Research Article

Zebrafish as a Model for Understanding Psoriasis Pathogenesis and Exploring Therapeutic Approaches: A Narrative Review

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Abstract

Psoriasis (Ps) is a chronic autoimmune disorder causing rapid skin cell proliferation, leading to itchy, scaly patches. Commonly found on the scalp, elbows, knees, and lower back, its exact cause remains unclear, but genetics and environmental factors play a role. comorbidities like psoriatic arthritis, cardiovascular issues, and psychological conditions are associated with psoriasis. Triggers include factors like genetic predisposition, stress, BMI, infections, and various medications. While no permanent cure exists, treatments like topical medications, light therapy, and systemic drugs help manage symptoms. Studying psoriasis has been challenging due to the lack of suitable animal models. However, researchers are now using zebrafish as a valuable tool in biomedical research. Transparent and affordable to breed, zebrafish allow scientists to observe cell and tissue growth in real-time. They have been utilized to study various human diseases, including psoriasis. Scientists have identified zebrafish with psoriasis-like symptoms and are investigating the genetic and environmental factors involved. These zebrafish models hold promise for testing new treatments and identifying drug targets. Although still in early stages, using zebrafish as a model organism for psoriasis research has the potential to significantly advance our understanding and development of treatments.

Keywords: Psoriasis, Zebrafish, Model system, Pathogenesis, Genetic, Proliferations, Dermal Cells.

1. Introduction

1.1 Psoriasis: A Global Burden

Psoriasis is an autoimmune skin illness that is persistent and affects a significant number of individuals all over the globe. It is characterized by the rapid buildup of skin cells, leading to thick, red, and scaly patches on the skin's surface. Psoriasis is not contagious, but it can significantly impact a person's physical and emotional well-being. The global burden of psoriasis is substantial, and it has been recognized as a significant public health problem[1]. This Psoriasis symptoms are classified as visible and invisible. Here are some key points regarding the global impact of psoriasis: Psoriasis is a skin condition that affects around 2% to 4% of the world's population, which amounts to around 125 million people worldwide.

Psoriasis imposes a significant financial burden that it places on people, healthcare institutions, and the community as a whole. The visible nature of the condition can lead to social stigma, discrimination, and a negative body image. Psoriasis is associated with comorbidities like psoriatic arthritis, cardiovascular issues, and psychological conditions, necessitating a comprehensive care approach (Antony Raharja, 2021). There have been ongoing efforts to raise awareness about psoriasis and improve the understanding of the condition among healthcare professionals, policymakers, and the general public. While there is currently no cure for psoriasis, several treatment options are available to manage the symptoms and control disease progression.

1.2 Current Challenges in Psoriasis Research

Psoriasis research has made significant progress in understanding the underlying mechanisms of the disease and developing effective treatments[2]. However, several challenges persist in the field. Here are some of the current challenges in psoriasis research:

Disease Heterogeneity: Psoriasis is a complex and heterogeneous disease, presenting with varying clinical manifestations and disease courses[3].

Genetic and Environmental Interactions: Psoriasis has a strong genetic component, but it is also influenced by environmental factors[4]. Chronic nature of the disease, associated comorbidities, and the need to consider factors like genetic predisposition, stress, BMI, infections, and various medications that can trigger or exacerbate psoriasis. (Alin Codrut Nicolescu, 2022)

Biomarker Identification: Identifying and validating biomarkers that accurately reflect disease severity, predict treatment response, and indicate potential comorbidities would greatly enhance patient management and therapeutic advancements[5].

Comorbidities and Systemic Impact: Psoriasis is classified as multisystem chronic inflammatory disease (Noori Kim, 2010). Psoriasis is associated with an enlarged risk of developing various comorbidities, containing psoriatic arthritis, cardiovascular disease, metabolic syndrome, and mental health disorders[6].

Long-Term Safety and Efficacy: While several treatment options for psoriasis exist, long-term safety and efficacy data are still needed, particularly for newer therapies such as biologics and targeted therapies[7].

Addressing these challenges requires continued research collaboration, funding, and engagement across multiple disciplines, including dermatology, immunology, genetics, and epidemiology. Advances in technology, such as genomics, proteomics, and bioinformatics, are expected to contribute significantly to unraveling the complexities of psoriasis and developing targeted therapies in the future.

1.3 Psoriasis Pathogenesis: Insights from Human Studies

Psoriasis is a chronic autoimmune skin disorder considered by the development of thick, red, and scaly patches on the skin's surface. Understanding the pathogenesis, or the underlying mechanisms that drive the enlargement and evolution of psoriasis, is crucial for developing effective treatments and improving patient care[8].

In recent years, extensive research has provided valuable insights into the pathogenesis of psoriasis, with a focus on human studies. By using Single Nucleotide polymorphism markers, Susceptibility genes of psoriasis are identified which gives a description about psoriasis heritability (Akira OKA, 2012) . These studies have elucidated the dysregulation of the immune system, genetic predisposition, abnormal epidermal proliferation, angiogenesis, microbiome dysbiosis, and the influence of psychological and environmental factors[9].

Genetic studies have identified susceptibility genes associated with psoriasis, shedding light on the dysregulated pathways involved. Additionally, abnormal proliferation and differences of keratinocytes in the skin, angiogenesis, dysbiosis of the skin microbiome, and the impact of psychological and environmental factors have been explored in human studies[10]. Here are some key findings from human studies:

1.4 Immune Dysregulation

Psoriasis is considered an autoimmune disease characterized by aberrant immune responses. Human studies have established the involvement of various immune cells and cytokines in psoriasis pathogenesis[11]. Psoriasis is a immune-mediated and inflammatory disease that is triggered and maintained by the dysregulation of the immune system. (Campanati, 2021)

In the case of psoriasis, the immune system specifically attacks the skin, leading to the characteristic symptoms and lesions associated with the condition[13].Several immune cells and molecules are involved in the immune dysregulation seen in psoriasis. Here are some key aspects of immune dysregulation in psoriasis:

i. **T Cells:** T cells, lymphocytes, which are a kind of WBC, perform an important part in the immune response in psoriasis. Th17 cells produce a pro-inflammatory cytokine called interleukin-17 (IL-17), which contributes to the inflammation and skin cell proliferation seen in psoriatic lesions[14].

ii. **Dendritic Cells:** Dendritic cells are antigen-presenting cells that help initiate and regulate immune responses. In psoriasis, dendritic cells in the skin become activated and mature, leading to the presentation of self-antigens to T cells[15].

iii. **Cytokines:** Cytokines are small proteins secreted by immune cells that regulate immune responses. In psoriasis, there is an overproduction of pro-inflammatory cytokines. These cytokines promote inflammation, immune cell recruitment, and abnormal skin cell growth[16]. Pro-inflammatory cytokines, such as IL-17 and IL-22, are generated by epidermal CCR6

T cells in a mouse model of psoriasiform dermatitis as a result of the interaction between these components. (Andreas Orsmond, 2021)

iv. **Keratinocytes:** Pro-inflammatory cytokines released by immune cells stimulate keratinocytes, leading to excessive proliferation, abnormal differentiation, and the characteristic thickening of the skin in psoriatic lesions[17]. Immune cells, particularly Th17 cells, activate keratinocytes through cytokines like IL-17, leading to their abnormal differentiation and proliferation. (Kamata, 2023)

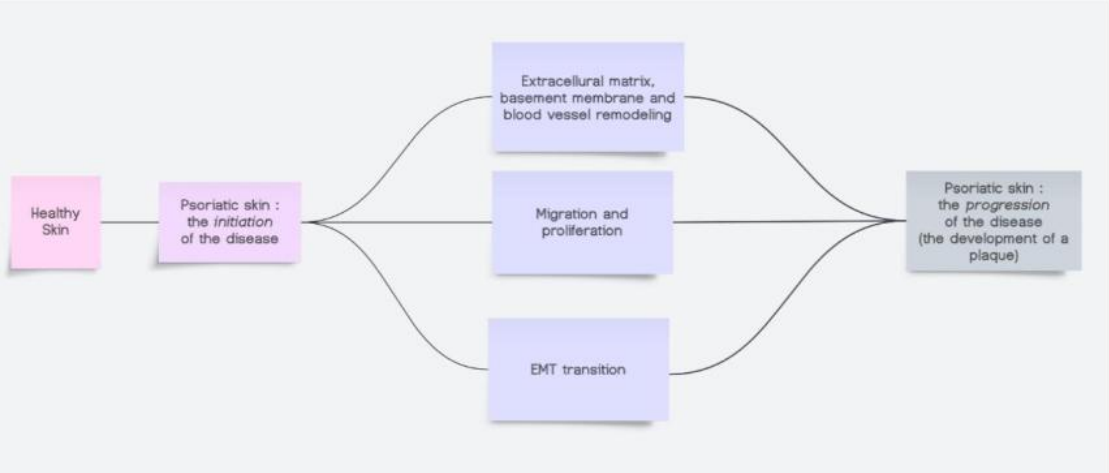

Figure 2. The progression of psoriasis (Kamata, 2023) (self)

a. **Immune Cell Infiltration:** Psoriatic lesions are characterized by immune cell infiltration, including neutrophils, T cells, dendritic cells, and macrophage

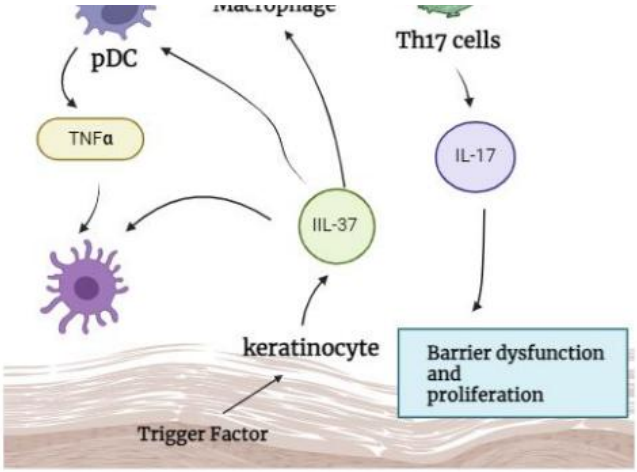

Figure 3. The pathogenesis of psoriasis (Rendon, 2019)

1.5 Genetic Factors

Genetic studies have identified several susceptibility genes associated with psoriasis. Variants in genes involved in immune regulation, skin barrier function, and epidermal differentiation have been implicated[19].The Genetic variants linked with Psoriasis are associated with different biological processes. This includes different immune activities like antigen presentation, inflammation and keratinocyte biology. (Rendon, 2019)

Epidermal Hyperproliferation: Human studies have revealed the abnormal proliferation and difference of keratinocytes in psoriasis. Dysregulation of key signaling pathways, such as the Wnt/β-catenin and Notch pathways, has been implicated in epidermal hyperproliferation[20].

Angiogenesis: Psoriatic lesions are characterized by increased blood vessel formation (angiogenesis). Studies have shown the upregulation of angiogenic factors, together with vascular endothelial growth factor (VEGF),angiopoietins and pro-angiogenic cytokines such as tumor necrosis factor (TNF), interleukin (IL)-8 etc.., in psoriasis[21].

Microbiome Dysbiosis: Alterations in the skin microbiome have been observed in psoriasis patients. Human studies have identified differences in the composition of the skin microbiota between psoriatic and healthy skin[22].

Psychological and Environmental Factors: Human education has highlighted the impression of psychological and conservation factors on psoriasis. Stress, smoking, obesity, and certain medications can exacerbate psoriasis symptoms and influence disease severity[23].

2. Zebrafish as a Model Organism

Zebrafish (*Danio rerio*) is a small, tropical freshwater fish that has gained significant popularity as a model organism in scientific research[24]. With around 70% of their genes having human orthologs. Zebrafish and humans have a significant degree of genetic similarities. Zebrafish embryos develop externally and undergo rapid and transparent development. This allows for easy observation and manipulation of embryonic development and organogenesis[25].

2.1 The Benefits of the Zebrafish Model

The zebrafish (*Danio rerio*) model organism offers several advantages for scientific research across different disciplines[26]. Here are some key benefits of using zebrafish as a model: Zebrafish share a significant portion of their genome with humans. Many genes associated with human diseases have counterparts in zebrafish, making them highly relevant for studying genetic and molecular mechanisms underlying diseases and developmental processes. Due to their transparency, zebrafish embryos enable scholars to directly watch the growth of organs, tissues, and physiological processes in real-time. Zebrafish embryos develop rapidly, with a complete embryonic development cycle taking only 24 to 72 hours. Zebrafish embryos develop externally, outside the mother's body. This external development makes it easier to manipulate and observe embryos, facilitating experimental interventions, genetic modifications, and high-throughput screening approaches. Genome of zebrafish has been completely sequenced and a high degree of homology with the human genome (Adams, 2018). Zebrafish are small in size, making it possible to house a large number of individuals in relatively small laboratory spaces.

2.2 Recapitulation of Psoriasis Features in Zebrafish

Zebrafish are a popular model organism for studying psoriasis because they share many of the same genetic and molecular pathways as humans. Sgk1 is a component of transcription that functions in the regulation of keratinocyte differentiation. In zebrafish with a mutation in the sgk1 gene, there is an increased proliferation of keratinocytes and the formation of psoriatic-like lesions. These lesions are characterized by thickened skin, increased inflammation, and the production of scales[27]. Similarly, zebrafish model is used for studying the role of tyrosine-protein kinase KIT in promoting the initial stages of psoriasis. By understanding the role of tyrosine-protein kinase KIT in zebrafish is crucial which help in development of treatment for psoriasis. (Webb, 2008)

The recapitulated psoriasis features in zebrafish have provided valuable perceptions into the pathogenesis of psoriasis in humans. These insights have led to the expansion of new and more operative treatments for psoriasis[27].

2.2.1 Immune Dysregulation in Zebrafish

Zebrafish possess a well-developed immune system that shares significant similarities with the human immune system, making them a valuable model organism for studying immune dysregulation and related disorders[28]. Zebrafish have fully developed and functional cells like T-cells, B-cells, macrophages, neutrophils, eosinophils and mast cells. (Martins, 2019)

Innate Immunity: Zebrafish possess innate immune responses that are similar to those of mammals. They have several different kinds of innate immune cells, which includes macrophages, neutrophils, natural killer cells, and dendritic cells[29].

Adaptive Immunity: Zebrafish also possess an adaptive immune system, characterized by the presence of T and B lymphocytes. The development and function of these lymphocytes can be studied in zebrafish, providing insights into the dysregulation of adaptive immune responses[30].

Inflammatory Responses: Zebrafish exhibit robust inflammatory responses similar to those observed in mammals.

Inflammation can be encouraged in zebrafish by various stimuli[31].Zebrafish's inflammatory response promotes regeneration in contrast to mammals, underscoring the special function that inflammation plays in tissue repair in zebrafish. (Iribarne, 2021)

Autoimmune-like Disorders: Zebrafish models have been developed to mimic autoimmune-like conditions observed in humans. By manipulating specific genes involved in immune regulation, researchers have induced autoimmune-like responses in zebrafish, leading to immune-mediated tissue damage and inflammation[32].

Host-Pathogen Interactions: Zebrafish can be infected with various pathogens, including bacteria, viruses, and fungi. By studying the host-pathogen interactions in zebrafish, researchers can gain insights into the dysregulation of immune responses during infections[33].

High-Throughput Screening: Zebrafish offer the advantage of high-throughput screening for immune dysregulation studies. Using zebrafish embryos or larvae, researchers can perform large-scale screens to identify genes, compounds, or environmental factors that modulate immune responses or induce immune dysregulation[34].

2.2.2 Hyperproliferation of Keratinocytes in Zebrafish

Hyperproliferation of keratinocytes, which is a hallmark feature of psoriasis, can be recapitulated in zebrafish models. By manipulating specific genes or introducing specific triggers, researchers have been able to induce excessive proliferation of zebrafish keratinocytes, leading to the thickening of the skin resembling psoriatic lesions[35]. The keratinocytes and ionocytes that make up the epidermis of fish skin carry ions and acid-base equivalents to keep bodily fluids ionic and acid-base balanced. Ionocyte progenitors in zebrafish embryos are specified from p63 + epidermal stem cells through a patterning process involving DeltaC (Dlc)-Notch-mediated lateral inhibition, which selects scattered dlc + cells into the ionocyte progenitor fate (Chen, 2019).

Genetic Manipulation: Researchers can genetically modify zebrafish to alter the expression or function of genes involved in keratinocyte proliferation. By overexpressing certain genes or knocking down others, they can induce dysregulated proliferation of keratinocytes[36].

Chemical or Environmental Triggers: Zebrafish can be exposed to certain chemicals or environmental triggers to induce hyperproliferation of keratinocytes[37]. The salinity, osmoregulatory demands, and pH of the aquatic environment can trigger hyperproliferation of keratinocytes of zebrafish by modulating through Klf4-mediated mechanisms in the ionocyte progenitor population. (Hatzold, 2016)

Wounding and Regeneration: Zebrafish possess a remarkable regenerative capacity, including the ability to regenerate damaged skin. By creating wounds or injuries to the zebrafish skin, researchers can observe the regenerative response, which involves keratinocyte proliferation and tissue repair[38].

2.2.3 Angiogenesis in Zebrafish

The procedure of new blood vessel creation is referred to as angiogenesis. It is an essential step in a wide variety of biological processes, such as the formation of an embryo, the healing of wounds, and the growth of cancer. Zebrafish are a prevalent model organism for studying angiogenesis because they are transparent embryos that allow for easy visualization of blood vessels[39]. Tryptanthrin, an active component of Indigo Naturalis, a traditional Chinese medication used to treat psoriasis, was discovered to be able to effectively suppress tumor angiogenesis Given that the development of abnormal blood vessels in psoriasis causes and sustains inflammation, which is a factor that induces angiogenesis, this implies that tryptanthrin may also have an impact on anti-tumor angiogenesis in psoriasis. (Lin, 2023)

Zebrafish studies have also shown that angiogenesis is a dynamic process. This means that the development of different blood vessels is not a one-time event, but rather a continuous process that is constantly being adjusted in response to changes in the environment[40].

2.2.4 Modeling Genetic and Environmental Factors in Zebrafish

Zebrafish provide a valuable platform for modeling genetic and environmental factors to study their effects on various biological processes and disease conditions[41].

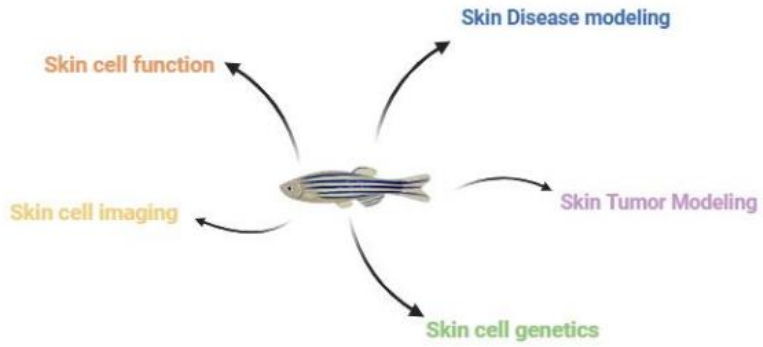

Figure 4. The Zebrafish model in dermatology (Russo I. S., 2022)

3. Therapeutic Applications of Zebrafish in Psoriasis Research.

Zebrafish have emerged as a promising model organism for studying psoriasis and exploring potential therapeutic interventions[42]. Here are some therapeutic applications of zebrafish in psoriasis research:

3.1 Drug Discovery and Screening

Zebrafish can be utilized for high-throughput drug discovery and screening assays. Researchers can test libraries of compounds or small molecules in zebrafish models of psoriasis to identify potential therapeutic agents[43].Drugs like amodiaquine, dihydrochloride and clonidine hydrochloride showed anti-inflammatory activity in zebrafish model (Xie, 2021)

3.2 Target Validation

Zebrafish models allow for the validation of probable therapeutic targets in psoriasis. Researcher used knockout zebrafish with IL1RL2 mutations to validate IL-36 as a viable psoriasis target. The role of IL-36 cytokines in pathogenesis of psoriasis by contributing to activation of neutrophils and Th17 cells in psoriatic skin (Mahil, 2017) .By manipulating the expression of specific genes involved in psoriasis pathogenesis, researchers can assess the effects on disease-related phenotypes[44].

3.3 Personalized Therapies

Zebrafish models can contribute to the development of personalized treatment approaches for psoriasis. By using patient-derived cells or genome editing techniques, zebrafish can be tailored to carry specific genetic variations associated with psoriasis[45]. Analyzing the genetic and transcriptomic profiles of zebrafish in response to drugs like dimethyl fumarate and apremilast can help identify biomarkers and predict individual patient responses. (Antonatos, 2023)

4. Translational Significance of Zebrafish Findings

The translational significance of zebrafish findings is the extent to which the results of zebrafish research can be applied to human health and disease. Zebrafish are a common organism for biomedical research since they are small, transparent, and have a relatively short lifespan[46]. In many cases, the findings from zebrafish research have led to the development of new drugs and treatments for these diseases[47].The translational significance of zebrafish findings in psoriasis research lies in their potential to inform and advance our understanding of the disease[48].

4.1 Comparative Analysis of Human Psoriasis with zebrafish model

Psoriasis is a persistent autoimmune condition that leads to an increase in the rate at which skin cells develop. It is distinguished by the color red, scaly patches of skin that can appear anywhere on the body. Zebrafish have been used to study psoriasis because they share many of the same genetic and molecular pathways as humans[49].

4.2 Advancing Precision Medicine Strategies

A method of providing medical treatment known as "precision medicine" takes into account individual differences in factors such as heredity, the environment, and lifestyle choices. for the purpose of optimizing disease prevention and treatment [50].

5. Adavantage of using zebrafish model in psoriasis research

The model organism like zebrafish shares unique comparative similarities and advantages with other model organisms for psoriasis research.

5.1 Genetic and Molecular Similarity

Zebrafish share a high level of genetic similarity with humans, making them valuable for studying genetic alterations and molecular mechanisms of psoriasis. This genetic resemblance is crucial for modeling human genetic disorders effectively. (Russo I. S., 2022)

5.2 Inflammatory Pathways and Immune Response

Zebrafish exhibit similar inflammatory pathways and immune cell types involved in psoriasis, providing a robust platform to assess immune pathology and potential therapeutic strategies This similarity in immune response aids in studying the immunological aspects of psoriasis. (Martínez-Navarro, 2019)

5.3 Disease Modeling Capabilities

Zebrafish models, including mutant, morphant, and environmentally inducible models, have been developed to mimic key features of human psoriasis, such as hyperproliferation of keratinocytes and inflammation. These models allow for the investigation of disease mechanisms and the evaluation of treatment modalities. (Arjmand, 2023)

5.4 Skin Biology and Development

Zebrafish models offer insights into skin biology, including epidermal development and cell cycle regulation in keratinocytes, providing a platform to study skin disorders like psoriasis. The zebrafish integument structure shares similarities with human skin, enhancing its relevance for dermatological research. (Webb, 2008)

6. Future Directions

Future directions in psoriasis research and precision medicine face several problems that need to be solved in order for us to make further progress in both the diagnosis and treatment of the condition and treatment of disease. Limitations like anatomical differences, complexity in pathogenesis of psoriasis and translational challenges has to be rectified in future research which will make zebrafish an efficient model for psoriasis research.

7. Conclusions

In conclusion, the zebrafish model has emerged as a valuable tool for investigating the pathogenesis of psoriasis. Its genetic similarity to humans, rapid development, optical transparency, and regenerative abilities makes it an excellent model organism for studying various aspects of psoriasis, including immune dysregulation, hyperproliferation of keratinocytes, angiogenesis. By synthesizing the available knowledge on psoriasis pathogenesis and the contributions of the zebrafish model, this evaluation article attempts to provide a complete and insightful resource for scientists and medical professionals that are interested in advancing our understanding of this complex skin disorder. The zebrafish models unique attributes, combined with its ability to recapitulate key aspects of psoriasis, hold significant potential for the detection of novel therapeutic targets and the progress of more effective treatments for patients affected by psoriasis.

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- **Conflict of Interest Statement**

The authors declare that there is no conflict of interest.

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