

Hypothesis

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Posted Date: 13 January 2026

doi: 10.20944/preprints202601.0911.v1

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Hypothesis

Psoriasis Up Close: A Metabolic Border-Zone Model of Disease Pathogenesis and Treatment

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Abstract

Psoriasis is traditionally defined and treated as a chronic inflammatory immune-mediated disease. In this manuscript, we propose an alternative, integrative model in which psoriasis is primarily a disorder of surface and border tissues driven by disturbed cellular metabolism, with inflammation representing a secondary phenomenon. Psoriasis predominantly manifests in anatomical border zones, such as skin folds, hairlines, nail beds, and joint surfaces, where cells depend critically on diffusion- and osmosis-based metabolic processes. These vulnerable regions are highly sensitive to alterations in microcirculation, oxygen delivery, nutrient availability, and blood composition. We argue that a range of comorbidities and risk factors, including thyroid dysfunction, obesity, hyperhomocysteinemia, smoking, nutritional deficiencies (notably vitamin D and zinc), stress-related vasospasm, and dietary imbalances, may impair mitochondrial aerobic metabolism in these border cells. This metabolic disruption promotes a shift from aerobic respiration to anaerobic glycolysis, leading to the accumulation of mitochondrial waste products and crystalline debris, particularly in confined tissue spaces such as joints. We hypothesize that this metabolic debris acts as the primary trigger for the characteristic inflammatory response observed in psoriasis. The dual metabolic and clinical efficacy of fumarates provides key support for this model, as these agents both restore mitochondrial metabolic balance and alleviate psoriatic inflammation. This observation suggests that inflammation is a downstream consequence of metabolic failure rather than the initiating cause of disease. Based on this framework, we propose that therapeutic strategies should prioritize correction of metabolic dysfunction and associated comorbidities, after which inflammatory manifestations are expected to diminish. Such an approach may not only improve cutaneous and articular symptoms but also reduce psychological burden and social stigma associated with psoriasis.

Keywords: psoriasis; psoriatic arthritis; metabolic processes; fumarates; mitochondrial

Notes on the manifestations and physiology of psoriasis: psoriasis up close

Psoriasis Before Inflammation Flares up: Comorbidity, Risk Factors, and Prevention

Psoriasis can be seen as a disorder of surfaces and border areas.

Psoriasis is primarily a condition affecting the surface of the body as a whole, the skin, in all its concave and convex forms, and a condition affecting the surfaces of the bones, namely in the joint cavities [1]. Moreover, as the outer covering of the body, the skin is the organ with the largest surface area [2 square meters in adults, weighing 15 kg], and is also the organ that, as a porous excretory organ, processes waste products from metabolism.

Psoriasis mainly occurs in skin folds, at the hairline, on tight areas (even at the transition to tendons), but also on soft areas of the skin; furthermore, on the nail bed; and on the mucous membrane of the joints.

All in all, psoriasis manifests itself beyond the capillary bed, in the outermost border cells, i.e. those cells that are entirely dependent on processes such as diffusion and osmosis for their metabolism.

These processes are vulnerable and can be disrupted by abnormalities in the speed of blood flow, in the structure of the blood vessels down to their very last branches, in the bedding of this flow area itself—due to unusual pressure or injury—and in the composition of the blood.

These processes can then have an epigenetic influence on the development of psoriasis, in addition to genetic predisposition [2,3].

The blood supply can be limited by a slow thyroid gland (myxoedema)[4], pressure from fat around the vessels (in cases of obesity), tissue defects in the vessel wall (in cases of high homocysteine levels [5], whether hereditary or acquired as a result of malabsorption in the intestine), or vasospasm due to tension (stress, anxiety), and this supply may also be deficient in composition due to a lack of oxygen (in the case of smoking), a lack of nutrients such as vitamin D [6] and zinc [7], but also due to an excess of certain substances such as alcohol and arachidonic acid (omega-6 fatty acid) [8].

All these possible irregularities therefore constitute risks or risk factors for psoriasis, especially if they arise from other diseases, also known as comorbidities.

This shows how, in the extensive bed of border cells, irregularities can arise in vulnerable areas in the logistics and transport of essential oxygen and nutrients, disrupting the very machinery or motor of the mitochondrial citric acid cycle; and how this disruption then can lead to a shift from aerobic to anaerobic glycolysis and thus to the formation of mitochondrial debris, including pyruvic acid/pyruvate maturing into crystals in affected areas or cavities and thus leading to swollen joints (hydrops).

Inflammation Itself as the Second Phase of Psoriasis

In our opinion, it is this debris or waste material that triggers the typical inflammation that clinically characterizes psoriasis in all its diversity, with an associated characteristic profile of inflammatory cells and proteins (immunoglobulins) [9].

Fumarates as the Unmasking of the Nature of Psoriasis

Fumarates now appear to play a unique role—if only in understanding this transition from mitochondrial metabolism to inflammation [10]. Fumarates work in two ways. They counteract the shift from aerobic to anaerobic glycolysis in the citric acid cycle, and are also effective against psoriasis as such. This dual property of fumarates offers insight into the significance of a lack of oxygen in the citric acid cycle for the development of psoriasis in the affected border cells. Fumarates thus reveal that the primary cause of psoriasis lies in a disturbed metabolism, and that the inflammatory symptoms are a secondary consequence of this, both clinically and immunologically.

Sequence of Treatment for Psoriasis

The primary treatment of psoriasis should therefore focus on the metabolic origin of the condition, as well as on the aforementioned risk factors and comorbidities; the secondary inflammation will then gradually subside and disappear.

Side Effects of This Treatment Sequence

Finally, this fundamental treatment will not only resolve the inflammatory symptoms of psoriasis, but also any psychological damage and social stigma.

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