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The kaleidoscope of autoimmunity – From genes to microbiome

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Close to 30 years ago we [Y.S. et al.] [1] came up with the notion that autoimmune diseases share a common background which they had termed the *mosaic of autoimmunity*. The various features of this background known already at that time were genetic, hormonal, environmental and immune system defects which are shared by many of the autoimmune diseases, and were thus termed as the *mosaic of autoimmunity* meaning that re-arranging factors known to be involved in the induction of autoimmune diseases, will lead to different patterns of diseases or different diseases. These various common factors involved in the induction of autoimmune diseases, obviously require a trigger mechanism in order for the disease to break out. Such triggers could be a drug, various environmental exposures both physical and chemical, with the major cause related being to various infections [2,3]. These are believed to trigger autoimmunity *via* few mechanisms such as molecular mimicry in the case of rheumatic fever, or *via* the induction of polyclonal activation or *via* changes in the gene function in the case of EBV or CMV related autoimmunity. Later on, some 25 years ago we (Y.S.) further described the phenomenon of shifts in autoimmune diseases, which we had termed the *Kaleidoscope of Autoimmunity* [4,5]. One of the long-known examples is that of Rhupus described by Panush who described the coexistence of features of both rheumatoid arthritis (RA) along with those of systemic lupus erythematosus (SLE) [6]. At times these patients make a full transition from one disease to the other. For example, primary antiphospholipid syndrome (APS) which was induced in a patient with myasthenia gravis two years following thymectomy [7], or two cases of immune thrombocytopenia (ITP) which developed chronic active hepatitis following a successful splenectomy which led to a complete recovery from the ITP [5]. This phenomenon of switching from one disease to another autoimmune disease in the same patient has since been described by many others, using the same terminology [8-10]. Other examples include scleroderma, mixed connective tissue disease (MCTD) and SLE, autoimmune thyroid disease and SLE, pernicious anemia and SLE, celiac and SLE, multiple sclerosis and SLE, myasthenia gravis and SLE as well as other combinations [11]. Occasionally drugs being used for one indication lead to the development of another autoimmune disease for example D-penicillamine which has been used in the past as a therapy for scleroderma, rheumatoid arthritis and Wilson's disease, and has been associated with the induction of lupus like syndromes. Thus, neutralizing an immune-related organ led to the cure of one autoimmune disease but to the emergence of another, apparently unrelated, second autoimmune disease. The introduction of biologics as treatment of many autoimmune diseases in the past 20 years has brought about similar phenomena of *de-novo* emergence immunogenicity of another disease. TNF-inhibitors in rheumatoid arthritis have been involved with new cases of SLE or SLE-like diseases as well as new onset of psoriasis [12]. Oter-Lopez et al. described a significant increase in ANA positivity during treatment of moderate-to-severe psoriasis patients with adalimumab or etanercept. This was however not associated with the onset of an autoimmune disease [13]. Ramos-Casals and coworkers described 77 cases of RA patients who did involve into SLE or SLE-like disease following 41 weeks of anti-TNF therapy [14]. The lupus-related manifestations improved however following discontinuation of the treatment with these agents and replacing them by other immunosuppressive agents. These authors later reviewed the literature for all autoimmune diseases induced paradoxically by treatment with anti-TNF agents, and found more than 50 different such systemic and organ-specific autoimmune processes, including *de-novo* psoriasis in patients being treated by TNF-

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inhibitors, the paradoxical induction of uveitis and inflammatory ocular diseases, autoimmune hepatitis, interstitial lung disease, demyelinating CNS involvement as well as peripheral neuropathies, vasculitis, sarcoidosis, inflammatory bowel disease, antiphospholipid syndrome and other autoimmune diseases [15,16]. Recently these authors have further updated their findings based on the BIOGEAS registry which was able to collect information of nearly 13,000 reported cases of autoimmune diseases developed in patients exposed to biologics including anti-TNF agents, immune checkpoint inhibitors, B-cell targeted therapies and growth factor inhibitors [17]. Based on their findings the authors calculated that an unexpected autoimmune disease may arise in around 8 out of 10,000 exposed patients.

Other features of the *Kaleidoscope of Autoimmunity* include the occurrence of multiple autoimmune diseases in one patient as well as the familial autoimmunity, both also described by us and others [18–20]. Examples of these include the co- occurrence of SLE and Hashimoto's thyroiditis, SLE and myasthenia gravis, Sjogren's syndrome with multiple autoimmune diseases, progressive systemic sclerosis and polymyositis, or primary biliary cirrhosis well as many other similar associations.

This phenomenon of familial autoimmunity as well as the occurrence of multiple autoimmune diseases in the same patient has drawn the attention to the genetics of autoimmune diseases as well as to the gene-environment interaction in the pathogenesis of autoimmunity. Autoimmune diseases are characterized by dysregulation of the normal immune response leading to autoantibody production followed by the systemic features of inflammation. Diseases which are antibody-mediated autoimmune diseases such as SLE, rheumatoid arthritis, Crohn's disease and type 1 diabetes, have been shown to cluster more closely with each other as opposed to autoantibody-negative diseases such as psoriasis, psoriatic arthritis, and ankylosing spondylitis, which instead, form a sero-negative cluster [21]. Familial autoimmunity could arise as a result of shared genetic or environmental susceptibility factors. Known such environmental factors thus far include cigarette smoking, gender, microbiota and infections, alcohol silica and others [22]. Obviously, such environmental risk factors may trigger the onset of autoimmunity in genetically susceptible individuals. All autoimmune diseases have been linked to genetic susceptibility and these genetic risk factors have been shown to overlap and are shared between different autoimmune diseases or are specific to a given disorder. Thus combinations of human leukocyte antigen (HLA) system alleles and alleles of non HLA genes, in interaction with other factors such as epi-genetics and environment, can determine the specific autoimmune phenotype over time [23]. It has been shown that specific polymorphisms in the *HLA-DRB1* are shared between more than one autoimmune disease, namely the allele *DRB1*04:01* is a strong risk factor for rheumatoid arthritis (RA) in multiple populations, as well as for type 1 diabetes mellitus (T1D), whereas *DRB1*03:01* has been shown to be associated with T1D, systemic lupus erythematosus (SLE) and Sjogren's syndrome, and *DRB1*04:05* with T1D, RA and autoimmune hepatitis [24]. Though SLE has been shown to be associated with the HLA system, other genetic associations have been shown to be linked to few autoimmune diseases. A single nucleotide polymorphism (SNP) in the protein tyrosine phosphatase N22 (*PTPN22*) was shown to be associated with SLE, TD1, RA, Graves' disease, Hashimoto's thyroiditis, idiopathic inflammatory myopathy, systemic sclerosis, autoimmune Addison's disease, juvenile idiopathic arthritis, and myasthenia gravis [25,26]. This individual SNP is one of the most strongly associated autoimmune risk variants after the HLA class II. Other genetic associations with autoimmune diseases include the Toll-like receptors (TLRs), which represent a family of pattern recognition receptors, involved in the recognition and defense of the host from invading microorganisms. Although the TLRs are involved in the protection of the host, increasing evidence supports a correlation between the presence of altered TLR expression and their critical role in the activation of immune-mediated tissue damage followed by the development of autoimmune diseases (27 l). SNPs or copy number variations in the TLR genes or in molecules involved in TLR signaling, have been shown to occur in T1D, RA, SLE, systemic sclerosis, multiple sclerosis, vitiligo, myasthenia gravis, Crohn's disease as well as in other autoimmune disease [27] (Fig. 1).

We have recently added the intestinal microbiome to the puzzle of the *Kaleidoscopic of autoimmunity* [28]. Various bacteria posses the ability to shape our immune network, and it is now believed that the microbiome is a major trigger of autoimmunity in genetically predisposed hosts [29,30]. Multiple microbes are able to alter the immune response; however, it is already known that changing the microbiome composition may on the one hand attenuate the original disorder, but on the other hand may induce another immunological disorder [31]. For example, it has been shown in human studies involving multiple sclerosis patients (MS), that extraction and sequencing microbial DNA from fecal samples of these patients, revealed enrichment of *Akkermansia* in untreated MS patients' samples, when compared with healthy controls. However, upon immunomodulatory treatment of beta-interferon or glatiramer acetate, this relative abundance of *Akkermansia* had been decreased nearly to the level of the healthy controls [32]. Thus, immuno-modulatory therapy alters the microbiome composition changes related to MS, to a similarly normal microbiome. Similar observations were shown in other immune-mediated diseases such as T1D and inflammatory bowel disease [33,34]. On the contrary, though *Prevotella* has been found to be increased in feces samples of new-onset RA patients, rather than in chronic RA patients. It also was found to have opposite relations with MS and type I diabetes [33–35]. Enrichment of the *Prevotell*a genera, corresponded with disease-modifying treatments of MS along with amelioration of the disease [33,34]. Moreover, in type I diabetes patients, Prevotella's abundance was decreased, whereas healthy controls demonstrated higher proportion of this bacteria [33]. These observations, point to the fact that different abundances of the same bacteria can yield opposite outcomes in different autoimmune diseases and thus an attempt to treat an autoimmune disease *via* changes in the microbiome, may on one hand lead to attenuation of the original disorder, but on the other hand may induce another immunological disorder.

Thus the phenomenon of switching from one disease to another which was coined by us as the *kaleidoscopic of autoimmunity*, suggests that some autoimmune diseases are not induced by autoantigen-driven mechanisms, but rather result from immune dis-regulation.

The recent introduction of immune checkpoint inhibitors as of 2011, as a major breakthrough and the standard of care for the immunotherapy of various malignancies, has led to a dramatic improvement in the overall survival of many of these patients [36,37]. Two of the leading authors in this field have just received the Nobel Prize in Medicine - 2018 for their breakthrough findings of unleashing the body's immune system to treat cancer [38,39]. These agents increase the antitumor immunity *via* blocking intrinsic down-regulators of immunity such as cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and programmed cell death-1 (PD-1) or its ligand (PD-L1). PD-1 and its ligands, ie. PD-L1 and PD-L2, are among the key factors responsible for the inhibitory T cell signaling, mediating mechanisms of tolerance as well as providing immune homeostasis. Increasing evidence points to the fact that impaired PD-1:PD-L function plays an important role in many autoimmune diseases such as T1D, RA, SLE, systemic sclerosis, inflammatory bowel diseases, autoimmune hepatitis, Sjogren's syndrome and others. Thus, the introduction of immune checkpoint inhibitors as a standard of care for the immunotherapy of various malignancies, has brought about a large and expanding spectrum of autoimmune and systemic inflammatory toxicities and reactions, known as immune-related adverse events (irAEs) [40]. Among the so far approved immune checkpoint antibodies are Ipilumuab, an anti-CTLA-4 which was the first to be introduced and approved for unresectable or advanced metastatic melanoma, and metastatic NSCLC, followed by two antibodies against the PD-1 pathway (nivolumab and pembrolizumab) and the antibodies against PD-L1 (avelumab,

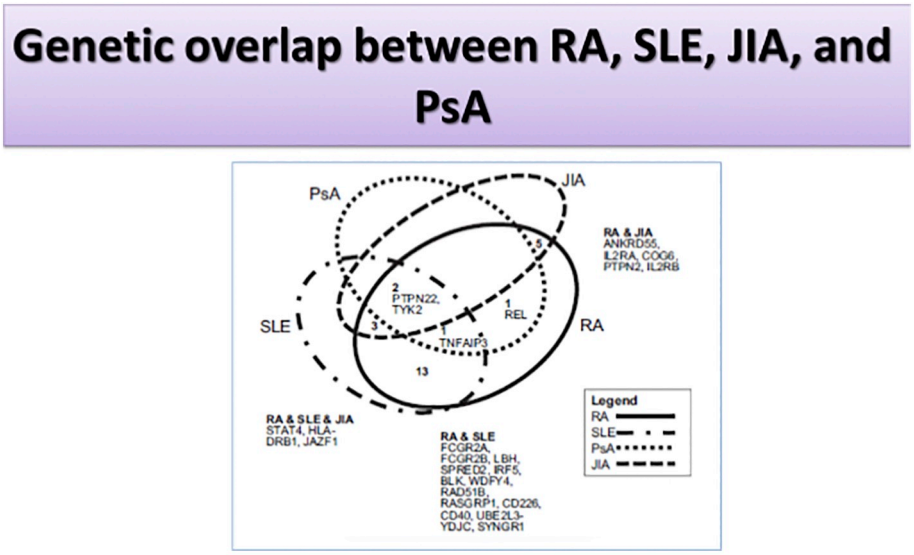

Fig. 1. Illustration of genetic overlap between four musculoskeletal immune-mediated inflammatory diseases (IMIDs), showing number of gene regions associated across two or more conditions with gene names listed.

atezolizumab, and durvalumab). All three groups of the immune-check point inhibitors are now approved for the treatment of multiple cancers. Nivolumab was approved for advanced melanoma, non-small cell lung cancer, classical Hodgkin's lymphoma, recurrent or metastatic head and neck squamous cell carcinoma, as well as for advanced RCC and bladder urothelial carcinoma. Pembolizumab was approved for renal cell carcinoma, head and neck cancer, Merkel cell carcinoma, refractory classical Hodgkin's lymphoma, and tumors of any organ with high microsatellite instability. Immune check-point inhibitors have also been used in combinations of either immunotherapy or with non-immunotherapeutic drugs.

Given the mechanism of action of the immunotherapeutic agents, who work in a variety of ways to block negative stimulatory signals which then increases the activation of T cells, causing a robust immune response against the malignant cells, it is not unexpected that these therapies are associated with a large and growing spectrum of autoimmune and systemic inflammatory toxicities and reactions known as immune-related adverse events (irAEs) [41–43]. These adverse events differ both in frequency and severity depending on the different agents as well as the affected organ. Distinct organ specific immune-related adverse events described thus far include colitis and enterocolitis, autoimmune hepatitis, pneumonitis, myocarditis, nephritis with renal dysfunction, endocrinopathies with hyperthyroidism and hypothyroidism, hypophysitis, hypogonadism, pancreatitis, primary adrenal insufficiency, and type 1 diabetes. Furthermore, various neurologic syndromes including myasthenia gravis-like syndrome, neuropathy, and transverse myelitis have been described as well as uveitis and episcleritis, and a growing spectrum of rheumatic irAEs. Among the diverse rheumatologic described side-effects are RA-like arthritis including both seronegative and RF and anti-CCP positive arthritis, psoriasis and psoriatic arthritis, Sjogren's syndrome, myositis and myalgia, lupus-like disease, scleroderma, polymyalgia rheumatic / giant cell arteritis, sarcoidosis and immune cytopenias. Other general adverse events related to immune activation, include fatigue, dermatitis with pruritus, rashes and vitiligo [40–43].

We propose the addition of the diverse irAEs of checkpoint immunotherapy to the *Kaleidoscope of autoimmunity* based on the shifts in the immune disease provoked by these agents leading to the emergence of an autoimmune disease while attempting to treat another disease.

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