Helminth therapy for organic diseases?

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Autoimmune and chronic inflammatory organic diseases represent a "postindustrial revolution epidemics," and their frequency has increased dramatically in the last century. Today, it is assumed that the increase in hygiene standards reduced the interactions with helminth parasites that coevolved with the immune system and are crucial for its proper functioning. Several helminths have been proposed and tested in the search of the ideal therapeutic. In this review, the authors summarize the translational and clinical studies and review the caveats and possible solutions for the optimization of helminth therapies. (Translational Research 2015;166:586–601)

Abbreviations: aaMac = alternatively activated macrophage; AR = allergic rhinitis; Arg = arginase; Asc = *A. suum* extracts; CD = Crohn disease; CIA = collagen-induced arthritis; CNS = central nervous system; DC = dendritic cell; DSS = dextran sodium sulfate; E/S = excretory/secretory products; IBD = inflammatory bowel disease; IFN-γ = interferon gamma; IL = interleukin; iNOS = inducible nitric oxide synthase; INS-GAS = male insulin gastrin; MIF = macrophage inhibitory factor; MOG = myelin oligodendrocyte glycoprotein; MR = mannose receptor; NKT = natural killer T cell; NO = nitric oxide; OVA = ovalbumin; PC = phosphorylcholine; RA = rheumatoid arthritis; STZ = streptozotocin; Th = T-helper cell; TLR = toll-like receptor; TNF = tumor necrosis factor; Treg = regulatory T cells; TSO = *T. suis* ova; UC = ulcerative colitis; TGF = transforming growth factor; CXCL = chemokine (C-X-C motif) ligand; MCP = monocyte chemoattractant protein; MS = multiple slcerosis; STAT6 = signal transducer and activator of transcription 6; MRI = magnetic resonance imaging; BALB/C = inbred mouse strain; TNBS = 2,4,6-trinitrobenzenesulfonic acid; SPF = specifiv pathogen free; ILC = innate lymphoid cells; CKBP = chemokine binding protein; K/BxN = mice expressing the KRN T cell receptor transgene and the MHC class II molecule Ag7; NF-κB = nuclear factor kappa B; DBA = mouse strain; MIP = Macrophage inflammatory protein; RANTES = regulated on activation, normal T cell expressed and secreted; UC = ulcerative colitis; SCCAI = simple clinical colitis activity index; PBMC = peripheral blood mononuclear cells; HLA-DR = human leukocyte antigen DR

HYGIENE AND THE "OLD FRIENDS" HYPOTHESIS

In the early years of the 19th century, industrialization led to a substantial improvement of the health system. At the same time, industrializing countries experienced a constant rise in the incidence of immunorelated disorders.[1] These disorders share a complex etiology and several genetic risk loci (Table I), suggesting a common etiology. The hygiene hypothesis suggests that modern hygienic standards reduced the exposure to stimuli that can prevent or reduce the severity of these disorders.[2] In particular, hygiene leads to the partial deprivation of microbial "old friends" that were previously abundant and shaped the evolution of the human immune system. Helminths are obvious "old friends candidates" that cause chronic carrier states or nonfatal subclinical diseases and need a customized immune response.

Two groups of helminths evolved zoo parasitism and were present during key periods in the evolution of the vertebrate immune system (Fig 1).[3,4] Platyhelminthes

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Table I. IBD risk loci shared with other immunorelated diseases

Disease	# Overlapping loci	Fold enrichment	Enrichment OR	95% CI	*P* value
Psoriasis	14	13.5	14.71	8.50–25.45	4.15×10^{-12}
Atopic dermatitis	3	12.1	12.32	3.93–38.62	2.05×10^{-3}
Rheumatoid arthritis	12	10.92	11.74	6.52–21.14	1.64×10^{-9}
Celiac disease	16	10.57	11.64	6.95–19.51	4.56×10^{-12}
Type 1 diabetes	20	9.99	11.28	7.06–19.03	2.35×10^{-14}
Multiple sclerosis	17	8.19	9.06	5.48–14.97	5.11×10^{-11}
Asthma	7	7.61	7.91	3.71–16.88	4.90×10^{-5}

Abbreviations: CI, confidence interval; IBD, inflammatory bowel disease; OR, odd ratios.
Adapted from: Jostins et al.[130]

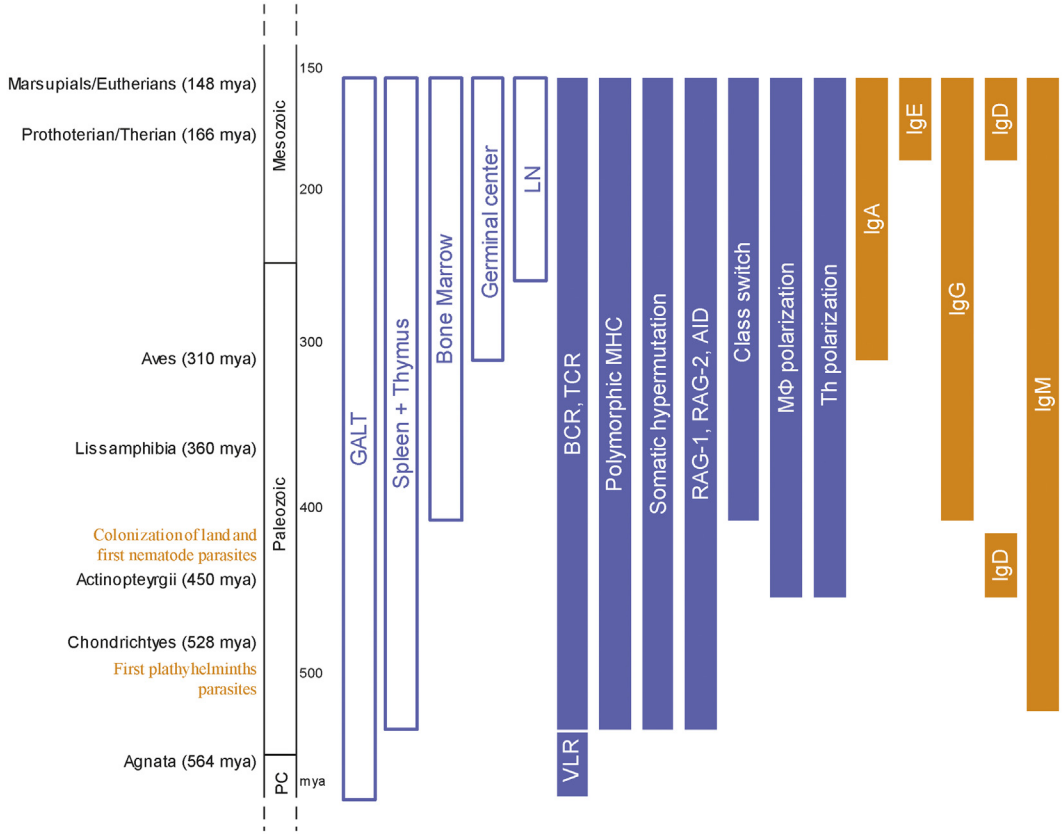

Fig 1. Milestones of the immune system evolution in vertebrates occurred in presence helminth parasites. AID, activation-induced cytidine deaminase; BCR, B cell receptor; GALT, Gut-associated lymphoid tissues; IgE, immunoglobulin E; LN, lymph nodes; MHC, major histocompatibility complex; PC, Precambrian; RAG, Recombination-activating gene; TCR, T-cell receptor; VLR, variable lymphocyte receptors. Adapted from Rook[5] and Litman et al.[3]

parasitism probably arose from a common parasitic ancestor in the first jawed fishes, whereas nematodes parasitism emerged independently at least 5 times in terrestrial vertebrates.[5] Helminths exerted a strong pressure on their host genome,[6] which led to the coevolution of an intricate host–parasite relationship where helminths assumed an essential role in the development of tolerance and immunoregulatory pathways.[5] The evolution of the T helper 2 (Th2) and regulatory T cells (Treg) subsets favors the persistence of the pathogen inside the host, avoids a destructive inflammatory response, and ensures a constant antigen source and