Pathogenesis of Psoriasis: Emerging Research

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THE EMERGING ROLE OF VITAMIN D IN DERMATOLOGY

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EVALUATION QUESTIONS
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This overview will explore the role of topical vitamin D in the skin, some of the cellular pathways by which it works, topical psoriasis therapy, and especially emerging research. The discussion will also focus in on corticosteroids, vitamin D analogs, and combinations of topical corticosteroids and vitamin D in the skin.

Pathogenesis of Psoriasis: Theory

I would like to focus on the pathogenesis of psoriasis. What we must remember is that this is a theory and a theory is always subject to change (Table 1).1 A number of years ago when I first finished my residency and fellowship in dermatology, psoriasis was thought of as a disease of the epidermis, or a hyperproliferative skin disease.1,2 Now it is considered an immune disorder.1,2

It is believed that abnormal activation of leukocytes leads to the accumulation of T cells and other immune cells in developing skin lesions.1,2 T cells secrete proinflammatory cytokines which cause keratinocyte hyperproliferation and altered differentiation.1,2 The turnover time of the epidermis speeds up significantly.1,2 Continued activation of these immune cells and keratinocytes sustains and leads to the characteristic psoriatic lesions that we’re used to seeing.1,2

Table 1.

Pathogenesis of Psoriasis: Theory

- Once thought to be a disease of the epidermis, now considered to be an immune disorder1,2
- It is believed that abnormal activation of leukocytes leads to accumulation of T cells and other immune cells in developing skin lesions1,2
- T cells secrete proinflammatory cytokines, which cause keratinocyte hyperproliferation and altered differentiation1,2
  - Turnover time of the epidermis speeds up from the normal 26 days to 4 days
- Continued activation of immune cells and keratinocytes sustains the psoriatic lesion1,2

Psoriatic Lesion Formation

Figure 1 is a cartoon that was in a recent review article, which I co-authored.1 It illustrates the role of T cells in the skin, what we thought was their key role in the initiation, and the sustaining of the inflammatory response in psoriasis leading to a hyperproliferative state in the characteristic lesions that we’re used to seeing in our patients with chronic psoriasis.1,2

Psoriasis Topical Treatment

Topical corticosteroids are certainly widely used and are very effective.3,4 Vitamin D analogs are used alone or in combination with topical steroids.3 Vitamin A analogs are used alone or in combination with topical steroids or other vitamin D drugs.3,4

Unfortunately, topical corticosteroids do lead to irritation which some people find objectionable and patient compliance is more reduced than with other agents.3

Figure 1.

Psoriatic Lesion Formation1,2

Table 1.

Pathogenesis of Psoriasis: Theory

Now when we look very specifically at topical steroids, they certainly have been and still are the basis of topical psoriatic treatment.\(^4\)

Reasons for this are that they are effective, work rapidly, quickly reduce erythema, scaling, and plaque elevation, come in a variety of vehicles and several potencies.\(^4,5\) Though there are risks involved with the treatment, such as, skin thinning, atrophy, telangiectasia, contact dermatitis, adrenal suppression, bruising, and increased risk of infection, all limit their long-term, chronic use.\(^4,6\)

And all these suggest that altered function occurs well before visible changes in the cutaneous morphology of the skin.\(^6\)

**Vitamin D in the Skin**

The keratinocytes are very important as we all know for barrier function (Table 2).\(^7,8\) Keratinocyte differentiation is tightly controlled.\(^7\) The active metabolite of vitamin D, 1,25(OH)\(_2\)D\(_3\), or calcitriol, helps regulate differentiation through a sequence of turning on and off of genes as the keratinocytes journey from the stratum basale to the stratum corneum where they function and have some role in permeability and barrier functions in the skin.\(^1,2\)

In summary, vitamin D and/or its receptor has many functions: stimulation of cell differentiation, inhibition of overproliferation of cells, and regulation of the hair follicle cycle.\(^7\) There seems to be an effect, at least in the literature, of suppression of tumor formation. More recently, emerging research has also suggested that vitamin D may have a role in the regulation of innate immunity.\(^7,9\)

The regulation of cathelicidins\(^7\) and defensins via the antimicrobial pathway has come into the literature recently when we look at diseases such as rosacea when there is an abnormality in the cathelicidin pathways.\(^9\) Again, this is something we must keep our eyes on.

*Table 2. Vitamin D in the Skin*

- Keratinocytes are the most important cells in the skin for its barrier function.\(^1,2\)
  - “It keeps what we need inside, and keeps what we don’t need outside.”\(^4\)
- Keratinocyte differentiation is tightly controlled\(^2\)
  - The active metabolite of vitamin D (1,25(OH)\(_2\)D\(_3\)) helps to regulate differentiation through a sequential turning on and off of genes as the keratinocytes journey from the stratum basale outwards to the stratum corneum, where they form the permeability barrier.\(^1,2\)

*References*


*Pathogenesis of Psoriasis: Cathelicidins*

More recently, the pathogenesis of psoriasis has gotten more complicated. We have learned a lot about antimicrobial peptides and specifically cathelicidins.

Cathelicidins, especially LL-37, are part of a protective family of antimicrobial peptides produced in the skin, in keratinocytes.\(^8\) They have direct antimicrobial and antifungal activity.\(^9\) They also initiate host response or alarmin activities with an inflammatory response.\(^9\) Higher amounts are found in injured and infected skin.\(^9\)

In psoriasis very specifically, vitamin D\(_3\) appears to block the cathelicidin pathways, seems to break the cycle, reduces inflammation, and reverses some of the changes that we have known to cause psoriatic lesions.\(^5,10\) Vitamin D directly targets cathelicidin genes via the vitamin D receptor pathways and also the vitamin D response genes.\(^10\)

We can see in Figure 2 that LL-37, or cathelicidin, combines with the overproliferation of DNA that occurs with injury, but in psoriasis with the overproliferation of the epidermal component.\(^11\)

This in turn stimulates plasmatic dendritic cells which are activated and stimulate the response of T cells and their inflammatory mediator which leads to the characteristic psoriatic skin lesions, the thickening due to the continued, enhanced response.\(^11\)

*Figure 2.*

And again this appears to be a circular pathway which repeats itself.11 So again, I think that the cathelicidin story is just one piece of this. Perhaps it’s not the only piece. There certainly is a lot more to be learned in psoriasis. 

Expression of Antimicrobial Peptides: Treatment With Vitamin D Analogs

In Figure 3, the first diagram shows the abnormally high levels of cathelicidins, defensins, and other inflammatory factors in the skin.12 The right diagram shows what happens when topical vitamin D and topical vitamin D analogs are used. We see a remarkable decrease in the defensins and other inflammatory mediators.12

While cathelicidins are not decreased, the active form, LL-37, is decreased.12 There’s something with vitamin D that decreases the active component and also the other defensins that are a part of this antimicrobial peptide system.12 Vitamin D appears to have a role in this antimicrobial peptide system that regulates the skin.

Summary

What does this mean to dermatology? Specifically in psoriasis, psoriatic lesions have increased antimicrobial peptide levels and increased inflammatory markers.11 Vitamin D$_3$ locally inhibits inflammatory markers and may induce regulatory T cells, leading to decreased inflammation and local clinical improvement.8,10,12

Topical vitamin D$_3$ inhibits keratinocyte proliferation, induces differentiation7,8—again a unique characteristic of the vitamin D family—and reduces inflammation5 with the benefit of mild side-effect profile6,13 and clinical use as monotherapy or in combination with other agents such as topical steroids or vitamin A derivatives.3,4

As you can see, vitamin D plays an important role in medicine, dermatology, and specifically in psoriasis.

Figure 3.
EVALUATION QUESTIONS

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