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Review

Animal models in idiopathic inflammatory myopathies: How to overcome a translational roadblock?

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ABSTRACT

Idiopathic inflammatory myopathies (IIMs) encompass a heterogenic group of rare muscle diseases with common symptoms including muscle weakness and the presence of certain histological features. Since the pathogenesis remains unclear, therapeutic approaches in general comprise unspecific immunosuppression strategies that have been met with limited success. Therefore, a deeper understanding of the underlying pathophysiological mechanisms is critically required to assist in development of targeted therapies. Animal models have proven to be tremendously helpful in mechanistic studies and allow researchers to overcome the inevitable restrictions of human research. Although the number of different IIM models has drastically increased over the last few decades, a model that exhibits the phenotypical and histopathological hallmarks of IIM is still missing. Recent publications have shown promising results addressing different pathophysiological issues like mechanisms of onset, chronification or relapse in IIM. However, a standardization of the methodology is critically required in order to improve comparability and transferability among different groups. Here we provide an overview of the currently available IIM models including our own C-peptide based small-peptide model, critically discuss their advantages and disadvantages and give perspectives to their future use.

Contents

Abbreviations: AD, Alzheimer's disease; AMPD, adenosine monophosphate deaminase; ANA, antinuclear antibodies; ANCA, anticytoplasmatic antibodies; AP-1, activating protein 1; APC, antigen presenting cell; APP, amyloid precursor protein; Aβ, amyloid β; BACE-1, β-APP cleaving enzyme 1; BiP, binding immunoglobulin protein; BMDC, bone marrow derived DC; *C. elegans*, *Caenorhabditis elegans*; CCL, C-C motif ligand; cdk5, cyclin dependent kinase 5; CFA, complete Freund's adjuvant; CHIKV, Chikungunya virus; CIM, C-protein induced myositis; CK, creatine kinase; CMMM, canine myositis of masticatory muscle; CP2, C-protein fragment 2; CPIM, C-protein peptide induced myositis; CPM, canine polymyositis; CVB, coxsackievirus B; CX3CL, chemokine C-X3-C motif ligand; CX3CR, chemokine C-X3-C motif receptor; Daf, decay accelerating factor; DC, dendritic cells; DM, dermatomyositis; dPGS, dendritic polyglycerol sulfate; EAE, experimental autoimmune encephalomyelitis; EAM, experimental autoimmune myositis; FOXP3, forkhead box 3; Grp78, glucose-regulated protein 78; GSK-3β, glycogen synthase kinase 3β; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HRS, histidyl transfer RNA synthetase; HSP, heat shock protein; i.m., intramuscular/ly; i.p., intraperitoneal/ly; i.v., intravenous/ly; ICAM-1, intercellular adhesion molecule 1; ICOS, inducible T cell costimulator; IIM, idiopathic inflammatory myopathies;; IVIG, intravenous immunoglobulin; KFL, Krüppel-like factor; *L. infantum*, *Leishmania infantum*; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; LT, lymphotoxin; Ly-6G, lymphocyte antigen 6 complex; *M. tuberculosis*, *Mycobacterium tuberculosis*; MAC, membrane attack complex; MB, myosin B fraction; MBL, mannose binding lectin; MCK, muscle creatine kinase; MCP, monocyte chemotactic protein; mer, monomer; MHC-I, myosin heavy chain I; MIF, migration inhibitory factor; MIP, macrophage inflammatory protein; MLC, myosin light chain; MPS, Methylprednisolone; mTOR, mechanistic target of rapamycin; MyD88, myeloid differentiation primary response gene 88, NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OLE, oleuropein aglycone; PBMC, peripheral blood mononuclear cells; PKM1/M2, pyruvate kinase M1/M2; PM, polymyositis; poly (I-C), polyinosinic:polycytidylic acid, PS1, presenilin-1; Ptx, pertussis toxin; Rag, recombination activating gene; rec., recombinant; ROS, reactive oxygen species; RRV, Ross River virus; RyR, ryanodine-receptor; s.c., subcutaneous/ly; sIBM, sporadic Inclusion body myositis; spCIM, small peptide CIM; SR, sarcoplasmic reticulum; Syt VII, synaptotagmin VII; ThS, thioflavin S; TLR, Toll-like receptor; TNF-Fc, TNF-α receptor fusion protein; TRE, tetracycline response element; Treg, regulatory T cell; TRIF, TIR-domain-containing adapter-inducing interferon-β; UPR, unfolded protein response; VCAM-1, vascular adhesion molecule 1; VLA-4, very late antigen-4.

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1. Introduction

Idiopathic inflammatory myopathies (IIMs) comprise a group of relatively rare muscle diseases (IIMs include dermatomyositis (DM), polymyositis (PM), sporadic inclusion body myositis (sIBM) and necrotizing myositis (NM)) that display heterogeneous clinical phenotypes and occur secondary to systemic disorders such as vasculitides or connective tissue disease [1–5]. The clinical characteristics of IIMs include progressive muscle weakness that is accompanied by intact sensitivity and tendon reflexes, muscle pain and elevated serum creatine kinase (CK) levels [1–3,6]. IIMs can be further distinguished by observing the pattern of affected muscles, patient's age at disease onset, additional involvement of organs, detected autoantibodies and response to treatment [1,3,4]. Diagnostic investigations frequently require electromyographic measurements and histological evaluation of muscle specimens [4,7].

Patients suffering from DM and PM predominantly present symmetric muscle weakness in the proximal parts of the extremities in an either chronically progressive or relapsing-remitting disease course [1,2,6,7]. DM is further characterized by additional skin alterations such as efflorescences, swelling, flush or telangiectasia and the increased coincidence of malignancies. Complement-mediated destruction of endomysial blood capillaries with autoantibodies directed against the endothelium is a pathological hallmark of DM. In response to antibody binding, an immunological cascade is triggered leading to the formation of membrane attack complexes (MACs). Histological stainings show a predominant presence of $CD4^+$ T and B lymphocytes in affected muscle specimens. Phenotypes including capillary necrosis, perivascular damage and loss of muscle fibers also correlate with the inflammatory response [1,2,4,6,8,9]. The progressive destruction of muscle fibers in PM is assumed to be mainly mediated by cytotoxic $CD8^+$ T cells that attack major histocompatibility complex (MHC) I expressing muscle fibers. Muscle biopsies from PM patients show an endomysial infiltration of $CD8^+$ T lymphocytes surrounding necrotic and non-necrotic muscle fibers [1–3,7,10].

Sporadic IBM starts by affecting the distal parts of the extremities and is accompanied by asymmetrically distributed muscle atrophy. In contrast to DM and PM, the pathophysiology is instead marked by the coincidence of neuroimmunological and neurodegenerative components whereby the causal link still remains unclear. Similar to PM, a predominant endomysial accumulation of $CD8^+$ T cells and the presence of necrotic muscle fibers are seen in immunohistological stainings. The neurodegenerative component is manifested by intracellular "rimmed vacuoles" consisting of aggregated misfolded proteins. Interestingly, as seen in Alzheimer's disease (AD), amyloid-related and hyperphosphorylated tau proteins are detectable in these pathognomonic aggregates [1,9,11]. Amyloid β (Aβ) has been proposed to be pathophysiologically relevant. Aβ is cleaved from the amyloid precursor protein (APP) by the β- and γ-secretase and is assumed to be (neuro)-toxic. In contrast, APP is cleaved under physiologic conditions by the a-secretase, releasing neuroprotective metabolites [12,13].

Despite the typical characteristics of different IIM subtypes, physicians struggle with the diagnosis due to inconsistent or overlapping histological and serological findings. A controversial debate has arisen concerning the diagnostic criteria proposed by Bohan and Peter almost 40 years ago [14]. Several adjustments have been made over the last few decades that suggest that common IIM subtypes should be diversified further into smaller entities characterized by specific hallmarks such as circulating antibodies or the presence of certain immunohistological features [15–18].

Although the incidence (1:100.000) of IIM is relatively low, affected patients suffer from onerous disabilities limiting quality of life and life expectancy. Up to now, causal and selective therapeutic concepts still show limited efficacy and severe side effects [9,19,20]. A better understanding of the underlying pathogenic mechanisms will enable novel therapeutic approaches emphasizing the necessity of intensified efforts in basic research of IIM. Although the usage of animal models in basic research has become a polarizing issue in societal debates, their value in the development and risk stratification of promising pharmacological approaches has been inevitably proven over recent decades [21,22]. Unfortunately, in the context of IIM, the variety and features presented by animal models are currently insufficient and lack the histological as well as phenotypic properties of IIM, hindering reproducibility and practicability [23,24]. Over the last 20 years, the number of publications referring to IIM has increased introducing different kinds of animal models with certain benefits and limitations (Fig. 1A–B). The range of animal models reaches from naturally occurring myositis to nutritional, transgenic, infectious and immunological models that mimic certain features of IIM first described by Wagner and Unverricht over a century ago (Fig. 1A, Tables 1 and 2) [25,26]. In this review, we will discuss important findings as well as advantages and disadvantages of different IIM models and provide perspectives to improve their relevance for translational research. Moreover, we demonstrate data on our own approach to establish a small-peptide mouse model of IIM.

2. Natural myositis in animals

Myositis in general is not exclusive to humans and can also occur in different species. Canine myositis has been investigated over the last 30 years and displays certain similarities to human IIM. Up to now, two types of canine myositis have been identified: a locally occurring form known as canine masticatory muscles myositis (CMMM) and a general form that symmetrically affects the extremities called canine polymyositis (CPM). Both types feature specific characteristics of IIM such as bilateral, symmetric generalized muscle atrophy and weakness, cutaneous lesions, electromyographic signs of myopathy (*e.g.* positive sharp waves, fibrillation potentials, high frequency discharges) and circulating immune complexes [27,28]. Recently, a member of the myosin binding protein-C family specifically expressed within and on the surface of masticatory muscle type 2M fibers was found to be responsible for the immune response in CMMM [29]. In addition to phenotypical differences, there are also histological differences that can be used to distinguish between CMMM and CPM. CMMM histologically resembles aspects of DM showing a predominant infiltration of both B and $CD4^+$ lymphocytes and an increased expression of MHC-II on the adventitia and endothelium of *endo*- and perimysial capillaries [30–32]. In contrast, CPM shows features of human PM where $CD8^+$ T cells predominantly infiltrate muscle fibers [30,31]. Shelton and colleagues investigated the expression of genes involved in innate and adaptive immunity in both CMMM and CPM specimens through microarray