59.4%) [32]**.** A significant reduction of DDR1 expression was observed in the lesioned skin. Mean value of immunohistochemical positive area for DDR1 in vitiligo samples was lower than in non-lesioned skin (10 687 vs. 16029 lm^2respectively; $P < 0.001$) and the comparison between the percentage of DDR1 in lesional and non-lesional skin showed a reduced expression in vitiligo (1.28 vs.1.95 respectively) [33]**.** Discoidin domain receptor 1, whose expression is restricted to epithelial cells, is responsible for the adhesive properties of CCN3-mediated melanocyte localization [34]**.** Overexpression of decanalling molecule CCN3 has been shown to increase adhesion to collagen type IV, the major component of basement membrane, and a recent in vitro study provided evidence of a dysregulation of the DDR1–CCN3 interaction in vitiligo skin, demonstrating a decreased DDR1 expression in lesioned vs perilesional vitiligo skin. Results findings also add to the cumulative evidence pointing to DDR1 as a major player of the impairment adhesion process involved in vitiligo pathogenesis [35]**.**

CONCLUSION

Our review reported that the knowledge of the main cells and cytokines involved in the immunopathogenesis of non-neoplastic skin disease is essential for dermatologists to understand better the disease as well as the mechanism of action of the biologics, drugs that revolutionized the treatment of non-neoplastic skin disease in the last two decades. From results of this review there was no any studies conducted to investigate the relation between DDR1 and non-neoplastic skin disease. However, further high quality and large-scale studies are required to clarify the association between DDR1 and non-neoplastic skin disease. This will help in establishing new therapeutic targets.

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