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Cellular stress and innate inflammation in organ-specific autoimmunity: lessons learned from vitiligo

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Summary

For decades, research in autoimmunity has focused primarily on immune contributions to disease. Yet recent studies report elevated levels of reactive oxygen species (ROS) and abnormal activation of the unfolded protein response (UPR) in cells targeted by autoimmunity, implicating cellular stress originating from the target tissue as a contributing factor. A better understanding of this contribution may help to answer important lingering questions in organ-specific autoimmunity, like what factors initiate disease, and what directs its tissue specificity. Vitiligo, an autoimmune disease of the skin, has been the focus of translational research for over 30 years, and both melanocyte stress and immune mechanisms have been thought to be mutually exclusive explanations for pathogenesis. Chemical-induced vitiligo is a unique clinical presentation that reflects the importance of environmental influences on autoimmunity, provides insight into a new paradigm linking cell stress to the immune response, and serves as a template for other autoimmune diseases. In this review I will discuss the evidence for cell stress contributions to a number of autoimmune diseases, the questions that remain, and how vitiligo, an underappreciated example of organ-specific autoimmunity, helps to answer them.

Keywords

cellular stress; innate immunity; organ-specific autoimmunity; vitiligo

Introduction

Organ-specific autoimmune diseases include type 1 diabetes, multiple sclerosis, thyroiditis, vitiligo, and others, and they are rapidly increasing in incidence (1). Genetic factors clearly influence disease susceptibility, and large genome-wide association studies (GWAS) have successfully identified a list of allelic risk variants for these diseases, yet in total genetic factors typically confer only about 25-50% of the risk (2-4). Environmental factors also contribute to this risk, but they are less well-studied, and are largely unknown (1). Much of our knowledge about the pathogenesis of autoimmunity is focused on mechanisms of disease progression, including adaptive effector cell types and the cytokines that modulate

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their activity. Mechanisms involved during the initiation of disease, and those that influence the type of organ or tissue to be targeted, remain largely a mystery. It is likely that a combination of genetic, environmental, and stochastic influences synergize to break tolerance to self-tissues and initiate the autoimmune attack, and that these influences are at least partially initiated within the targeted tissue.

While there has been a strong interest in studying mechanisms of organ-specific autoimmunity, many questions remain unanswered. First, what are the factors that initiate autoimmunity? Autoreactive T cell clones targeting self-tissues can be identified in most healthy individuals that may or may not eventually develop autoimmunity, and therefore do not appear sufficient for disease. Environmental factors such as toxins or viral infections are suspected to play a role in disease initiation, yet well-documented examples are sparse. Second, what is responsible for the tissue specificity of organ-specific autoimmune diseases? Many of the risk alleles identified in recent GWAS in autoimmune diseases fall squarely in the immune compartment, implicating T cell signaling, antigen presentation, and peripheral tolerance, yet they should not directly confer tissue-specificity. Indeed, a predisposition toward autoimmunity has been reported to run in families, including type 1 diabetes, thyroiditis, pernicious anemia, vitiligo, Addison's disease and others (5-7). However why, for example, one individual gets diabetes, another thyroiditis and another vitiligo is unknown, and suggests that these are either strictly stochastic events or that additional environmental factors drive tissue specificity.

Recent studies implicate a role for the cellular stress response in a wide number of autoimmune diseases. However in contrast to the characterization of immune contributions to these diseases, understanding the scope of this contribution is far from complete, gleaned from a sparse number of reports for each disease, and most coming from animal models. The cellular stress response encompasses multiple signaling components and pathways within the cell, including the generation and sensing of reactive oxygen species (ROS), activation of the unfolded protein response (UPR), and initiation of autophagy (8-10). ROS consist of highly reactive oxygen free radicals that can be generated by a number of events, including normal cell metabolism, other enzymatic reactions, perturbation of endoplasmic reticulum (ER) homeostasis, inflammatory cytokines, environmental toxins, and light or ionizing radiation (8). The UPR is primarily activated by improperly folded proteins produced within the endoplasmic reticulum, which can occur as a result of increased protein synthesis, improper post-translation modifications, hypoxia, nutrient starvation and other events (11). Autophagy is a process through which cells sequester damaged organelles (mitochondria and others) or other potentially damaging agents (including bacteria) into double membrane-bound compartments that are then released from the cell or degraded through fusion with lysosomes (10). ROS, ER stress, and autophagy pathways can exacerbate or suppress one another, creating signaling loops that amplify each (10, 12). In general, all three pathways are activated by dysregulation of normal cell processes, which may result from viral or microbial infections. Since these changes may be harmful to the organism, it is likely that stress pathways have evolved to instigate immune surveillance, and over-activation could result in inappropriate immune responses to the affected tissue (10, 13, 14).

How cellular stress is first detected by the immune system is unclear. The process would necessarily begin within the peripheral target tissue, but whether the stressed cell directly produces inflammatory mediators (such as cytokines and chemokines) that recruit immune effectors, or whether an innate immune population first senses target cell stress, is not clear. Innate immunity evolved as a rapid protective response against pathogens, and requires recognition of “danger signals” present during infection. This recognition is dependent on innate PRRs and their ability to identify pathogen-associated molecular patterns (PAMPs). In addition to defense against pathogens, PRRs are involved in sterile inflammation, including anti-tumor responses, crystal-induced inflammation (i.e. asbestos, Alzheimer’s disease, and gout), and autoimmunity (15). Therefore, they recognize not only PAMPs, but non-pathogen associated patterns as well, including altered self-molecules that are released following cellular damage, referred to as damage-associated molecular patterns (DAMPs). One of the best-characterized examples of DAMPs that activate innate immunity is oxidized mitochondrial DNA (mtDNA), generated during oxidative stress from infection, which is sensed by the NOD-like receptor NLRP3 (16, 17). ROS, the UPR, and autophagy can all modulate inflammation through PRRs (10), and thus it is conceivable that similar innate responses within peripheral tissues first detect cellular stress and initiate inflammation within the target tissue.

Much of the research to better understand mechanisms of autoimmunity conducted to date has been performed in animal models, which have provided important insights into disease progression. However the initiation of disease is difficult to study in constructed animal models, since they are largely insulated from both the genetic and environmental influences so important for developing autoimmunity in humans. This is particularly true for models of autoimmunity that are induced through transfer of adaptive immune populations, or by intentionally breaking tolerance. This review will focus on mechanisms of cellular stress and innate immune activation during organ-specific autoimmune diseases, where most of the data was gathered in human subjects or their tissues. I will begin with an extensive discussion of vitiligo pathogenesis, as this is perhaps the most extensively studied and best-understood organ-specific autoimmune disease in humans and their tissues, and will thus provide a template for understanding the complex interplay between cellular stress and innate mechanisms in other diseases of autoimmunity.

Vitiligo

Vitiligo is an under-recognized organ-specific autoimmune disease of the skin that results from cytotoxic T cell-mediated attack on melanocytes, the pigment-producing cells in the epidermis (18). The result is the loss of pigment in the skin, visible as white spots (Fig. 1) (19). The availability of the skin and ability to culture melanocytes *in vitro* has resulted in decades of translational research in vitiligo, using human subjects and their tissues both *in vitro* and *in vivo* (20). An early recognition that melanocytes suffer from high levels of stress led to investigation of stress pathways in this autoimmune disease, instigating an ongoing discussion about whether vitiligo is primarily a degenerative or autoimmune disease (21). Differing views in vitiligo have been described as “hotly disputed for as long as one remembers...a magnet for endless speculation” (21), however recent translational studies of chemical-induced vitiligo, a clinical variant, now reconcile the two theories and reveal

important mechanisms that tie cell stress and immune responses together, all discovered using human tissues. Therefore, vitiligo is an autoimmune disease where cell stress and immune responses cooperate to drive pathogenesis, and therefore offers important answers to the questions presented above.

The risk of developing vitiligo is ~1% in the general population (19), although the risk in siblings of vitiligo sufferers is 6.1% and in an identical twin is 23% (7), implying a genetic component. The remainder of the risk has been described as environmental (22). A large number of genetic associations have been reported using GWAS, confirming a genetic contribution, and these will be discussed in more detail below. A significant environmental risk factor is exposure to phenolic compounds, a phenomenon known as “chemical leukoderma” or chemical-induced vitiligo. As I will discuss, this phenomenon reveals important connections between cell stress and autoimmunity, and provides some hints as to how disease is initiated and targets specific tissues.

Observations by practicing clinicians generated the earliest theories about vitiligo pathogenesis, as familial clustering of vitiligo cases strongly suggested a genetic component (23). Guilt by association implied that vitiligo was an autoimmune disease – patients with vitiligo and their close relatives appeared to have an increased risk of type 1 diabetes, thyroiditis, and pernicious anemia (6). The first laboratory investigations in vitiligo identified elevated levels of melanocyte-specific autoantibodies in vitiligo patients (24-26), which could damage melanocytes both *in vitro* (27) and *in vivo* (28), supporting an autoimmune pathogenesis. However, antibodies do not necessarily correlate with disease activity (29), and distinct patches of skin are involved in vitiligo despite the systemic presence of antibodies in the serum, suggesting that antibodies were not the entire answer. Thus alternative theories were sought, beginning an interesting sojourn to identify the true pathogenesis of vitiligo.

Theory of melanocyte-intrinsic pathogenesis: cellular stress

Shortly after the identification of autoantibodies in the serum of vitiligo patients, multiple groups observed that melanocytes isolated from unaffected skin of vitiligo patients were difficult to culture *in vitro*, in contrast with melanocytes from healthy patients. Melanocytes from the normal-appearing skin of vitiligo patients took longer to grow, exhibiting a slow replication rate (30). Culture conditions had to be modified to improve survival and growth, including the addition of growth factors (31) or catalase (32, 33) to the culture media. Electron microscopy of cellular substructure revealed that the endoplasmic reticulum (ER) in melanocytes from vitiligo patients was dilated compared to healthy controls (32), a characteristic that implies elevated levels of cellular stress.

These *in vitro* observations led to the hypothesis that melanocytes were intrinsically abnormal in vitiligo patients, injured internally from stress, which challenged previous characterizations of melanocytes as otherwise healthy, passive targets of autoimmunity. This hypothesis was supported by reports of elevated *in vivo* levels of H₂O₂ and oxidative byproducts in vitiligo patient epidermis compared with controls, a general measure of the level of ROS (34-37). Consistent with these observations, the enzyme catalase, which reduces H₂O₂ to O₂ and H₂O thereby “detoxifying” the molecule and relieving oxidative

stress, was found to be deficient in lesional skin (38), which may be either a cause or an effect of increased H_2O_2 (39).

Exposing cultured human melanocytes to exogenous stress *in vitro* (heat shock, peroxide, etc), led to cell death in melanocytes from vitiligo patients, but not from healthy controls (40, 41). However these stimuli were administered at very high levels, not comparable to typical exposures *in vivo*. What was the endogenous source of stress in melanocytes? The answer may come from understanding the mechanism of melanin synthesis – it is hazardous work. First, the production of large amounts of cellular proteins increases the risk of generating misfolded proteins, which activates the UPR. Second, the increased energy requirements of protein production lead to the creation of ROS from energy metabolism in mitochondria (11). Third, the position of melanocytes in the epidermis exposes them to UV light, which generates intracellular ROS, hydrogen peroxide, and superoxide anions. Finally, and most specific for melanocytes, the chemical modifications made by tyrosine hydroxylase and phenylalanine hydroxylase required to convert the amino acid tyrosine into melanin liberates hydrogen peroxide, a precursor to ROS (42).

Therefore, the melanocyte-intrinsic theory of vitiligo pathogenesis suggested that, while melanocytes in all humans were subject to cellular stress, vitiligo patients either have a lower sensitivity threshold to normal stress levels, or experience higher levels of stress than healthy individuals. The theory seemed reasonable, resulting in a healthy skepticism for any role of autoimmunity in the disease. However, therapeutic attempts to counteract melanocyte stress *in vivo*, through topical treatment of lesional skin with an exogenous catalase analog (pseudocatalase), has had disappointing results (43). An important observation by Gilhar, *et al.* strongly suggested that melanocyte-intrinsic defects were not sufficient for disease. Rather, he found that transplantation of lesional, depigmented skin from patients with vitiligo to nude mice resulted in rapid repigmentation of the skin graft, thereby implicating additional, systemic factors outside of the skin as necessary for disease (44).

Theory of autoimmune pathogenesis: T cell cytotoxicity

In the mid-1990's, clinical observations in skin biopsies from vitiligo patients revealed a patchy T cell infiltrate in the superficial dermis that localized to the dermal-epidermal junction, where melanocytes reside. In particular, T cells were able to infiltrate the epidermis, and were found in direct apposition to dying melanocytes and melanocyte fragments. The majority of these cells were $CD8^+$ /perforin⁺/granzyme⁺, consistent with a cytotoxic phenotype (45). While initial studies examined lesional skin of patients with inflammatory vitiligo, an uncommon, highly inflammatory form of the disease (46), these observations were later extended to typical, non-inflammatory forms as well (47).

Another group further implicated cytotoxic T cells in vitiligo by identifying melanocyte-reactive $CD8^+$ T cells in the blood of patients via tetramer staining. Melanocyte-specific, tetramer-positive cells were more prevalent in vitiligo patients compared to healthy controls, and were specifically able to kill a melanoma cell line *in vitro* while tetramer-negative cells did not (48). These findings were later confirmed by identifying elevated levels of melanocyte-reactive $CD8^+$ T cells in both blood and perilesional skin from vitiligo patients compared to controls using tetramers loaded with additional melanocyte-specific peptides,

including those from gp100 and tyrosinase (18). T cells isolated from perilesional skin indeed showed cytotoxic activity toward autologous melanocytes, providing the first direct line of evidence that skin-infiltrating CD8⁺ T cells mediate the killing and loss of melanocytes in vitiligo (49). However the definitive observation implicating melanocyte-specific, cytotoxic T cells in the pathogenesis of vitiligo was reported by van den Boorn, *et al.* In this study, T cells were isolated from perilesional vitiligo skin and cocultured with unaffected, normally pigmented skin explants from the same patient. Total T cells and CD8⁺ T cells infiltrated the normal skin explants, migrated to the epidermis, and induced apoptosis in melanocytes, while CD8⁺-depleted T cells did not (18). These data revealed that cytotoxic CD8⁺ T cells were both necessary and sufficient to mediate depigmentation in vitiligo.

Using human tissues and a mouse model we developed, we then determined that IFN- γ , and the IFN- γ -induced chemokine CXCL10 drive vitiligo pathogenesis through the recruitment of autoreactive CD8⁺ T cells to the epidermis. We found that melanocyte-specific, autoreactive T cells in vitiligo patients expressed CXCR3, the receptor for CXCL9 and CXCL10, in both the blood and lesional skin. Functional studies in our mouse model revealed that IFN- γ , the IFN- γ receptor, STAT1, CXCL10, and CXCR3 are critical for the development of depigmentation in the skin [(50-52) and unpublished observations]. We also found that blocking CXCL10 with neutralizing antibody was able to both prevent and even reverse established vitiligo, strongly suggesting that targeting the IFN- γ -CXCL10 pathway could be an effective treatment strategy (52). Supporting this hypothesis, a recent case report described a patient with vitiligo who experienced rapid reversal of disease after treatment with tofacitinib, an inhibitor of Janus Kinases (Jaks) (53), which are required for IFN- γ signaling (54).

These data, combined with the historical observations of co-inheritance of vitiligo with other autoimmune diseases, the production of melanocyte-specific autoantibodies, the fact that “adoptive transfer” of vitiligo has been observed in patients receiving bone marrow/stem cell transplants (55-57), and the immunosuppressive nature of all effective therapies for vitiligo (topical steroids, topical calcineurin inhibitors, and narrow-band UVB light) (19), clearly define a critical role for cellular immunity in vitiligo pathogenesis. However, this understanding had not yet been reconciled with the previously described, well-documented intrinsic defects in melanocytes. Le Poole, *et al.* first suggested that these conflicting observations might be reconciled into a “convergence theory”, requiring multiple steps in vitiligo pathogenesis (58), a hypothesis that was later updated (21). Experimental evidence for this theory would come almost 20 years after its inception, in the form of chemical leukoderma.

Chemical leukoderma: The convergence of two theories

For years clinicians have recognized the phenomenon of depigmentation following skin contact with certain chemicals. First recognized in 1939 by Oliver, *et al.* and labeled “occupational vitiligo”, chemically-induced depigmentation was described in a subset of workers who wore acid-cured gloves in a leather factory. Monobenzyl ether of hydroquinone, or monobenzene, was identified as the causative agent (59). Since then, a large number of reports have confirmed this observation, adding to the list of chemicals that

induce depigmentation. Offending agents include phenolic and catecholic chemicals found in dyes (including hair dyes), resins/adhesives, leather footwear and wallets, and other substances. While depigmentation begins localized to the site of exposure, it often (~26% of the time) spreads to distant sites as well (60, 61). Monobenzone is currently used therapeutically to complete the depigmentation of patients with severe vitiligo, through topical treatment with 20% monobenzone cream, applied twice daily to areas of remaining pigment (62). Over 4-12 months, patients gradually lose this pigment and become white all over, or “bleached”, and most are pleased with the results. Because many assumed that monobenzone was directly cytotoxic to melanocytes, it was a surprise that depigmentation is not restricted to the treated area, but can depigment areas remote from contact with the agent. The mechanism of depigmentation following treatment with monobenzone, or any agent inducing chemical leukoderma, has long been a mystery.

Recent studies have revealed potential mechanisms of chemical leukoderma, providing a connection between the two seemingly opposing theories, cellular immunity versus cellular stress. In 2005 Kroll and colleagues found that 4-tertiary butyl phenol (4-TBP), a mediator of chemical leukoderma that also initiates cellular stress in melanocytes, induced the production of heat shock protein 70 (HSP70) in cultured melanocytes. HSP70 was released into the cell culture media and induced the activation of dendritic cells (DCs) co-cultured with the melanocytes to become cytotoxic and kill melanocytes *in vitro* (63, 64). In 2011, van den Boorn, *et al.* connected melanocyte stress to T cell-mediated (antigen-specific) autoimmunity when they described the effects of monobenzone on melanocytes. Because monobenzone, like other phenols, has a chemical structure similar to tyrosine, it is taken up by tyrosinase, which attempts to oxidize the chemical to produce melanin. However monobenzone becomes covalently bound to the enzyme, which results in production of ROS, autophagy, and the release of melanocyte antigen-laden exosomes into the surrounding media. Exosomes are nanoparticle-sized, membrane-bound structures derived from endosomes and secreted from cells under a variety of conditions, and may directly induce inflammation (65). Dendritic cells co-cultured with stress melanocytes take up the exosomes, become mature antigen presenting cells, and activate melanocyte-specific CD8⁺ T cells, therefore initiating an autoimmune response (66). It may be that the form of HSP70, reported by Kroll, *et al.* to be released by melanocytes in response to 4-TBP, is actually packaged into exosomes. Finally, a recent study revealed that 4-TBP induces the UPR in melanocytes, which results in the XBP1-dependent production of inflammation-inducing cytokines IL-6 and IL-8 (67). Thus, phenols appear to act as tyrosine analogs that are taken up by melanocytes and disrupt melanin production, and increase cellular stress. Interestingly, IL-6 has been reported to be elevated in the skin and serum of vitiligo patients compared to healthy controls (68-70), and therefore this mechanism may occur during intrinsic (not chemically-induced) melanocyte stress as well.

Genetic evidence

While entirely focused on chemically-induced melanocyte stress and death *in vitro*, these studies provide a plausible connection between inherent melanocyte stress observed in vitiligo patients, and the clear role for autoimmunity in disease pathogenesis. GWAS have recently provided additional evidence for this hypothesis. The earliest genetic associations

were with the HLA-A haplotypes (71), supporting an autoimmune pathogenesis. The first non-HLA gene found to confer risk for vitiligo was NACHT, LRR and PYD domains-containing protein 1 (NLRP1), also called NALP1. NLRP1 is a major component of the innate immune response, confirming a causative role of the immune system in vitiligo (72). Further studies revealed a large number of additional genes, the majority of which also play roles in immune responses (PTPN22, TSLP, HLA class I/II/III, CCR6, IL2RA, UBASH3A, and FOXP3), including specifically cytotoxic T cell responses (GZMB), supporting earlier histologic and *in vitro* mechanistic data (22).

Importantly, two additional associated genes include *tyrosinase* (*Tyr*), the enzyme responsible for melanin production (73), and *X-box binding protein 1* (*Xbp1*) (74). The high-risk allele of *Tyr*, the R402Q polymorphism, is prone to misfolding in the endoplasmic reticulum. While this misfolding was reported to increase presentation of tyrosinase antigens on class I MHC and therefore may promote vitiligo as an autoantigen (75, 76), it would likely also induce the UPR, potentially serving as an initiator of melanocyte-specific cellular stress. As mentioned above, XBP1 is a critical member of the UPR and may form the critical connection between stress-associated activation of the UPR and proinflammatory signals, including induction of class II HLA expression (important for antigen presentation to CD4 T cells) (77), as well as IL-6 and IL-8 production (67, 78).

Innate immune activation as a bridge between cellular stress and adaptive immunity

Innate immunity evolved as a rapid protective response against pathogens and requires recognition of “danger signals” present during infection. This recognition is dependent on innate pattern recognition receptors (PRRs) and their ability to identify pathogen-associated molecular patterns (PAMPs). Toll-like receptors (TLRs), which are membrane-bound, were the first PRRs to be described. Some TLRs are located on the cell surface, while others are located inside the cell, within endosomes. Nucleic acid PAMPs (viral RNA, bacterial DNA, etc) are sensed by endosomal TLRs and other receptors that induce the activation of NF- κ B and downstream gene transcription. In contrast, cytoplasmic receptors like NOD-like receptors (NLRs) and AIM2 induce the assembly of inflammasomes, which require initial activation of the receptor and recruitment of the adaptor ASC, followed by recruitment and activation of caspase 1 and cleavage of pro-IL-1 β and pro-IL-18 into active, secretable forms (79-81).

In addition to defense against pathogens, PRRs are involved in sterile inflammation, including anti-tumor responses, crystal-induced inflammation (i.e. asbestos, Alzheimer’s disease, and gout), and autoimmunity (15). Therefore, they recognize not only PAMPs, but non-pathogen associated patterns as well, including altered self-molecules that are released following cellular damage, referred to as damage-associated molecular patterns (DAMPs). As mentioned above, ROS is generated by stressed melanocytes, and HSP70 is released to activate dendritic cells in co-culture. HSPs reportedly activate TLR2, TLR4, and other PRRs (81), and the NLRP3 inflammasome is activated by ROS and mitochondrial stress (82, 83). Thus chemical-induced stress may induce inflammation through innate receptors (84). In addition, natural killer (NK) cells, macrophages, and inflammatory dendritic cells infiltrate lesional skin in vitiligo (45, 64, 85), reflecting innate immune activation and response during

disease progression. NLRP1 activation and IL-1 β production are increased in subjects that are homozygous for the NLRP1 risk haplotype, and both have been associated with progressive vitiligo in patients without clear chemical exposures, suggesting that innate immunity plays a role in non-chemically induced disease as well (86, 87). Since innate immune cells release cytokines and chemokines that promote T cell recruitment to peripheral tissues, innate immunity may serve as a bridge between cellular stress and T cell-mediated destruction in vitiligo (84).

Similarities between vitiligo and a subset of other organ-specific autoimmune diseases

In vitiligo, melanocytes are specifically targeted for destruction, resulting in a loss of pigment that becomes clinically apparent in the skin as white spots. This process typically spares other nearby cell types, and is asymptomatic, likely due to the fact that it targets specific antigens and the effector cells are CD8⁺ cytotoxic cells capable of single cell destruction. This is in contrast to other more inflammatory diseases, like psoriasis and cutaneous lupus, which damage multiple cell types and result in pain or itch, redness, and scaling of affected skin. An analogy might be the difference between the targeted killing performed by a sniper, without harming bystanders, versus dropping napalm, a non-targeted approach with significant, widespread damage. The “sniper” approach in vitiligo is also seen in a subset of other organ-specific autoimmune diseases that result in selective destruction of a particular cell type and are asymptomatic, resulting in a loss of function that becomes clinically apparent. These types of autoimmune diseases include type 1 diabetes, Hashimoto’s thyroiditis, multiple sclerosis, pernicious anemia, and Addison’s disease, many of which are more common in vitiligo patients and their families, and share genetic risk alleles with vitiligo (22).

The targeted autoimmune diseases affect highly secretory cell types: type 1 diabetes targets insulin-secreting β -cells, Hashimoto’s thyroiditis targets thyroid hormone-producing thyrocytes, multiple sclerosis targets myelin basic protein-producing Schwann cells, pernicious anemia targets intrinsic factor-producing gastric parietal cells, and Addison’s disease targets steroid hormone-producing cells of the adrenal cortex. Each β cell is estimated to produce about one million molecules of insulin every minute (88), which reflects the tremendous amount of work required by secretory cells, and the amount of energy expended. Targeting of specific cell types during organ-specific autoimmunity may be due to the cellular stress that results from energy consumption and ROS generation required to produce large amounts of protein, as well as the inevitable protein misfolding and UPR activation that occurs as a result. The following sections will discuss existing evidence for a role of cellular stress and innate immunity in the initiation of other organ-specific autoimmune diseases, and unique contributions each makes to our larger understanding of cell stress in autoimmunity. For example, type 1 diabetes is largely influenced by insulin misfolding, Hashimoto’s thyroiditis is partly induced by chemical exposure, multiple sclerosis is associated with mitochondrial damage, and inflammatory bowel disease can be driven by genetic influences on the UPR. The majority of this knowledge is drawn from translational and clinical studies using patients and their tissues, and gaps in knowledge for diseases that are more challenging to study may be filled from our understanding of vitiligo pathogenesis.

Type 1 diabetes

Type 1 diabetes is also a cytotoxic, CD8⁺ T cell-dependent organ-specific autoimmune disease in which T cells infiltrate the pancreas and islets, destroying insulin-producing β cells (89, 90). Like vitiligo, IFN- γ and CXCL10 are expressed in affected human islets, and are functionally required in mouse models of disease (91, 92). Also similar to vitiligo, β -cells from patients possess an activated UPR (93, 94). In addition, UPR activation in β -cells is associated with the production of innate cytokines, although it is currently unknown whether this is a cause or an effect of inflammation (95). However *in vitro*, initiation of the UPR in human β -cells by thapsigargin resulted in the activation of thioredoxin-interacting protein (TXNIP), which itself triggered the innate PRR NLRP3 (96, 97). In addition, type 1 diabetes patients are prone to innate inflammation, suggesting a hypersensitivity toward PRRs, however the details concerning which innate immune subsets are activated and how they become activated in type 1 diabetes is not clear (98). Translational research in type 1 diabetes is difficult, due to the fact that the autoimmunity is largely complete at the time of diagnosis, and that the pancreas, the site of autoimmune attack of β -cells, is inaccessible to tissue sampling except postmortem (98). Thus, the relationship among ROS, UPR, innate inflammation, and adaptive immunity in type 1 diabetes is still unclear, and progress in the understanding of these processes may be better understood in the context of organ-specific autoimmune diseases like vitiligo, which are easier to study using a translational research strategy.

GWAS in type 1 diabetes have identified 55 individual susceptibility loci in addition to HLA alleles, which include genes associated with both adaptive and innate immunity (98, 99), similar to vitiligo (4). Like vitiligo, in which melanocyte-specific proteins also appear as risk alleles, one of the most prominent risk loci in type 1 diabetes is insulin (99). Insulin is produced in β -cells by proteolytic cleavage of its precursor, proinsulin, which itself is produced following cleavage of preproinsulin. Proinsulin is prone to misfolding in the endoplasmic reticulum – it is estimated that up to 20% of newly synthesized protein fails to fold properly. Under circumstances where misfolding is increased, the UPR may be activated, and thus contribute to β cell stress, autophagy, and damage (100). For example, in Mutant INS-gene induced Diabetes of Youth (MIDY), individuals inherit any of a number of mutant forms of proinsulin, which result in very early onset of diabetes. These mutations are inherited in a dominant fashion, suggesting that the MIDY results from a gain-of-toxic function of proinsulin. Most of these mutations (>70%) are thought to be due to misfolding of the affected proinsulin in the endoplasmic reticulum, activating the UPR and resulting in β cell apoptosis and death (101). While this process appears to be directly cytotoxic to the β -cell in MIDY, it is plausible that more mild forms of proinsulin misfolding, either due to subtle mutations or increased demand for production, activate the UPR and subsequent innate inflammation to induce autoimmunity (102), as seen in vitiligo.

Similar to vitiligo, genetics can be attributed to only part of the risk, while environmental factors are thought also to contribute, and possibly may be responsible for the increase in incidence. While viral infections are assumed to play a major role in environmental risk for type 1 diabetes, specific examples in humans have remained elusive (99). It is possible that,

like vitiligo, chemical exposures predispose β -islets to stress and inflammation, but examples have not yet been identified.

Hashimoto's thyroiditis

Despite their prominence as possibly the most common autoimmune diseases in the population (103), relatively little is known about the pathogenesis of autoimmune thyroid diseases, which generally include Hashimoto's thyroiditis and Graves' Disease (104). While Graves' Disease is autoantibody-driven, Hashimoto thyroiditis is T cell-mediated and, like vitiligo, is correlated with the expression of IFN- γ and CXCL10 (104). It is currently unclear whether CD4⁺ T cells, CD8⁺ T cells, or both are required for disease progression (104). Innate immune activation is suggested by increased TLR expression in affected thyroid tissue, although the significance of this expression has not been determined (105). In comparison to other organ-specific autoimmune diseases, GWAS are more limited, but reveal key genes linked to adaptive immunity, including those shared with vitiligo and other autoimmune diseases, like PTPN22, CTLA4, IL2RA, BACH2, and RNASE2. Importantly, thyrocyte-specific genes have also been implicated, including the thyroid stimulating hormone receptor (TSH) and possibly thyroglobulin (104, 106, 107).

Like other organ-specific autoimmune diseases, Hashimoto's thyroiditis has a genetic component, although environmental factors also play an important role, as monozygotic twin concordance is 30-60% (108, 109). One of the environmental risk factors for developing Hashimoto's thyroiditis is the ingestion of iodine, particularly in populations that were previously iodine-deficient (110, 111). The incidence of thyroiditis has increased with progressively increased iodine in the diet. In one study, restriction of dietary iodine reversed hypothyroidism in over half of patients, while re-exposure to dietary iodine resulted in relapse (111). The importance of dietary iodine as a risk factor for disease has been mechanistically supported in animal models of the disease, where the onset of autoimmune thyroiditis is precipitated and accelerated by the ingestion of iodine (110), which is associated with increased production of ROS, and antioxidants are able to prevent iodine-induced disease (110).

In human thyrocytes, ROS are generated as a normal consequence as iodine is added during the production of thyroglobulin. Iodine exposure may result in decreased or increased thyroglobulin production (depending on underlying thyroid function) and associated ROS, leading to lipid peroxidation and modification of thyroglobulin itself, which may increase its antigenicity (107, 111). Iodine-exposed thyrocytes also express a number of inflammatory cytokines and other markers, and may become damaged from iodine-induced ROS, releasing DAMPs capable of activating innate immunity (105, 110, 111). While iodine exposure can induce thyrocytes to alter their production of thyroglobulin both in quantity and quality (107), it is unclear whether this leads to activation of the UPR, as in β -cells when they increase production of insulin. The details concerning how iodine exposure, ROS, innate inflammation, and adaptive immunity connect in Hashimoto's thyroiditis are not yet known. However the parallels with chemical-induced vitiligo may help inform our understanding of environmental exposures in the induction of autoimmune thyroiditis.

Multiple Sclerosis

Multiple sclerosis is a disease of weakness, and potentially paralysis, due to loss of myelin in the brain, possibly through direct destruction of myelin-producing cells. Weakness may be progressive, relapsing and remitting, or stable, depending on the patient. Like T1D, autoimmunity in multiple sclerosis is challenging to study in humans due to the difficulty in obtaining samples of brain from patients during ongoing disease. Current data is limited to tissue from autopsy, sampling of cerebrospinal fluid (CSF), and animal models. There appears to be a T cell infiltrate within active lesions that consists of both CD8⁺ and CD4⁺ T cells (112), like other diseases discussed above. IFN- γ and IFN- γ -induced chemokines have been implicated in disease pathogenesis (113), and IFN- γ administration results in worsening symptoms in MS patients (114).

IL-17 has been suggested as an important player as well, observed in human tissues and important in experimental autoimmune encephalomyelitis (EAE), a mouse model of disease. One hypothesis is that pathogenic T cells produce both IFN- γ and IL-17, and that the cytokines synergize during inflammation to induce tissue damage and lesion formation (113). Future studies to test IL-17 neutralizing antibodies may help to reveal the role of IL-17 in human disease. Active demyelination is always associated with inflammation, and the severity of pathology correlates with degree of T cell infiltrate (115). However since strong evidence of cellular stress exists in multiple sclerosis, whether inflammation is a cause or effect of tissue damage has been debated (112, 116), as done previously in vitiligo (21). Lessons from vitiligo suggest that inflammation is responsive to cellular stress, and that inflammation is indeed pathogenic. GWAS in multiple sclerosis support T cell-mediated mechanisms in disease susceptibility (117).

Like vitiligo, cellular stress is also strongly implicated in the pathogenesis of multiple sclerosis (112). ROS is generated within neurons following their activation by glutamate and other ionotropic receptors (118). Increased free radical activity and decreased antioxidant activity is reported in lesional plaques (119), and oxidized DNA and lipids appear to be increased in affected neurons (120, 121). As in vitiligo, HSP70 is suggested to contribute – HSP70-myelin basic protein fusions have been described (122), which may act as neoantigens for autoreactive T cells, or may activate dendritic cells or other cell types to become proinflammatory (113). Gene expression studies in multiple sclerosis lesions reveal increased expression of components of the UPR, although this was thought to be primarily in microglia, rather than neurons, and further details about UPR involvement in multiple sclerosis are still lacking (123, 124). Innate immunity has been partially implicated in MS pathogenesis as well, suggested by elevated TLR expression within lesions and expression of NLRP1 in neurons (125, 126). However the administration of IFN- β , an innate cytokine, has been somewhat effective as a treatment for multiple sclerosis (127), possibly by attenuating the activation of NLRP1 and NLRP3 inflammasomes, and subsequent release of IL-1 β (128).

One unique contribution that understanding the pathogenesis of multiple sclerosis contributes to this topic is the role of mitochondrial damage, which has been demonstrated to cause degeneration of axons in the brain. In patients with progressive multiple sclerosis,

neurons in areas without inflammation contained mitochondrial abnormalities, including oxidative damage to mitochondrial DNA (mtDNA) and enzymes (129), as well as mutations in mtDNA with an apparent clonal expansion of mitochondria with specific mutations (130). Mitochondrial injury results in decreased energy production, and the release of ROS, both of which are damaging to highly active cells like neurons (112). Damaged mitochondria, and in particular membrane alterations, can initiate autophagy (10). Mitochondrial membrane alterations have been described within melanocytes from vitiligo patients (37), and mitochondria may be the source of ROS in vitiligo. Whether specific mutations in mtDNA occur and are propagated in vitiligo, and whether they contribute to disease pathogenesis, is worth exploring further.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is mediated by uncontrolled inflammation targeting the intestinal epithelium, which typically results in diarrhea and abdominal pain. It can present as broad, shallow ulcers and primarily affect the colon, labeled as ulcerative colitis, or with deep fissures and affect the small intestine and/or colon, labeled as Crohn's disease. Translational studies suggest a complex pathogenesis that may involve defective barrier function of the intestinal epithelium, an influence of colonizing microbes, a hyperactive T cell response, dysregulated innate immunity, and alterations in cellular stress and autophagy (10, 131-133). GWAS in Crohn's disease reveal a significant association with *Nod2* and *Atg16L1* genes, which play important roles in innate immune signaling through the inflammasome and autophagy, respectively (134-136).

Compared to the organ-specific autoimmune diseases described above, it is less clear that CD8⁺ T cells are the primary effectors, and whether a single cell type is targeted or whether generalized inflammation against microbes is the primary response. Analysis of T cells infiltrating the intestinal epithelium during active disease suggest a dual contribution of Th1-type and Th17-type cytokines, including IFN- γ and IL-17, in Crohn's disease (137), and Th2-type cytokines (particularly IL-13) in ulcerative colitis (138). However, targeting either IFN- γ or IL-17 in Crohn's disease or IL-13 in ulcerative colitis failed to show efficacy in early clinical trials (139-141), while TNF- α targeting has met with some success in both (142). This may indicate that innate inflammation through TNF- α plays a critical role in disease pathogenesis, or that multiple pathways are either redundant or synergize to drive the pathology. It's possible that different microbes drive different inflammatory pathways, resulting in mixed inflammation that will be difficult to target with a single therapy (131). Thus, IBD appears to stray from the prototypic pathogenesis described above for vitiligo, thyroiditis, type 1 diabetes, and multiple sclerosis.

However one recent observation concerning the role of the UPR to maintain intestinal homeostasis and prevent inflammation may contribute some understanding about the interface between cellular stress and innate immunity. Hypomorphic variants of *Xbp1*, a member of the UPR that normalizes the stress response, were found to confer risk for IBD in humans (143). The intestinal mucosa of patients with disease exhibit signs of elevated ROS and endoplasmic reticulum stress when compared to healthy controls, even in noninflamed tissue, supporting a role for the stress response in the pathogenesis of IBD in human patients

(14, 144). Consistent with this hypothesis, induction of endoplasmic reticulum stress within the intestinal epithelial cells of mice via a targeted deletion of *Xbp1* induced spontaneous enteritis targeting these cells, and also increased susceptibility to experimental colitis (143). Adding defective autophagy to impaired UPR results in a synergistic effect, as mice lacking both *Xbp1* and *Atg16L1* specifically in Paneth cells have severe, Crohn's disease-like inflammation (145). Additional studies in mice report spontaneous intestinal inflammation resulting from other protein folding abnormalities that induce endoplasmic reticulum stress in intestinal mucosal epithelium (14). Since *Xbp1* is also a risk factor identified in vitiligo GWAS (4), these observations suggest that the UPR, and cellular stress in general, may be an important contributing factor during the initiation of organ-specific autoimmune inflammation.

Conclusions

Organ-specific autoimmune diseases, in particular the asymptomatic, cell-targeted diseases of secretory cells like vitiligo, type 1 diabetes, Hashimoto's thyroiditis, multiple sclerosis, and possibly inflammatory bowel disease, seem to require tissue-specific signals in order to initiate autoimmunity. Cell stress and innate inflammation appear to play a key role in this tissue-specific initiation event, and this is summarized in Fig. 2 and Table 1. The pathogenesis of vitiligo has been investigated using translational approaches for over 30 years, and lessons learned in vitiligo may help to inform investigation of similar autoimmune diseases that are more difficult to study in humans and their tissues.

An understanding of vitiligo pathogenesis provides important insight into three questions concerning the pathogenesis of autoimmunity: 1) Initiating factors: The presence of elevated cell stress in cultured melanocytes, which are separated from immune influences, supports the hypothesis that stress can be a cause of inflammation as well as a result of it. While its presence does not prove causality, the fact that stress-inducing chemicals like monobenzene and 4-TBP can initiate disease in an otherwise unaffected individual does suggest that stress within a cell can be an initiating factor. 2) Tissue specificity: Melanocytes and other secretory cells are particularly susceptible to cellular stress due to production of large amounts of protein. In addition, the propensity for risk alleles of tyrosinase (76) and insulin (146) to misfold presents another reason why melanocytes or β -cells could become specific targets. Because vitiligo-inducing chemicals require tyrosinase, a melanocyte-specific enzyme, to activate the stress response, they reveal that environmental factors can be responsible for tissue specificity. 3) Connecting stress and inflammation: Vitiligo reveals that cellular stress can initiate autophagy, promote the release of proinflammatory HSP70 and antigen-carrying exosomes, and induce the XBP1-dependent secretion of IL-6 and IL-8. The contribution of cell stress mechanisms to autoimmunity is garnering increased attention, but will require many more studies in both patients and animal models to fully understand its role.

Therapeutic targeting of cellular stress has been attempted in autoimmunity, however this approach has been largely disappointing. Topical pseudocatalase has been tested in vitiligo to normalize melanocyte stress, but has not been consistently shown to benefit patients (43). Oral antioxidants have also been tested in a small number of vitiligo patients in conjunction

with other established therapy, with only modest improvement (147). Clinical trials to test oral antioxidant supplementation for multiple sclerosis had no effect on disease severity (118). Superoxide dismutase mimics reduce damage from ROS free radicals, and reportedly increase survival of human islets *in vitro*, and also reduce the incidence of diabetes in a mouse model (148, 149). An inhibitor of UPR activation reportedly reduced the incidence of diabetes in mouse models (94). A number of other small molecules have been developed that target the UPR, and have been proposed as potential treatments for autoimmunity. However the ubiquitous role that the UPR plays in tissue homeostasis, particularly in secretory organs, suggest severe side effects from such treatment (150). Chemical modulators of autophagy have been identified, including the immunosuppressive drug rapamycin, however clinical studies to determine their effects on autoimmunity are lacking (10). It is unclear whether normalizing cell stress will be an effective therapy after autoimmunity is initiated, or whether stress is solely an initiating event, and thus dispensable during progression. Further studies to test this strategy in autoimmune patients after disease onset will be required.

While this review has focused largely on cell stress and innate inflammation in organ-specific autoimmunity, T cells appear to drive the progression of disease, and therefore cellular stress and innate inflammation must eventually lead to the priming and activation of adaptive immune cells. This is typically thought to occur within tissue-draining lymph nodes, and thus long-distance communication from the tissue to the lymph nodes is necessary, most likely through emigration of innate cell populations like macrophages or dendritic cells that carry tissue-specific antigens, activated by DAMPs that are released during cellular stress. There is currently little known about how and where the stress-innate-adaptive interface lies, and this will be an important focus for future studies.

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Figure 1.
Patchy depigmentation of the skin is characteristic of vitiligo.

Figure 2. Initiation of autoimmunity through the stress-immune interface

Secretory cells produce large amounts of protein, which requires energy and releases ROS as a byproduct. ROS may originate in mitochondria and damage mitochondrial DNA and membranes. The risk of protein misfolding correlates with increased protein production and the presence of intracellular ROS. Protein misfolding activates the UPR, which may initiate autophagy and stimulate the production and secretion of exosomes or other proinflammatory molecules. Exosomes contain cell-specific antigens and DAMPs, which are absorbed by nearby dendritic cells and mature them into efficient stimulators of autoreactive T cells, resulting in T cell priming and ultimate induction of cell-specific autoimmunity. Chemical exposures and genetic factors modulate these pathways, and thus influence the predisposition to develop autoimmune diseases.

Table 1
Comparison of risk factors and pathogenesis of vitiligo and other organ-specific autoimmune diseases

Vitiligo, type 1 diabetes, Hashimoto’s thyroiditis, multiple sclerosis, and inflammatory bowel disease are compared in light of relative genetic and environmental contributions, their target cells, and the role of ROS, the UPR, autophagy, innate immunity, and effector T cells in their pathogenesis. Unique contributions of each disease to our understanding of the role of cell stress in disease induction are included. Red shaded cells highlight aspects of disease pathogenesis that are currently unknown.

Disease	genetic %	environmental exposures	Target cell	protein produced	Pathogenesis					CD8 T cells	Unique features
					ROS	UPR	autophagy	exosomes	innate immunity		
vitiligo	23%	Yes (phenols)	melanocyte	melanin	Yes	Yes	Yes	Yes	Yes	Yes	best understood
type 1 diabetes	50%	unknown	beta-cell	insulin	Yes	Yes	unknown	unknown	Yes	Yes	protein misfolding
Hashimoto’s thyroiditis	30-60%	Yes (iodine)	thyrocyte	thyroid hormone	Yes	unknown	unknown	unknown	Yes	Yes	iodine exposure
multiple sclerosis	25%	unknown	Schwann cell	myelin	Yes	Yes	unknown	unknown	Yes	Yes	mitochondrial defects
inflammatory bowel disease (Crohn’s/UC)	58/6%	unknown	unknown	unknown	unknown	Yes	Yes	unknown	Yes	unknown	XBP1/UPR