TLRs, DAMPs, PAMPs, and Muscle Injury: Newfound Explanations for Myositis

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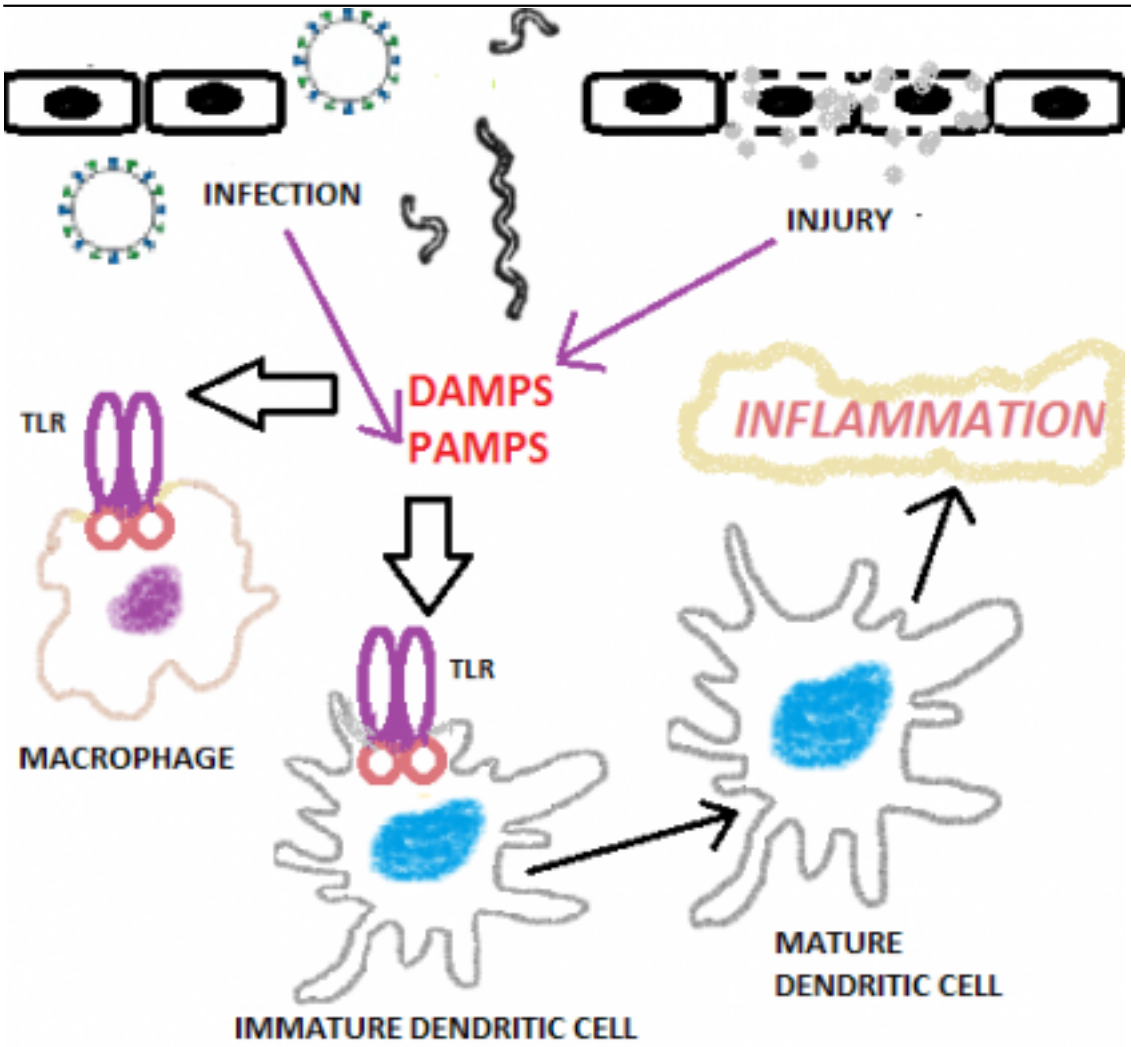
Polymyositis and dermatomyositis appear to be triggered by the response of certain receptors to danger signals from damaged cells. This offers a new avenue for treatments now in testing.
Source: Rheumatology Network

The toll-like receptors that identify danger signals from damaged cells may be keys to a destructive inflammatory response involving regenerating muscle fibers in forms of myositis. Drugs that suppress them offer a new approach to therapy. In brief, below, I review the basics.

1. Autoinflammatory diseases cause systemic inflammation due to problems in the innate immune system, the set of first-responders to infection that (such as neutrophils, macrophages, and natural killer cells). New auto inflammatory diseases are being identified with increasing frequency. Probably the best-known are the **periodic fever syndromes.** In recent years, **some evidence has suggested that** for **polymyositis (PM) and dermatomyositis (DM), disorders generally regarded as autoimmune (rheumatic) diseases,** due to a complex of innate and extrinsic factors **may share some aspects of their pathology with autoinflammatory conditions.**
2. Cells of the innate immune system identify pathogens by recognizing molecular patterns present in common to many types of pathogens, via pattern recognition receptors (PRR). The key PRRs that drive auto-inflammatory diseases are the **toll-like receptors (TLRs)**, which identify molecules common to bacteria, viruses, and parasites.
(There are other PRRs:
- NOD-like receptors or NLRs, which bind bacterial nucleotides;
- C-type lectin receptors or CLRs, which bind beta-glucans; and
- RIG-I-like receptors (RLRs), which bind nucleic acids.)
The focus here is on the role of TLRs in causing auto-inflammatory disease.
3. These PRRs recognize two kinds of molecular patterns: Structures common to proteins and nucleic acids present in or on **infectious organisms** (pathogen-associated molecular patterns or **PAMPS**) and molecules released by released by **dead and dying cells**, known as damage-associated molecular patterns (**DAMPS**) or “alarmins”. DAMPs include amyloid beta, saturated fatty acids, nucleic acids, and heat-shock proteins.
4. Binding of PAMPs or DAMPs to a TLR can lead to a self-sustaining autoinflammatory response. This:
- promotes the maturation of dendritic cells, whose main function is to prime and active T-lymphocytes
- can also directly promote the production of pro-inflammatory cytokines, via the nuclear factor kappa-beta pathway, the master controller of inflammation
- can also, in susceptible individuals, lead to the development of autoreactive T and B cells, promoting autoimmune disease. Besides activating effector T cells, they can also
- directly or indirectly modulate the function of regulatory T cells, breaking tolerance to self antigens.
Although usually associated with the innate immune system, some of these agonists are such powerful promoters of the adaptive immune system that they have been used as adjuvants in vaccines and cancer immunotherapy.



5. One of these agonists in particular, high mobility group box 1 (HMGB1), has been associated with autoimmune rheumatic disease. HGMB1 binds to nucleic acids and promotes their interaction with 3 TLRs (TLR3, TLR7, and TLR9). Concentrations of HMBG1 are **elevated** in the blood of patients with **systemic lupus erythematosus**[1] and in muscle cells as well as the interstitial space in **muscle from patients with myositis**.[2] Biopsies of skeletal muscle from **myositis** patients also show **significantly increased expression of TLRs** -2, -3, -4, and -9.

6. Considerable evidence implicates activation of TLR pathways and abnormal muscle cell regeneration after muscle injury in the pathogenesis of myositis.

- A mouse model of myositis (myosin-induced experimental autoimmune myositis or EAM) shows evidence for activation of TLR-4 and the inflammatory NF-kB pathway.[2]
- In humans, DAMPs appear to leak from injured skeletal muscle after exercise, thereby plausibly perpetuating an inflammatory response in susceptible individuals.[2]
- Muscle cell death is characteristic of PM and DM, and with the overexpression of autoantigens associated with RNA translation and chromatin remodeling (Mi2).[3]
- Muscle cell regeneration is a typical feature of inflammatory myositis. The specific expression of HLA class 1 antigens, myositis specific antigens, TLR3 and TLR7 by immature muscle precursors suggests a critical role for these cells in pathogenesis. Cytotoxic T cells triggered by TLRs responding to DAMPs after muscle injury may cause inflammation in these immature cells.[2,3]
- The abnormal accumulation of activated dendritic cells in muscle from patients with DM or PM reflects an ongoing local immune-mediated reaction that could lead to further muscle damage. This may explain both the defective repair in myositis and the observed autoimmune attack.[3]

7. TLR antagonists are a promising new avenue for myositis therapy. A new synthetic antagonist of TLR -7, -8, and -9, known to date only as IMO-8400, has been tested in preclinical

safety studies of autoimmune diseases including psoriasis, lupus, and arthritis. It is now in testing for PM and DM under a collaboration between the Myositis Association and Idera Pharmaceuticals.[4] Along with TLR-3 (which works by a different pathway), TLR-7 is the major toll-like receptor involved in inflammatory responses in myositis.

References:

1. Mills KH. TLR-dependent T cell activation in autoimmunity. *Nat Rev Immunol* (2011) 11:807-822. doi:10.1038/nri3095. Published online 18 November 2011

2. Rayavarapu S, Coley W, Kinder TB, Nagaraju K. Idiopathic inflammatory myopathies: pathogenic mechanisms of muscle weakness. *Skeletal Muscle* (2013) 3:13 doi:10.1186/2044-5040-3-13

3. Tournadre A and Miossec P. A critical role for immature muscle precursors in myositis. *Nat Rev Rheumatol* (2013) 9:438-442. doi:10.1038/nrrheum.2013.26 Published online 12 March 2013.

4. Partnership Formed for Development of Myositis Treatment. Press release. Myositis Association. August 7, 2014.

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