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Psoriasis and Stem Cells

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1. Introduction

Psoriasis is a chronic inflammatory skin disorder characterized by hyper-proliferation of basal keratinocytes, thickened and scaly epidermis, and recruitment of inflammatory cells to the skin. It affects approximately 2% of the world's population. The disease follows a pathogenic pathway involving various immunocytes and immune molecules. Activated T cells have been shown to trigger a chain of cellular and molecular reactions leading to the formation of psoriatic lesions. Fusion proteins that can block T cell activation or the function of anergized T cells, and cytokines and biologics that can inhibit T cell migration are effective in the treatment of psoriasis. Intradermal injection of T cells from psoriatic patients into human skin/severe combined immunodeficient (SCID) mice can induce spontaneous psoriatic conversion of skins from healthy human or non-lesional skin from psoriatic patients. Thus, it is widely accepted that psoriasis is a T lymphocyte-mediated autoimmune disease. Although the roles of T cells in psoriasis have been confirmed, the exact mechanisms of psoriasis and the origin of abnormal T cells are still unclear.

Beside T cells, psoriatic patients have a wide variety of other immune abnormalities such as B cells, monocytes, neutrophils and erythrocytes. As the precursor of immune cells, bone marrow hematopoietic stem cells have been suggested to be responsible for immune dysregulation of T cells in psoriasis. Several recent studies have indicated that abnormal T cells may be closely related to anomalous hematopoietic stem cells (HSCs) determined by psoriatic hereditary background. In addition to HSCs, aberrant bone marrow mesenchymal stem cells have also been demonstrated in patients with psoriasis.

2. The clinical cue of relationship between psoriasis and bone marrow cells

Although various exogenous and endogenous factors are believed to activate the immune system leading to imbalance of the system and initiation of psoriasis, increasing evidences suggest that inherent and intrinsic rather than extrinsic factors are more important in psoriasis pathogenesis. These intrinsic factors may be involved in spontaneous T-cell activation or proliferation, regulation of cytokine production, hematopoietic cell development, and T-cell development in the thymus. Allogeneic bone marrow transplantations (BMT) have been reported to either eliminate or aggravate psoriasis.

Leukemia patients with psoriasis reportedly have long-term psoriasis remission or amelioration. On the other hand, non-psoriatic leukemia patients can develop psoriasis after transplanting bone marrow from psoriatic donors. These clinical reports indicate that psoriatic immune abnormalities transferred by BMT may have originated from bone marrow HSC.

3. Bone marrow derived hematopoietic stem / progenitor cells from psoriatic patients are anomalously proliferative

Based on the above evidence, many researchers begin to pay close attention to bone marrow abnormality of psoriatic patients. *In vitro* studies have shown that monocytopoietic activity is enhanced in psoriasis and functional bone marrow scintigraphy using ⁹⁹Tcm-labelled human serum albumin millimicrospheres has shown hyperplasia of phagocytes in psoriasis.

Bone marrow, with its rapidly renewing cell populations, is one of the most sensitive tissues to various stimulations of exogenous or endogenous factors. Once activated the pathogenic peripheral immunocytes in psoriasis and their released soluble factors, such as gamma-interferon (IFN- γ), interleukin-2 (IL-2), IL-8 and tumor necrosis factor-alpha (TNF- α), may influence hematopoietic microenvironment, and even hematopoiesis. *In vitro* assessment using high proliferative potential colony-forming cell (HPP-CFCs) and colony formation units (CFU) is used as a surrogate marker of hematopoietic activity and can play a key role in linking hematopoiesis to psoriasis. Supernatant of *in vitro* cultured psoriatic peripheral blood mononuclear cells was found to suppress the proliferative activity of normal bone marrow HPP-CFCs, CFU-GM (granulocyte-macrophage colony-forming units) and CFU-E (erythroid colony-forming units). These results support the hypothesis that aberrant psoriatic peripheral immunocytes and cytokines can influence hematopoiesis.

Recently, besides the influence of aberrant peripheral immunocytes and cytokines, researchers began to pay attention to the intrinsic deficiency of psoriatic bone marrow hematopoietic cells. Zhang *et al.* cultured psoriatic bone marrow mononuclear cells in methylcellulose semisolid medium and observed their colony formation ability in the presence of exogenous cytokine combinations. These studies show a decreased colony formation ability of HPP-CFC, CFU-GM but not CFU-E, implying that the proliferative activity of HSCs in patients with psoriasis may be intrinsically decreased. They further investigated the molecular mechanisms of abnormal proliferative activity of HSCs in psoriasis and found that promoter methylation of p15, p16 and p21 genes is significantly decreased and transcription levels of these genes are enhanced in *ex vivo* cultured bone marrow HPP-CFCs from psoriatic patients in comparison to those from healthy volunteers. The P15, P16 and P21 proteins belong to the INK4 kinase family of cyclin-dependent kinase inhibitors and can negatively regulate the cell cycle through competitive inhibition of cyclin-dependent kinases 2, 4 and 6. Higher expression of these genes may contribute to the low proliferative activity of psoriatic hematopoietic cells.

Expression of Notch receptors and their ligands in hematopoietic system has been widely reported, and Notch signaling has been shown to influence hematopoietic cell proliferation and differentiation at several stages. The activation of Notch signaling results in transcriptional activation of *E(spl)/HES* genes, which function as negative regulators of cell proliferation and differentiation. Moreover, Notch1 and Hes-1 expression is significantly

enhanced in psoriatic CD34⁺ bone marrow cells compared to normal controls. Beside *HES* genes, another transcription factor RUNX-1, which is essential for hematopoietic cell development, has long been suspected to be involved in the pathogenesis of psoriasis because loss of RUNX1 binding site located between the SLC9A3R1 and NAT9 genes at 17q25 has been found increased expression in the psoriatic CD34⁺ cells. These studies suggest that the dysfunction of immune cells in psoriatic patients can be traced back to the early development of hematopoietic cells.

4. T cells differentiated from bone marrow derived hematopoietic cells of psoriatic patients are functionally different from normal T cells

Since T cells are derived from bone marrow hematopoietic cells, it is suggested that hematopoietic cells are partly relevant to the dysfunction of T cells in psoriasis. To demonstrate whether T cells are produced inherently dysfunctional from the immune system, Zhang et al. cultured bone marrow CD34⁺ cells from psoriatic patients and induced them to differentiate into T cells and CD4⁺CD25⁺ regulatory T cells *in vitro*. A further functional study revealed abnormal characters of these cells compared to normal bone marrow derived ones.

The main hallmark of CD4⁺CD25⁺ T cells is their immune regulatory function by interacting with effector T cells. Several studies have reported that the CD4⁺CD25⁺ T-lymphocyte subpopulation in peripheral blood and lesional skin demonstrates a less inhibitory effect on effector T cells, leading to accelerated proliferation of pathogenic/effector T-cells in autoimmune diseases, especially in psoriasis. Although the proportion of CD4⁺CD25⁺ T cells and FOXP3 gene expression are comparable in both psoriatic and healthy samples, proliferation of psoriatic bone marrow derived CD4⁺CD25⁺ T cells is significantly attenuated and secretion of cytokines IL-2 and IL-10 is decreased compared to normal controls in response to streptococcal superantigen (Strep-A). In particular, CD4⁺CD25⁺ T cells differentiated from psoriatic CD34⁺ cells are functionally insufficient to restrain proliferation of activated effector T-cells. That is to say, the function of CD4⁺CD25⁺ T cells derived from psoriatic bone marrow CD34⁺ cells *in vitro* is similar to that of peripheral CD4⁺CD25⁺ T-lymphocytes of psoriatic patient *in vivo*.

In another study, bone marrow CD34⁺ hematopoietic cells from psoriatic patients with family history were induced into effector T cells and their functions such as *in vitro* proliferation ability, secretion of cytokines IL-4, IL-8 and IFN- γ , and their ability to induce human keratinocytes producing C-myc, Bcl-xL, and Ki67 proteins were compared with their counterpart from healthy objects. The differentiated T cells from CD34⁺ cells of psoriatic patients showed higher proliferative activity and stronger capacity to secrete Th1 cytokines in response to streptococcal superantigen and could induce expression of C-myc and Ki67, but not Bcl-XL in keratinocytes co-cultured with psoriatic differentiated T cells.

These studies show that regulatory as well as effector T cells differentiated from CD34⁺ cells of psoriatic patients, but not normal controls, are functionally similar to those psoriatic circulating T cells and suggest that dysfunctional activity of T cells in psoriatic patients can be traced back to the early development of hematopoietic cells.

5. The bionomics of psoriatic bone marrow mesenchymal stem cells

Mesenchymal stem cells, also referred as marrow stromal cells, are another important type of stem cells in bone marrow. Cytokines secreted by bone marrow mesenchymal stem cells (BMSCs) along with extracellular matrix compose the hematopoietic microenvironment and influence hematopoiesis. More than 30 hematopoietic cytokines and growth factors including TNF- α , IL-1, IL-6, IL-7, IL-8, IL-10, IL-12, IFN- γ and IL-18 are reportedly secreted by BMSCs and many of them could influence immune reaction of peripheral blood. Secretion of SCF, granulocyte colony-stimulating factor (G-CSF) and IL-6 is increased in *in vitro* cultured BMSCs from psoriatic patients, while that of IL-1 α , IL-1 β , IL-3, IL-8, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), TNF- α , leukaemia inhibitory factor (LIF), hepatocyte growth factor (HGF) and platelet-derived growth factor (PDGF) is decreased and the levels of GM-CSF, IL-11 or IL-7 is not altered. *Pearson* correlation analysis demonstrates that those cytokine levels are not correlated with PASI scores, indicating that abnormal secretion of cytokines is due to anomaly of BMSCs themselves rather than systemic inflammatory response.

On the other hand, BMSCs are also characterized by their ability to differentiate into multiple mesenchymal lineages, including osteocytes, chondrocytes, adipocytes, endothelial cells and skeletal muscle cells under controlled *in vitro* conditions. Studies have found that BMSCs from psoriatic patients have lower proliferative and passage ability and are more prone to differentiate into vascular endothelial cells (VEC) compared with those from healthy subjects under the same induction conditions. Moreover, this differentiation ability is paralleled with the disease severity. In addition, specimens from a patient whose parents also have psoriasis could spontaneously differentiate into VECs. Further studies on gene expression using RNA sequencing showed a total of 475 genes mostly enriched in prostaglandin (PG) and prostanoid metabolic process (unpublished data) are differentially expressed in this patient.

Studies on differential gene expression of BMSCs from 4 psoriatic patients and 3 healthy subjects found a total of 1617 genes were differently expressed by more than 2-fold between the two groups, among which 324 genes were upregulated and 1293 genes were downregulated in psoriatic patients. GO analysis revealed the first five gene-enriched GO terms were immune response, inflammatory response, antigen processing and presentation of peptide, chemotaxis, and cell adhesion. While the first five highly enriched factor terms were positive regulation of CD4+CD25+ alpha-beta regulatory T cell differentiation, lipoprotein particle clearance, antigen processing and presentation of peptide, negative regulation of peptidase activity, and positive regulation of cholesterol storage (unpublished data). These terms have been confirmed to participate in the onset and development of psoriasis.

Taken together, these studies suggest that BMSCs of psoriatic patients are abnormal in proliferation, differentiation, passage ability, secretion of multiple cytokines and gene expression, and may partly participate in the occurrence and development of psoriasis. In other words, psoriasis is a multi-system disease that involves not only the epidermis, but also the hematopoietic system, immune system, neuroendocrine system, and so on. With continued research, various stem cells may be confirmed to be involved in the generation and development of psoriasis.

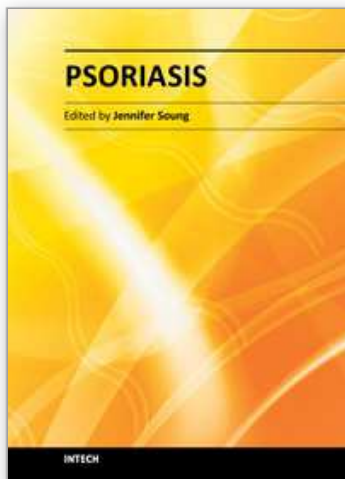
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We hope you enjoy and find the information provided in this book useful in your research or practice. We urge that you continue to keep abreast of the new developments in psoriasis and share your knowledge so that we may advance treatment and cures of psoriasis.

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