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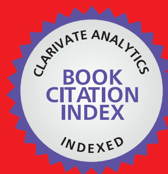

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Peptidylarginine Deiminases and Protein Deimination in Skin Physiopathology

Shibo Ying[1], Michel Simon[2], Guy Serre[2] and Hidenari Takahara[1]
[1]*Ibaraki University*
[2]*CNRS-University of Toulouse III*
[1]*Japan*
[2]*France*

1. Introduction

Post-translational modifications of proteins are crucial because they may alter the physical and chemical properties, folding, distribution, stability, activity, and consequently the functions of the targets, some of which being involved into diseases. Recently, one of these post-translational modifications, deimination (also called citrullination), became of an increasing concern. It corresponds to the conversion of protein-bound arginine residues to citrulline residues in the presence of calcium ions (Figure 1). This modification dramatically alters the charge of residues from positive to neutral, probably resulting for the targets in loss of conformation, in aggregation ability, or in depolymerization tendency. Peptidylarginine deiminases (PADs, EC 3.5.3.15) have been found as the enzymes that catalyze deimination (Rogers and Taylor, 1977; Sugawara et al., 1982; Takahara et al., 1983). These enzymes belong to the family of hydrolases, those acting on carbon-nitrogen bonds other than peptide bonds, specifically in linear amidines.

Protein deimination has been demonstrated to be implicated in several skin physiological and pathological processes in human. PADs have long been suspected to be responsible for protein citrullination in the epidermis, as well as in some skin appendages, and their biological roles to be important. Thereby, there is an increasing interest about PAD research in dermatology and biomedicine. However, the molecular mechanisms controlling their expression and activity in human skin are still not fully understood.

In this chapter, we review PAD gene family, the regulation of their expression in keratinocytes, their known skin substrates, their physiological roles in the epidermis and skin appendages, and their associations with skin diseases. It is anticipated that these investigations will provide novel therapeutic and prophylactic targets for future approaches to the treatment or prevention of severe psoriasis and other skin diseases.

Peptidylarginine deiminases (PAD) hydrolyze arginine residues within proteins to create the non-native amino acid citrulline (see Figure 1, next page). Calcium ion is essential for the enzyme activation. Enzymatic deimination abolishes positive charges of native protein molecules, inevitably causing significant alterations in their structures and functions.

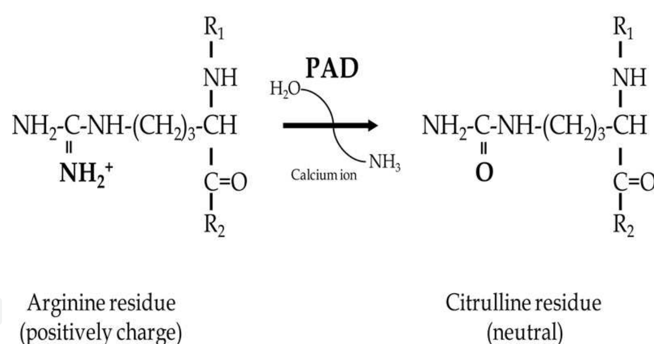

Fig. 1. Schematic representation of the deimination reaction catalyzed by a peptidylarginine deiminase.

2. Peptidylarginine deiminase family

Recently, vertebrate PADs were categorized into five isotypes, named PAD type I (PAD1), type II (PAD2), type III (PAD3), type IV (PAD4), and type VI (PAD6), based on their amino acid sequences, substrate specificities and tissue location (Chavanas et al., 2004; Méchin et al., 2005; Nachat et al., 2005a, 2005b). PAD4 has been previously designated as PAD5 (Vossenaar et al., 2003). Three isotypes are known in birds (*Gallus gallus*), whereas only one seems to exist in amphibians (*Xenopus laevis*) and fish (*Danio rerio*, *Takifugu rubripes, Tetraodon nigroviris,* and *Oncorhynchus mykiss*) (Vossenaar et al., 2003; Ying et al., 2009; Rebl et al., 2010). In mammals, all five isotypes of PADs have definitely been found in mouse (*Mus musculus*), rat (*Rattus norvegicus*) and human (*Homo sapiens*) (Terakawa, et al., 1991; Vossenaar et al., 2003). The five mammalian PADs are highly conserved at the amino acid sequence level with 59-71% of homology between human paralogs (45-55% identity). In addition, the genes (named *PADI*) encoding each mammalian PAD type are clustered on single chromosomal locus, and they display the same exon/intron structure and a high nucleotide sequence homology in exons.

In human, all *PADI* genes are located at a single cluster which spans an about 334.7 kb region on the short arm of Chromosome 1 near the telomere (1p36.1). Conservation has been demonstrated at the levels of nucleotide sequences and organization of the human and murine *PADI* gene loci (Chavanas et al., 2004; Balandraud et al. 2005). Human PADs are proteins of 74.1-77.7 kDa predicted molecular mass (663-694 amino acids) with a rather acidic pI (4.97-6.15). Human PAD1 is mainly found in the epidermis and hair follicles. This isotype is involved in the late stages of epidermal differentiation. In corneocytes, it deiminates filaggrin and keratin K1, which maintains hydration of the stratum corneum, and hence the epidermal barrier function. This enzyme may also play a role in hair follicle formation (Chavanas et al., 2006). Human PAD2 enzyme is the most widely expressed family member (Ishigami et al., 2002, 2005). In particular, PAD2 is the only one among PAD isotypes to be expressed at a high level in central nervous system. Myelin basic protein, glial fibrillary acidic protein and vimentin are its known substrates. PAD2 is thought to play a role in the onset and progression of neurodegenerative human disorders, including Alzheimer disease and multiple sclerosis, and it has also been implicated in glaucoma pathogenesis (Bhattacharya et al., 2006; Moscarello et al., 2007; Cafaro et al., 2010). Human PAD3 modulates hair follicle structural proteins, such as trichohyalin and S100A3 in the

inner root sheath (Rogers et al., 1997; Kanno et al., 2000; Kizawa et al., 2008). Together with the PAD1 enzyme, PAD3 may also play a role in terminal differentiation of the epidermis (Senshu et al., 1996; Méchin et al., 2007). Human PAD4 was first identified from the myeloid leukaemia cell line, HL-60 (Nakashima et al., 1999). It is normally found in the nucleus and in cytoplasmic granules of eosinophils and neutrophils. It has been reported to be involved in granulocyte and macrophage development leading to inflammation and the immune response (Wang et al., 2004). PAD4 is also expressed in rheumatoid arthritis synovial tissues (Vossenaar et al., 2003; Foulquier et al., 2007). Moreover, PAD4 is important for epigenetics, since the deimination of arginines and/or monomethylated arginines on histones 3 and 4 can act to antagonise arginine methylation (Kouzarides, 2007). Human PAD6, also known as ePad in mouse, was first identified in the year of 2004 (Chavanas et al., 2004). PAD6 mRNAs have been detected in ovary, testis, peripheral blood leucocytes, oocytes and early cleavage stage embryos (Chavanas et al., 2004; Esposito, et al., 2007; Yurttas, et al., 2008). However, the detail functions of PAD6/ePad are not well-known yet, even if it is essential for mouse fertility. Indeed, its absence induces an early zygote/embryo developmental defect (Esposito et al., 2007).

3. Expression of peptidylarginine deiminases in human skin

Although all *PADI* genes share significant identities at the level of their coding nucleotide sequences, the mechanisms responsible for their patterns of expression have been suspected to diverge. As described in section 2, each *PADI* gene has its own specific pattern of expression depending on the considered tissue, cell type or differentiation stage of the cells. Among the human PADs, only PAD1, PAD2 and PAD3 are expressed in the skin (Kanno et al., 2000; Ishigami et al., 2002; Guerrin et al., 2003). Here, we will sum up the actual findings on PAD expression in the human epidermis and skin appendages.

3.1 Peptidylarginine deiminases in the epidermis

Using RT-PCR experiments we have shown that only three PAD genes are expressed in human skin and epidermis at the mRNA level, namely the *PADI*1, 2 and 3 genes (Kanno et al., 2000; Ishigami et al., 2002; Guerrin et al., 2003). Messenger RNAs encoding PAD 4 and 6 are not detected in the normal tissue. Using anti-peptide antibodies specific for each isoform, we have confirmed this result at the protein level (Nachat et al., 2005a; Chavanas et al., 2006). Moreover, PAD1 is localized in the cytoplasm of keratinocytes throughout the whole human epidermis, with a higher expression in the granular layer, and in the corneocytes. PAD2 has been detected in the cytoplasm of the spinous keratinocytes and at the periphery of the granular ones, with a more intense staining of the latter. Anti-PAD3 antibodies have produced a punctate staining in the cytosol of the granular keratinocytes. PAD3 has also been observed in the matrix of the lower corneocytes, colocated with filaggrin, but could not be detected beyond the third or fourth corneocyte layer. Immunoelectron microscopy analyses have been used to specify the location at the ultrastructural level: PAD1 and PAD3 are located in the keratohyalin granules, together with profilaggrin, and in the fibrous matrix of the corneocytes together with filaggrin. PAD1 is also associated with the keratin intermediate filaments in the granular cells. Immunoblottings carried out on samples obtained from the superficial horny layer using adhesive tape stripping, confirmed that only PAD1 persists in the upper

corneocytes, where keratins K1 and K10 are deiminated. Based on their biochemical properties and location within the fibrous matrix of the lower corneocytes, we have proposed PAD1 and PAD3 as the isoforms responsible for the deimination of filaggrin (Méchin et al., 2005; Nachat et al., 2005a; Chavanas et al., 2006). Therefore, PAD1 and 3 may participate in, and possibly control, the production of the amino acid components of the Natural Moisturizing Factor (NMF). In the upper cornified layer, the NH_2- and COOH-termini of keratins K1 and K10 are deiminated by PAD1 since it is the only PAD isoform detected there. In agreement, PAD1 is less sensitive than the other isoforms to a pH of 5.2, closed to the acidic pH of the upper stratum corneum (Méchin et al., 2007). The effect of keratin deimination is not really known, but it is concomitant with and therefore could be involved in the modifications of the intracorneocyte fibrous matrix observed at the ultrastructural level. In addition, PAD1 and/or PAD3 could be involved in the deimination of filaggrin-2, a recently described protein of the S100-fused type protein family that may participate in the formation of the NMF (Hsu et al, 2011). The epidermal targets and the function of PAD2 in the epidermis have not been identified so far.

3.2 Peptidylarginine deiminases in skin appendages

We have also been able to localize PADs in human skin appendages using the same specific antibodies (Nachat et al., 2005b). PAD1 has been observed, together with PAD2, in the secretory and myoepithelial cells of the sweat glands, and in the arrector pili muscles (Nachat et al., 2005b; Urano, et al.; 1990). However, no deiminated proteins have been detected in these appendages. For the moment, the role of PADs in cells of sweat glands and arrector muscles is completely unknown. So far, no PADs have been detected in human sebaceous glands.

PADs have also been detected in hair follicles in the anagen stage. PAD1 is expressed in the cytoplasm of keratinocytes in the concentric epithelial sheaths forming the hair follicles: first (starting from the hair bulb) the cuticle of the inner root sheath, then the Huxley's layer of the inner root sheath and finally the companion layer between the inner and the outer root sheaths. PAD3 is present within the inner root sheath and the medulla of the hair follicles. PAD3 has been shown to be perfectly colocalized with trichohyalin, which is the first protein shown to be deiminated. Trichohyalin is a major structural protein of cells in the inner root sheath and in the medulla of the hair shaft. Moreover, *in vitro* deimination by PAD3 of this alpha-helix-rich insoluble protein makes it more soluble and renders it available for efficient cross-linking by transglutaminase 3 (Tarca et al., 1997; Kanno et al., 2000). This strongly suggests that *in vivo* deimination by PAD3 allows trichohyalin to be solubilized from cytoplasmic granules where it is aggregated and then to be associated with hair keratins and other cornified cell components through covalent cross-links carried out by transglutaminases. Interestingly, some of these hair keratins, namely the inner root sheath-specific type-I keratin 27 and its mouse ortholog, are also deiminated before being cross-linked (Steinert et al., 2003). Therefore, PAD3 plays a major role in the establishment of the mechanical resistance of cells in the hair follicles and particularly in the hair shaft. PAD3 is also colocalized with S100A3, a calcium-binding protein of the S100 protein family supposed to be involved in hair cell differentiation. *In vitro* deimination by PAD3 of S100A3 at the Arg-51 promotes the assembly of a homotetramer, and increases its affinity for calcium ions (Kizawa et al., 2008).

4. Regulation of peptidylarginine deiminase expression in keratinocytes

As the specific expression and distribution of PADs in human epidermis and skin appendages became clear, it appeared another question “how is the PAD gene expression controlled?” In fact, the *PADI* gene locus represents an interesting model to study the mechanisms which direct the spatial and temporal expression of genes in the epidermis. Indeed *PADI* gene expression is accurately regulated during the keratinocyte differentiation steps. PAD1 is detected throughout the epidermis with an increased expression in differentiated cells, PAD2 in the suprabasal layers, and PAD3 only in the terminally differentiated keratinocytes. Therefore PAD expression clearly depends upon the keratinocyte differentiation state. Until 2010, several original papers, shown in Figure 2 for a chronologic study, were published by our groups on *PADI* gene regulations at the transcriptional level.

These publications support the hypothesis of multiple DNA/transcription factor chromatin modules regulating PAD expression in normal human epidermal keratinocytes (NHEK), at the transcriptional level through a complex and original mechanism. The following sections will review what is known about the transcriptional regulation of *PADI*1-3 expression, remark the multiple regulatory modules, and highlight their significant features.

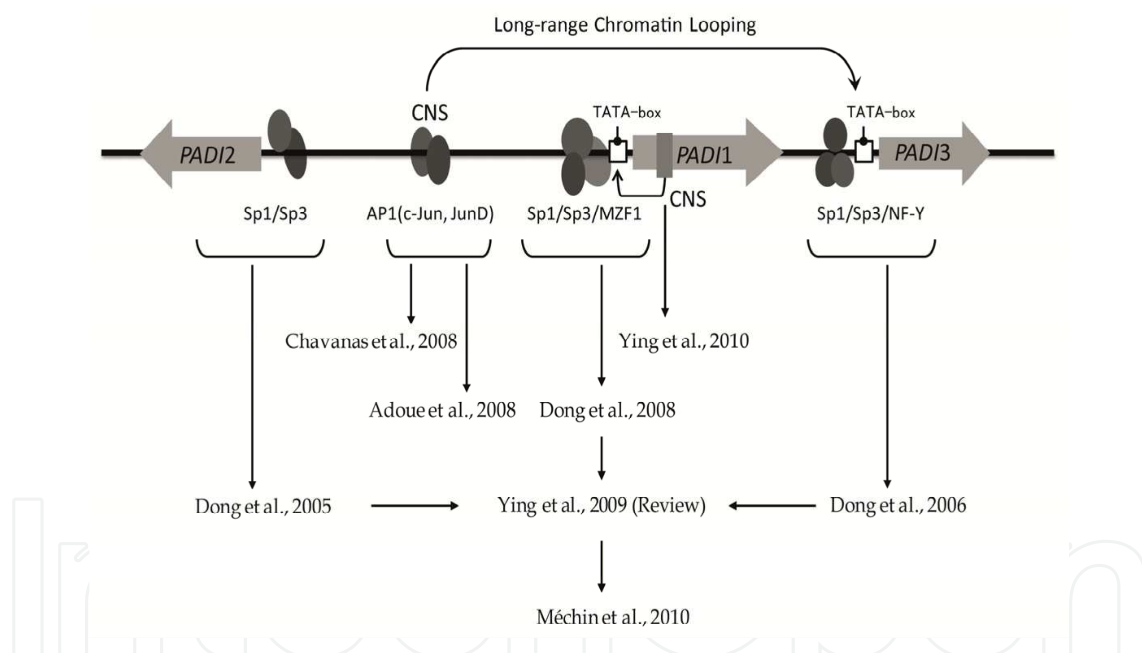

Fig. 2. History of transcriptional regulation of *PADI*1-3

Until 2010, the promoters of *PADI*1, 2 and 3, including the transcriptional factors and their binding sites, have been identified (Dong et al., 2005; Dong et al., 2006; Dong et al., 2008). Moreover, conserved non-coding sequences (CNSs) have been found in the *PADI* gene locus. They have been shown to contribute to long-distance transcriptional regulations of *PADI*1 and *PADI*3 promoters. One is an intronic enhancer located in the first intron of *PADI*1. Driven by NF-κB, it is able to enhance the *PADI*1 promoter activity (Ying et al., 2010). The other one located between *PADI*2 and *PADI*3 regulates *PADI*3 transcription by a long-range chromatin looping (86-kb) during keratinocyte differentiation (Chavanas et al., 2008; Adoue et al., 2008). See detail in the text. Note that the scale is not respected.

4.1 Basal regulation of proximal promoters

Proximal promoter elements are required for basal expression of all *PADI*1, 2 and 3 genes. The characterization of the *PADI*1-3 promoters has revealed several *cis*-elements for a number of distinct transcription factors. In the case of *PADI*1, chromatin immunoprecipitation (ChIP) assays have demonstrated that MZF1 and Sp1/Sp3 bind to its promoter region *in vivo*. Furthermore, either MZF1 or Sp1, but not Sp3, small interfering RNAs have effectively diminished the *PADI*1 expression in NHEK cultured in both low- and high-calcium containing medium (Dong et al., 2008). In addition, it also has been found that the expression of MZF1 and PAD1 increases synchronously during epidermal keratinocyte differentiation *in vivo*. Probably, MZF1 acts as an activator of the basic transcriptional activity, in response to the extracellular Ca^{2+} signaling cascades that lead to *PADI*1 expression during cell early differentiation (Dong et al., 2008). Although it lacks canonical TATA and CAAT boxes, the minimal promoter region of *PADI*2 contains some typical eukaryotic promoter elements, including four canonical GC boxes. Electrophoretic mobility-shift assays and super-shift analyses have demonstrated that both Sp1 and Sp3 actually bind to the GC boxes, and shown their marked involvement in the transcription regulation of *PADI*2. *PADI*3 proximal promoter has two CCAAT boxes, two GC boxes and a typical TATA box (Dong et al., 2005, 2006). Electrophoretic mobility-shift and ChIP assays have revealed that nuclear factor Y (NF-Y) present in keratinocyte nuclear extracts actually bind the two CCAAT boxes, while Sp1/Sp3 bind the two GC boxes both *in vitro* and *in vivo*. Either deletion or site-directed mutagenesis of one of the CCAAT or GC boxes dramatically decreases the promoter activity (Dong et al., 2006). Furthermore, Sp1 or NF-YA (one of the three subunits of NF-Y) small interfering RNAs effectively diminish *PADI*3 gene expression in NHEK cultured in both low- and high-calcium medium. Therefore, both Sp1 and NF-Y are necessary for the expression of *PADI*3.

In the transcriptional regulation of *PADI*1, 2 and 3 in NHEK, Sp1/Sp3 is a common basic transcriptional factor. Sp-family of ubiquitous transcription activators is known to regulate the constitutive expression of a considerable number of genes, and to take part in virtually all aspects of cellular functions, including proliferation, apoptosis and differentiation (Kaczynski et al., 2003). Our results suggest that the ratio of Sp1 and Sp3 factors bound to the promoter of *PADI* genes is responsible for the basal regulation of PAD1-3 in the upper keratinocyte layers of the epidermis (Ying et al., 2009).

4.2 Enhancer activity of conserved non-coding sequences

Eukaryotic gene transcription is controlled not only by promoters but also by intragenic *cis*-elements. More recently, a number of CNSs in vertebrate genomes have been shown to be transcriptional regulatory regions (Adams, 2005; Pennacchio, et al., 2006). Curiously, some highly conserved *cis*-regulatory regions are preferentially linked to developmental regulatory genes such as transcription factors and certain cell communication signals (Strähle & Rastegar, 2008). Regarding to *PADI* genes, nineteen CNSs are clustered in an 8-kb region between *PADI*1 and *PADI*2. Interestingly, this region shows remarkable sequence conservation between several species, further suggesting its functional relevance (Chavanas et al, 2004). Subsequently, this region has been shown to contain a calcium responsive enhancer called CNS2 or PIE (for PAD intergenic enhancer segment), which dramatically triggers the activity of the *PADI*3 gene promoter upon epidermal keratinocyte

differentiation, and links *PADI*3 expression to the AP-1 transcription factors c-Jun and JunD (Chavanas et al., 2008; Adoue et al., 2008). AP1 and Sp families have been suggested to play a central role in the regulation of epidermal gene expression during keratinocyte differentiation.

Moreover, except *PADI*6 gene, each of the human *PADI* genes contains a long first intron (10-23 kb), suggesting the first introns of these *PADI* genes are conserved during the speciation. In past, it has generally been assumed that the introns correspond to junk DNA without any function. More recently, however, this was disputed: more and more evidences revealed that introns are involved in transcriptional regulation and other functions (Eckert and Welter, 1996; Eckert et al., 1997). In particular, *in silico* analysis identified a conserved putative enhancer region within the first intron of *PADI*1. This region contains several consensus binding motifs for transcription factors, such as NF-κB, ELK1 and CREL. Furthermore, ChIP results provided powerful evidence that both p50 and p65 NF-κB subunits directly bind to a *cis*-element (named CNSi) identified within the first intron of the *PADI*1 gene, and are critical for the *in vivo* expression of this gene via transcriptional regulatory mechanisms (Ying et al., 2010).

4.3 Regulatory mechanism by an intra-chromatin loop

Of great interest, chromosome conformation capture (3C) technique recently testified that distant enhancers co-localize and thus that chromatin has necessary to form loops to put them in contact within the nucleus (Dekker et al., 2002, 2006). The 3C technique has confirmed that the enhancer CNS2 described above, is physically close to the *PADI*3 gene promoter, thanks to a chromatin loop formation. Indeed, as shown in Figure 2, the enhancer is located 86 kb away from the *PADI*3 promoter (Chavanas et al., 2008; Adoue et al., 2008). Afterwards, 3C has also provided conclusive evidence for a potential interaction between the intronic CNSi, including the NF-κB *cis*-element, and the *PADI*1 gene promoter by way of chromatin looping (Ying et al., 2010). Long-range *cis*-elements are recently known as important regulators of gene transcription, particularly for paralogous genes clustered on a unique chromosomal region (for examples, see Ying et al., 2010). Such a contact between chromatin regions in calcium-stimulated keratinocytes suggests that intra-chromatin loopings govern the specific expression of *PADI*1 and 3 genes in a dynamic and united mechanism. Since long-range enhancers have been identified in a variety of other chromosomal regions distant from their cognate promoters and shown to be functional in keratinocytes (Carter et al. 2002; Li et al., 2002; Fraser, 2006; Bartkuhn et al., 2008), such a gene regulation at a distance might be a key feature in keratinocytes. These intrachromosomal chromatin loops constitute an important element in the architecture of the nucleus and in the regulatory control of a number of genes.

4.4 Other modules

Calcium ion has long been suspected as a major regulator of *PADI* genes at the transcriptional level. Similarly to the increased detection of PAD1-3 in the epidermis in the course of differentiation (Ying et al., 2009), the expression of *PADI*1-3 mRNAs is enhanced about two fold in NHEK cultured in 1.2 mM calcium (differentiating conditions) as compared to 0.15 mM (proliferating conditions). Local calcium ion concentrations could also regulate the subcellular localization of PADs, and their activity (Ying et al., 2009). In

addition, high NHEK density increases PAD1 (threefold) and 3 (fivefold), but not PAD2, at the mRNA and protein levels, and up-regulates protein deimination (Méchin et al., 2010). By contrast, vitamin D increases PAD1–3 mRNA amounts, with distinct kinetics, but neither the corresponding enzymes nor the deimination rate (Méchin et al., 2010).

5. Peptidylarginine deiminases in skin physiology and diseases

As well-known, the skin provides a mechanical protection and is an important barrier for preventing the invasion of pathogens, the unintentional entrance of exogenous substances, and the uncontrolled loss of water and solutes (Madison, 2003). More and more evidence indicate that protein deimination and PADs are involved in several epidermal physiological and pathological processes. Thus, the identification of the targets of PADs is considered critical for advancing research on skin physiology and diseases.

5.1 Deimination and peptidylarginine deiminases in skin physiology

In human skin, all known substrates of PADs are cytoskeletal and cytoskeleton-associated proteins, crucial components for human skin homeostasis involved in forming rigid structures and keeping moisturizing of the horny layer. It has been found that filaggrin, filaggrin-2, keratin 1 (K1) and keratin 10 (K10) in the epidermis (Senshu et al., 1996; Kamata et al., 2009; Hsu et al, 2011), as well as trichohyalin and S100A3 in the hair follicles are the major deiminated proteins (Rogers et al., 1997; Tarcsa et al., 1996, 1997). The presence of deiminated proteins mainly in the stratum corneum suggests a function for deimination during cornification, the last steps of terminal differentiation of keratinocytes.

Deimination of filaggrin is a critical step in the production of a pool of amino acids necessary for the epidermal barrier functions (Kamata et al., 2009). Filaggrin is one of structural basic proteins found in abundance in the epidermis, and produced by the keratinocytes for organizing the keratin matrix. Filaggrin is synthesized by keratinocytes of the granular layer as a large precursor (400 kDa in human) called profilaggrin, an essential component of type F keratohyalin granules. During the granular keratinocyte to corneocyte transition, profilaggrin is proteolysed into filaggrin units. These histidine- and arginine-rich units associate with the keratin intermediate filaments facilitating their aggregation and the resulting formation of the intracorneocyte fibrous matrix. After its deimination in the stratum corneum, each filaggrin unit is thought to dissociate from the matrix and to be fully proteolysed to generate free amino acids of the NMF, a complex mixture of osmotic agents essential to maintain 10–15% water in the stratum corneum (Rawlings & Matts, 2005; Méchin et al., 2007; Kamata et al., 2009). The NMF is composed of glycerol, urea, lactate, ions and free amino acids (52%), of which two derivatives have been characterized: pyrrolidone carboxylic acid and trans-urocanic acid. The amino acid content of NMF are nearly all produced from the degradation of filaggrin, their relative proportion being closely related to the filaggrin composition (Méchin et al., 2007; Simon et al., 2008; Kamata et al., 2009). However, filaggrin-2 degradation is strongly suspected to participate to the NMF formation (Hsu et al., 2011). Deimination of both filaggrin and filaggrin-2 increases the rate of their degradation by calpain 1 ad bleomycin hydrolases (Kamata et al., 20009; Hsu et al., 2011). Recently, non-sense mutations of the filaggrin gene have been defined as very strong pre-disposing factors for atopic dermatitis (OMIM 603165) and causative factors of ichtyosis

vulgaris (OMIM 146700) (Irvine & McLean, 2006; Palmer et al., 2006; Smith et al., 2006; Nomura et al., 2007; Sandilands et al., 2007). We have demonstrated the capacity of purified recombinant PADs to deiminate human filaggrin *in vitro* with different calcium and pH sensitivities according to the isotype of the used enzymes. These differences could regulate filaggrin deimination *in vivo* as calcium- and pH-gradients are known to exist in the stratum corneum (Méchin et al., 2005, 2007). The exact role of keratin deimination is not well known. We can suspect an effect on the structure of the intracorneocyte filamentous matrix, or on their partial proteolysis in the upper part of the stratum corneum.

As mentioned in Section 3.2, trichohyalin is a structural protein of cells in the inner root sheath and in the medulla of the hair shaft. The deimination of trichohyalin catalyzed by PAD3 is crucial for the properties of trichohyalin, as well as for S100A3, another major protein of the hair follicles (Tarcsa et al., 1996, 1997; Steinert et al., 2003; Kizawa et al., 2008). Thereby, PAD3 is likely to play a major role in the establishment of the mechanical resistance of cells in the hair follicles and particularly in the hair shaft. However, the exact function of PAD1 and PAD2 in the hair follicles, including their targeted proteins, remains unknown.

5.2 Deimination and peptidylarginine deiminases in skin diseases

In recent years, more and more evidences suggested that the deimination and PADs are associated with skin diseases, especially with psoriasis. For example, decreased levels of keratin, in particular K1, deimination were observed in the epidermis of patients with bullous congenital ichthyosiform erythroderma (OMIM 113800) and psoriasis (OMIM 177900) (Ishida-Yamamoto, et al., 2000, 2002). Moreover, the PAD inhibitor paclitaxel, a well known molecule for cancer therapy, has been shown to improve severe psoriasis in a prospective phase II pilot study (Ehrlich et al., 2004). Furthermore, since vitamin D is beneficial in the treatment of psoriasis (Durakovic et al., 2004), it is tempting to speculate that the three PADs (PAD1, 2 and 3) expressed in the epidermis are possible therapeutic targets in the disease.

Interestingly, it is also thought that PADs might be involved in skin cancer. Indeed, PAD4 is abnormally expressed in some cutaneous cancers, as skin malignant melanoma (Chang et al., 2006, 2009). Especially, expression of PAD4 has been observed in some malignant tumors including skin carcinomas, with a concominant increased in deiminated keratins, and in extramammary Paget's disease (OMIM#167300) (Urano et al., 1990; Chang et al., 2006, 2009). PAD4 expression is not detected in the corresponding human normal tissues. In agreement with the hypothesis of a possible involvement of PADs in tumorigenesis, inhibition or depletion, in osteosarcoma U2OS cells, of PAD4, the isotype responsible for the deimination of histones and involved in gene-expression regulation, has recently been shown to result in cell cycle arrest and apoptosis (Li, et al., 2008). So, PAD4 is becoming a target for an epigenetic cancer therapy (Slack et al., 2011). As a new finding, differential expression of the *PADI*1 gene has been claimed as a hallmark of squamous cell carcinomas of the oral cavity and oropharynx (Chen et al., 2008).

6. Conclusion

Nowadays, PADs are more and more considered as important in cellular physiology and human diseases. Over-expression of PAD and accumulation of citrullinated proteins could

have a negative role. As we know, citrulline produced by PADs is a "non-natural" amino acid. Thereby, citrulline may stimulate the immune system and induce immune responses. More and more reports claim that citrullinated autoantigens are the possible cause of several autoimmune inflammatory diseases, including neurodegenerative disorders (multiple sclerosis and Alzheimer disease) and rheumatoid arthritis. Indeed, the current knowledge attests that multiple sclerosis is strongly linked to overcitrullination of the myelin basic protein (reviewed in Méchin et al., 2007). As another similar example, the patients with Alzheimer's disease have significantly elevated rate of citrullination (vimentin and glial fibrillary acidic protein) in their central nervous system, mainly in the hippocampus, which is the region of the brain mostly affected by the disease (Ishigami et al., 2005). Therefore PADs are now taken as potential drug targets.

Because of the description of their involvement in the late steps of keratinocyte terminal differentiation and the stratum corneum barrier functions, dermatologists are expected to take a great interest in these enzymes. In future, some approaches should provide new insight into *PADI* gene regulatory networks and discover the elaborate mechanisms of their signalling pathways upon cell dynamic state. More work is of great significance to definitively conclude on their contribution to skin diseases, especially in psoriasis and other inflammatory disorders.

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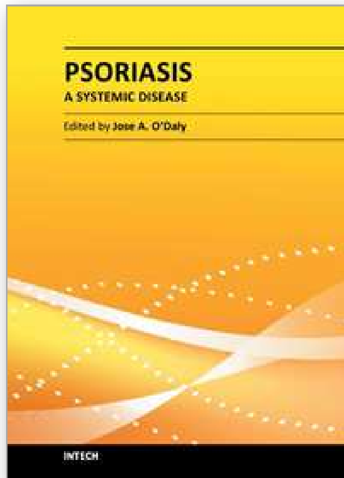

Psoriasis - A Systemic Disease

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The purpose of this book is to present a comprehensive analysis of Psoriasis, a disease that affects approximately 2-3% of humanity in all countries. Psoriasis existence is surveyed since the clay tablets of Assyrians and Babylonians 3.000-5.000 years ago, thru the middle ages, the renaissance, XIX and XX centuries.

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51000 Rijeka, Croatia
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Phone: +86-21-62489820
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