Domande estratte nn. 1-2-3

1. Si descrivano le tecniche utili per lo studio dello stress ossidativo e dei suoi marcatori analitici in vitro e in vivo su prelievi ematici

2. Si descrivano almeno due metodiche utili allo studio dell'espressione e la localizzazione intracellulare di proteine di interesse

3. Si descrivano i passaggi principali per la messa in coltura di cellule primarie umane e le relative criticità

4. Si descrivano alcuni possibili modelli per lo studio del metabolismo cellulare

Istituti Fisioterapici Ospitalieri - ROMA -

Domande estratte nn. 1-2-3

1) Cos'è word?

2) Cos'è un database?

3) Che cos'è Excel?

4) A cosa serve Power Point?

Domande estratte nn. 1-2-3

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Targeting Innate Immunity to Combat Cutaneous Stress: The Vitiligo Perspective

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Multiple factors are involved in the process leading to melanocyte loss in vitiligo including environmental triggers, genetic polymorphisms, metabolic alterations, and autoimmunity. This review aims to highlight current knowledge on how danger signals released by stressed epidermal cells in a predisposed patient can trigger the innate immune system and initiate a cascade of events leading to an autoreactive immune response, ultimately contributing to melanocyte disappearance in vitiligo. We will explore the genetic data available, the specific role of damage-associated-molecular patterns, and pattern-recognition receptors, as well as the cellular players involved in the innate immune response. Finally, the relevance of therapeutic strategies targeting this pathway to improve this inflammatory and autoimmune condition is also discussed.

Keywords: innate immunity, vitiligo, PAMPs, DAMPs, ILC, DC, melanocytes

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INTRODUCTION

Clinical, translational, and fundamental research studies performed over the last decade have tremendously improved our understanding of vitiligo physiopathology and new therapeutic perspectives are emerging for this disease which suffers from the lack of effective treatments. Vitiligo is a puzzling disease combining multiple intertwined components including environmental triggers, genetic predisposition, increased oxidative stress, and abnormal immune and inflammatory response (1, 2). Vitiligo is defined by the loss of epidermal melanocytes, nonetheless several cell subsets of immune and non-immune cells are involved to induce and/or contribute to their disappearance. Vitiligo skin is consistently associated with infiltration of T cells with a Th1/Tc1 skewed immune profile which target melanocytes (3, 4). Besides the role of the adaptive immune response, increasing data highlight a major role of innate immune cell subsets and their immune-related pathways that could spark the induction of the disease in the "normal-appearing" skin. Therefore, this short review is focusing on the innate side of the disease, discussing how genetic and transcriptomic data revealed the importance of innate immunity in vitiligo, as well as the interplay between epidermal cells (keratinocytes and melanocytes) and innate immune cells to contribute to the initiation and/or progression of the disease through the release of danger signals, cytokines, and chemokines, leading to activation of the adaptive immune response and ultimately the loss of

melanocyte. This better understanding now offers novel insight into the development of targeted therapies that could prevent the induction as well as the recurrence of the disease.

GENETIC AND TRANSCRIPTOME DATA

Genome wide association studies (GWAS) have identified over 50 susceptibility loci involved in melanogenesis and immunity in vitiligo patients (5). On the other hand, a delay in vitiligo age-of-onset over the past 30 years emphasizes the key role of environmental factors in triggering vitiligo in genetically predisposed individuals (6, 7). These GWAS studies not only demonstrated the implication of genes involved in melanogenesis and adaptive immunity but also revealed allelic variations in key genes involved in the innate immune responses, such as IFIH1, NLRP1, or TICAM1 (7–9).

Transcriptional analysis comparing gene expression profiles of skin from vitiligo patients with normal skin of healthy volunteers also emphasized the role of innate immunity (10, 11). Thus, natural killer (NK) cell activation markers, such as NKG2D, KLRC2, and KLRC4, ligands for NK receptor (CLEC2B), as well as markers of oxidative stress (CANP and POSTN) and innate immunity (DEFB103A) were shown to be increased in vitiligo skin (10). In our study, we also found a significant increase in NK receptors, including NKTR and KLRC1, as well as trends for increased EOMES (master regulator of NK cells), CCL20, and NK-related cytokines (TNFα and IL-15) (11). Interestingly, activation of these innate immunity markers was found in the non-lesional skin of vitiligo patients, suggesting that the activation of the innate immunity may be present throughout the entire skin surface of patients (10, 11).

Taken together, these data illustrate that vitiligo patients have genetic predisposition affecting their innate immune response in their apparent non-affected skin. Such findings may be indicative of a subclinical activation of innate immunity, loss of protective mechanisms to stress (such as defective unfolded protein response in target cells following endoplasmic reticulum stress), and/or increased sensitivity to endogenous or external stress, such as several damage-associated-molecular patterns (DAMPs) or pathogen-associated-molecular patterns (PAMPs) (12).

ACTIVATION OF INNATE IMMUNE CELLS BY DANGER SIGNALS

DAMPs

Several DAMPs have been detected in perilesional skin of vitiligo patients. Previous studies have shown that the chromatin-associated nuclear protein High-mobility group-box-1 (HMGB1) could be released by melanocytes under oxidative stress and could directly impact melanocyte survival (13–15). Additionally, HMGB1 could bind free DNA and HMGB1-DNA complexes and induce maturation of vitiligo patients' dendritic cells (DC), as well as the production of cytokines and chemokines by keratinocytes (16). Another candidate for sensing the immune system in vitiligo is calreticulin (CRT). In response to stress, CRT can localize at the surface of immune cells, affecting their antigen presentation, complement activation, and clearance of apoptotic cells. Moreover, CRT can translocate to the melanocyte surface when these cells undergo H_2O_2-mediated oxidative stress, increasing melanocyte immunogenicity. CRT may also enhance the immunogenic potential of melanocytes through their induction of pro-inflammatory cytokine production, such as IL-6 and TNFα (17).

Heat shock proteins (HSP) are likely important candidates bridging stress to the skin with the innate immune response. Indeed, inducible HSP70 (HSP70i) released in the context of cellular stress, notably by epidermal cells (including keratinocytes and melanocytes) has been shown to accelerate the progression of the disease in a preclinical model (18–20). Likewise, modified HSP70i prevented or reversed vitiligo in a mouse and Sinclair Swine models of the disease (21, 22). In vitiligo patients, the expression of HSP70 in the skin correlated with disease activity and was lower in patients with stable disease (23). As discussed below, HSP70i could interact with several cell subsets, leading to their activation.

Pattern Recognition Receptors

PAMPs are critical in initiation of the innate immune response through activation of pattern recognition receptors (PRRs). Implication of PRRs in vitiligo has been demonstrated in several GWAS, in particular genes encoding TLRs and their signaling pathway (24, 25). In addition, polymorphisms in NLRs have been described in patients with non-segmental vitiligo. Upregulated NLRP3 expression has been detected in perilesional keratinocytes in vitiligo skin and associated with higher cutaneous IL-1β expression and increased severity of the disease (26, 27).

Viral components are likely involved in vitiligo pathogenesis, as they can trigger activation of the immune system, however whether viruses can activate the innate immune response in the context of vitiligo is poorly described. Viruses possess several structurally diverse PAMPs, including surface glycoproteins, DNA, and RNA species (28). Virus infection could thus activate the innate response and potentially trigger a vitiligo flare. There is some evidence that viral infections in a genetically predisposed host may induce excessive ROS production by recruited lymphocytes leading to destruction of epidermal melanocytes (29). Furthermore, IFIH1, encoding intracellular virus sensor MDA5, has been identified as a vitiligo susceptibility gene capable of inducing secretion of CXCL10 and CXCL16 from keratinocytes and inducing infiltration of $CD8^+$ T cells in vitiligo (30).

Bacteria are among the top producers of PAMPs and could directly trigger PRRs activation and therefore participate in activation of the innate immune response in vitiligo, however their direct role in triggering vitiligo has yet to be proven. While gut dysbiosis has been reported in several auto-immune disorders, there exists only one study suggesting skin dysbiosis in lesional zone of vitiligo patients compared to their non-