Section 2

Understanding the Disease
2.1.1 From Where to Start? A Good Hierarchy of Relevant Data Is Needed

The discussion on the pathogenesis of vitiligo has been for decades, a magnet for endless speculation, and this indicates that some aspects of vitiligo are still confused. Several theories have been proposed to explain the disappearance of functioning melanocytes, but even the concept of “disappearance” is a matter of debate [4, 6, 14, 15, 18, 20]. There is, however, a general consensus that common NSV originate from melanocyte loss and not from simple melanogenesis inhibition. Several morphological, functional or metabolic alterations of the melanocytes, apparently not related, have been described. In the 1970–1980s, the immune-mediated, the autolysis, or the neural mechanisms were considered as independent pathways accounting for melanocyte damage (Part 1.1).
Progressively, the researchers come across cell biology, genetics, biochemistry, immunology, and microbiology with new insights. The first step, as delineated in Part 1, is to start from a firm ground, with clear definitions, and to postpone interpretation after data collection. Ideally, the observation of the disease and its natural history/treatment influences, annotated databases and biological collections for clinical and epidemiological studies, tissue collection for histopathology and other direct in vivo approaches are needed to provide the pathophysiological debate with solid arguments, before going to in vitro experiments and animal models.

2.1.2 Time for a Critical Reappraisal of the Convergence Theory

Starting from the proposal of a convergent theory with the melanocyte at its centre [14], several authors have contributed their point of view attempting to solve the puzzle. However, some clinical issues such as the link of SV to NSV have not been clearly integrated [21]. Furthermore, for defining a good starting point we need to reconcile the convergent theory with clinical and experimental data supporting an underlying generalized intrinsic biochemical defect, independent of melanocyte-specific metabolisms, enlarging thus, the spectrum of possible involved cells [1, 3, 8, 10, 13, 17]. Is this defect primary or secondary? Is it just more pronounced in pigment cells, as the emerging tip of an iceberg?

2.1.3 Melanocyte Loss: Survival Defect, True Destruction, or Multistep Process with Immune Acceleration?

Current theories, based on the newest basic science trends, give indications on putative mechanisms explaining how epidermal melanocytes may actually disappear or become non-functional. Death by cytotoxicity, apoptosis or following detachment have likewise been proposed [2, 5, 12, 22]. The in vivo data from skin biopsies has been so far disappointing as far as tracing this event is concerned (“crime without cadaver” as pointed out by Gauthier). It is possible that biopsies of vitiligo lesions gave little arguments just because early lesions are rarely biopsied. Biopsy material from established lesions contains no or few melanocytes, and it is difficult to capture the essence of the mechanism. Peripheral biopsies of progressive NSV lesions, even in non clinically inflammatory cases, demonstrate predominantly CD8+ T cell lichenoid infiltrates. These are in tune with a possible cell-mediated cytotoxic mechanism of the loss and form the basis of the concept of vitiligo being a microinflammatory skin disease. But the early initiating events of this phase are not known.

2.1.4 The Genetics Angle: Unbiased and Productive?

The genetic approach suggests a wide range of predisposing factors, none being universal, major differences having been detected across population of various ethnic backgrounds (Chap. 2.2.1). Most cases of NSV occur sporadically, but about 15–20% of patients have one or more affected first-degree relatives. Familial aggregation of NSV follows a non-Mendelian pattern suggesting complex polygenic, multifactorial inheritance. Case–control studies have reported the link of NSV with genes (such as CTLA4, PTPN22, MBL2, and IL10) already associated with autoimmune diseases. Genetic associations between vitiligo and other candidate genes (GCH1, CAT, COMT, ACE, GPX1, AIRE) have been suggested, even if the concerned case–control studies are small and require further validation. Targeted family-based association analysis recently proposed NALP1 as a breakthrough susceptibility gene for NSV associated with other autoimmune diseases. NALP1 is central to the innate immune system. The binding of bacterial derivatives or other environmental ligands can induce the assembly of NALP1 within the inflammasome, with subsequent production of active interleukin-1β [19]. This emerging new rationale for an increased skin susceptibility towards hazardous stimuli, stimulating the innate immune system and possibly cutaneous inflammation (Sect. 2.2.7.2) is now being closely scrutinized in vitiligo patients, and gene expression profiling may prove helpful to follow this idea.
2.1.5 Inflammation and Auto-Immunity. The Role of Stress

Arguments for a humoral immune response targeting melanocytes exist in a subset of patients (Sect. 2.2.7.3). Mainly, the CD8+ T cell infiltrate present in progressing vitiligo is probably, if not primarily, the cause of the disease, at least implicated in its acceleration phase clearly noted in some NSV patients, which may lead to vitiligo universalis (Chap. 1.3.3). However, its (probably) melanocytic targets are not yet clearly identified (Sect. 2.2.7.4). Experimental data highlight a link between oxidative stress and immune system activation. Following an external danger stimulus, an oxidative stress can frequently occur inside the cell, also determining the expression and the release of proteins that belong to the heat shock protein family. Melanocytes may produce and release the highest amount of hsp70, thus activating immune responses [12]. The pathogenetic role of the production of the hsp70 has also been tested in mouse through the gene gun vaccination with melanocyte differentiation antigens (TRP1 or gp100) and hsp70. The mouse hsp70 vaccinated early developed depigmentation, testifying for the ability of hsp70 to enhance antigen uptake by dendritic cells [6].

2.1.6 Identifying and Characterizing Skin and Non Skin Cellular Anomalies in Vitiligo

The main target cell of the disease is the epidermal and/or hair follicle melanocyte. There is evidence of the involvement of non skin melanocytes in common NSV (Chap. 1.3.7) [5]. This exceptional involvement seems to be related to an acceleration phase of the disease in extensive/universalis cases and characterizes the very rare Vogt-Koyanagi-Harada syndrome (Chaps. 1.3.3 and 1.3.8). There are marked clinical differences between SV and NSV in hair follicle melanocyte involvement, which may correspond to a different, even if poorly understood, pathogenesis. Vitiligo lesional melanocytes show morphological alterations, including cytosol vacuolization and limited dendrite formation [11] (Sect. 2.2.3.2). Associated with these structural features, several functional alterations have been described. In fact, vitiligo lesional and non-lesional melanocytes are characterized by an altered redox status, possibly due to the compromised activity of the intracellular antioxidants (catalase and glutathione peroxidase, mainly) or increased ROS production (Chap. 2.2.6). The final effect of this condition would be the high susceptibility to toxic compounds, including melanin derivatives, and to physical trauma [5, 12, 18]. The other major epidermal cell type, the keratinocyte, appears to be involved (Chaps 2.2.5 and 2.2.10). A defective intracellular signal transduction of the TNF-α-activated pathway in vitiligo keratinocytes has been reported, possibly accounting for limited survival and subsequent loss of production of specific melanocyte growth factors [1, 9, 13, 16, 17]. So far, neglected neighbouring cells such as dermal fibroblasts, may control adhesion checkpoints and might actually be involved in vitiligo, through the release of soluble factors [2].

As discussed before, besides the recognition of the major target cell of the disease, it is not completely settled whether or not melanocyte alterations can be the consequence of a more generalized biochemical/biological defect. Peripheral blood mononuclear cells appear to be characterized by metabolic deregulations and oxidative stress, similar to those found in melanocytes and epidermis [3, 8].

2.1.7 The Need for Translational Research

The multifactorial pathogenetic process leading to the functional loss of melanocytes may benefit from the data obtained in animal models (Chap. 2.2.4) [7]. The spontaneous autoimmune vitiligo Smyth line chicken provides, indeed a good chance to study vitiligo at onset and during progression. Smith chicken becomes depigmented after the hatch and the depigmentation can be complete or partial. Smyth chicken vitiligo is associated, as in humans, with uveitis and thyroid disorders. The relevance of the chicken model is also supported by the occurrence of intrinsic melanocyte defects (irregularly shaped melanosome, low catalase activity), genetic background, cell-mediated immune response (CD8+ T cell infiltrate and Th1 cytokines production), and external danger triggers (turkey herpesvirus). Other avian models support the intrinsic melanocyte fragility (Barred Plymouth Rock and White Leghorn chicken breeds). Other animal
models have been proposed, including grey horses, the vitiligo mouse and the Sinclair pig, in which vitiligo spontaneously develops.

2.1.8 Conclusions and Scope of this Book Section

Vitiligo is still a poorly understood disease, and its multifactorial basis is indubitably a disadvantage to pick up a relevant item among so many, to begin unfolding the puzzle. The immunological and genetic approaches have provided until now, the most powerful insights. However, they cannot indicate with certainty the initial event causing the immune activation and subsequent amplified melanocyte damage. The following chapters of this section provide a more in depth analysis of the pathomechanisms mentioned in this overview.

References
