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Review Article

MAMMALIAN MODELS OF PATHOGEN-ASSOCIATED MUSCLE DEGENERATION

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ABSTRACT: Studies on pathogen-associated muscle degeneration (PAMD) seem not to progress despite the recent advancements in omics. The limited and outdated literature about pathogen-associated muscle degeneration in different animal models contradicts the thorough understanding of their genome. In this paper, we review the pathophysiology of pathogen infection through association with the physiologic, biochemical, and molecular changes happening in the skeletal, cardiac, and smooth muscles of different well-established mammalian models, namely rats (*Rattus sp.*), mice (*Mus musculus*), and rabbit (*Oryctolagus cuniculus*). The use of model organisms is beneficial to the advances in muscle degeneration research since they are inexpensive, low maintenance, and can be used for genetic screenings. This review illuminated an understanding of the potential application of well-established model organisms in advancing the current knowledge about pathogen-associated muscle degeneration.

Key words: Animal models, *Mus musculus, Oryctolagus cuniculus,* Pathogen-associated muscle degeneration, *Rattus sp.*

INTRODUCTION

Remarkable morphological changes and altered basic functions are the common hallmarks of muscle degeneration (Wallace and McNally 2009). There are several causes of muscle degeneration, such as hereditary, nutrition, injury, disease, and aging (Cooper *et al.* 2015). Some studies have shown that oxidative damage may lead to muscle deterioration (Ligouri *et al.* 2018). This principle arises from the idea that muscles like the heart and skeletal muscles contain plenty of mitochondria. Oxidative phosphorylation is one of the essential processes that take place in this subcellular organelle, which makes these tissues vulnerable to oxidative stress (Guo *et al.* 2013). Oxidative stress occurs after the leakage of free radicals during oxidative phosphorylation, which is prominent during infection (Bhattacharyya 2014). Reports have shown that some pathogens release toxins in the system that may cause oxidative damage to the host cells. These pathogens have contributed to muscle tissue deterioration (Pham-huy *et al.* 2008).

Pathogens are infectious agents that cause diseases in their hosts. There are different kinds of pathogens, namely viruses, bacteria, fungi, and nematodes.

A study suggests that infections caused by pathogens can induce or trigger the production of reactive oxygen species or ROS (Ivanov *et al.* 2017). Oxidative stress occurs when the body has difficulty maintaining the balance between the accumulated ROS and the body's ability to detoxify those (Nas *et al.* 2021a). Sub cellular components, including membrane-bound proteins, lipids, lipoproteins, and nucleic acids, are damaged when oxidative stress occurs (Pizzino *et al.* 2017). Oxidative damage impairs mitochondrial respiration, attenuating ATP synthesis, crucial during muscle contraction (Guo *et al.* 2013).

Muscle degeneration involving different pathogens triggers various complex biological processes, such as the innate and adaptive immune response, which may lead to difficulty in assessing the immediate effect of specific compounds against muscle degeneration (Tidball *et al.* 2010). The use of model organisms is beneficial to expedite ethical experimentations in studying various diseases, for they share the same degree of genetic similarities to humans. Model organisms are widely used in different studies because they are easily maintained in the laboratory, easily manipulated, and robust (Nas *et*

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al. 2021b). In this paper, we will review the mechanisms of PAMD in different model organisms.

Through model organisms, advances in drug discovery have been made possible. Usually, animal models are used in testing the drug's toxicity and other preclinical studies. Studying this would minimize resources, time, and effort before doing clinical trials. Numerous factors like handling, replicability, large-scale screening, and genetic manipulation were some desired features of model organisms (Pandey 2011). It is well understood that some substances are unable to demonstrate efficacy comparable to pre-clinical studies during clinical trials, which can be attributed to genetic differences between human and animal models (Podyacheva *et al.* 2021). Genetic variations among humans and non-human primates make it challenging for pathogens to induce human-like diseases, as well (Dash *et al.* 2021). Some pathogens like the Zika virus, human immunodeficiency virus, etc., cannot elicit the same human-like diseases in some models, such as mice, rats, and rabbits (Dash *et al.* 2021). Hence, incorporating a fragment of a human gene, tissue, or microbiome into these models paved the way for a better understanding of host-pathogen interactions, as well as how a particular genetic variation could affect disease prognosis (Skelton *et al.* 2018). This paper will discuss three mammalian models, namely, rats (*Rattus sp.)* and mice (*M. musculus*), and rabbit (*O. cuniculus*) to evaluate the physiological, biochemical, and molecular changes in the skeletal, cardiac, and smooth muscle tissue during pathogenic infection.

SPECIESWISE EFFECTS

A. Rats (*Rattus sp.)*

Rats are mammalian models from the Muridae family known for their significant contribution to the field of science. After sequencing the rat's genome, the genes, transcripts, *etc*., of the rat supplemented the extensive experiments done to understand various human diseases (Shimoyama *et al.* 2015). Some of the advantages of using rats in experiments are their relatively short life span, size, and propagation (Delwatta *et al.* 2018). Their life span ranges from 2 to 5 years with an average weight of 200 to 900 grams (0.4 – 2 lbs.), while the gestation period of a female rat lasts for about 21 to 23 days with an average litter size of eight (Delwatta *et al.* 2018). Various medical, psychological, and biological experiments have been done on rats to study toxic substances, anticancer drugs, cardiovascular diseases, neurological diseases, etc. (Iannaccone and Jacob 2009, Makhija *et al.* 2014, Tupper and Wallace 1980).

From a clinical standpoint, surgical procedures and serial blood draw for pharmacological research are more accessible in rats than invertebrate models. (Iannacone and Jacob 2009). Secondly, visualizing the effects of a lesion, drug administration, and interventions in its organs and anatomical areas is meaningful and translatable to humans. In cancer research, rat models of breast cancer surpass other non-human primate models in terms of hormonal dependence, histology, and premalignant stages that closely resemble human cancer (Costa *et al.* 2020, Iannacone and Jacob 2009). Molecular studies in rats show that they have characteristics of human diseases, such as susceptibility to pollutants, stressors, nutrition, and immunization, which influence the illness (Chenouard *et al.* 2021, Iannacone and Jacob 2009).

Skeletal muscle degeneration

In a study conducted on five-week-old female Sprague Dawley rats infected with *Klebsiella pneumonia* (*K. pneumonia*), significant changes in body temperature and blood sugar levels were observed (Dong *et al.* 2012). In skeletal muscles, oxygen and glucose are essential for various metabolic processes that diminish the supply, resulting in lactic acid formation and acidosis (Nas 2020a). An insufficient supply of glucose leads skeletal muscles to make a shift in nutrient source to lipids and further to proteins (Argilés *et al.* 2016). An early study showed that proteolysis is evident during bacterial infection; apart from this protein synthesis is impeded (Breuillé *et al.* 1998). The breakdown of proteins reduces muscle mass, which may cause profound changes in the muscle's membrane potential and contractile strength. Evidence shows that lipopolysaccharides from *K. pneumoniae* induce muscle fatigue in rats (Goubel *et al.* 1997). A recent investigation backs up this earlier experiment, where *K. pneumoniae*-induced chronic obstructive pulmonary disease rats displayed muscle weakness and exhaustion, which may be associated with Bcl-2 nineteen-kilodalton interacting protein 3 affecting cytochrome c and the mitochondrial respiratory chain complex (Dong *et al.* 2015).

After *K. pneumoniae* infection, triglyceride, unsaturated fatty acid (UFA), polyunsaturated fatty acid (PUFA), Omega-3 fatty acid, lactate, and N-acetyl glycoprotein (NAG) concentration increased by several folds (Dong *et al.* 2012). Likewise, lipoproteins and creatinine displayed a 4-fold increase (Dong *et al.* 2012). High levels of these metabolites suggest the presence of bacteremia in rats that eventually progressed to sepsis.

On the other note, *Streptococcus pneumoniae* disrupts electrolyte homeostasis in infected rats (Ruff and Secrist 1984). Typically, the regulation of the ions in the body

heavily influences the fluid shift in an organism. These ions have a pivotal role during muscle contraction (Blaine *et al.* 2015). The disparity in the level of these ions may affect the membrane potential of the cell and sub-cellular organelles (Fanzani *et al.* 2012). Insufficient amounts of calcium ions interfere with the action of myosin and actin. Also, calcium ions are integral during the release of neurotransmitters from the motor endplate (Fanzani *et al.* 2012).

Escherichia coli (*E. coli*) infection in rats leads to sepsis promoting muscle wasting (Voisin *et al.* 1996). Evidence show protein breakdown through calcium-independent and ubiquitin-proteasome dependent mechanism (Voisin 1996). Moreover, chronic substrate ubiquitylation during sepsis triggers calcium-dependent and liposomal protein degradation (Voisin *et al.* 1996). Probiotics were used in a recent experiment to reduce the growth of *E. coli* and *S. aureus* in the rats' gut (Hor *et al.* 2019). Consequently, this prevented the rats from growing weak and tired, which is consistent with the down-regulation of the p53 gene expression, suggesting delayed senescence (Hor *et al.* 2019).

Bacterial endotoxins elevate interleukin-6 in rats leading to skeletal muscle proteolysis (Goodman 1994). This study claims that bacterial endotoxin upregulates interleukin-1 and tumor necrosis factor in rats, responsible for inducing interleukin-6. It has been revealed that macrophages and T cells remained in the injured muscle for several weeks post-trauma, suggesting their relevance in the healing process of the skeletal muscle (Hurtgen *et al.* 2017). In addition, phagocytes and lymphocytes swiftly permeate the affected tissues to stimulate the growth and maturation of satellite cells (Ziemkiewicz *et al.* 2021). Neutrophils and macrophages also emit several growth factors and cytokines that draw other immune cells to the injured muscle (Ziemkiewicz *et al.* 2021). Moreover, evidence showed that endotoxins deteriorate ventilatory muscles due to cellular and hemodynamic interference (Hussain 1998).

One of the critical processes in skeletal muscles necessary for survival and performance involves coordinated protein turnover, where dysfunction may result in opathies (Blondelle *et al.* 2020). Catabolic hormones, inflammatory cytokines, tumor necrosis factors, IL-1, and IL-6 are potential mediators of muscle atrophy (Frost and Lang 2005). The inability to eliminate pathogen molecules or the occurrence of muscle injury may evoke a prolonged stimulation of transcription factors and enzymes that drive muscle loss (Frost and Lang 2005). The Cop9 signalosome and E3 ligases are regulatory proteins of the ubiquitin-proteasome system designated for protein degradation, which may be a potential target during PAMD (Blondelle *et al.* 2020).

Cardiac muscle degeneration

Rats and humans have similar morphological characteristics regarding myofibril volume densities, intercalated disc distribution, T-tubule opening, gap junction, and heart-to-body ratios (Joukar 2021). Rats have a peak diastolic potential of -58 mv, which is somewhat higher than that of humans (-62 mv), and also has a similar pattern to their respective resting membrane potentials (-70 to -80 mv and 90 mv) (Joukar 2021). The PR interval, QRS complex, and QT intervals on their ECG are more protracted in humans than in rats (Konopelski *et al.* 2016). Despite these variations, the changes in the ECG patterns of rats and humans following cardiac injury, myopathies, and arrhythmias are comparable (Joukar 2013).

A study reveals that bacteria, such as *Staphylococcus aureus* (*S. aureus*), *E. coli*, *Neisseria meningitides*, and *Neisseria gonorrhoeae* have high adherence to the endothelial cells of the heart (Schollin and Danielsson 1988). Similarly, the tight-adherence (*tad*) genes of *Actinobacillus actinomycetemcomitans* have long been studied to localize in the heart during infection (Schreiner *et al.* 2013).

S. aureus and *Streptococcus mutans* in rats lead to endocarditis through binding with fibronectin (Veloso *et al.* 2011, Kuo *et al.* 2022). Another study demonstrated that *S. aureus* infection disrupted the heart valve severely, and a large amount of fibrin was detected on the thickened valve (Fogarasi *et al.* 1999). Damaged myocytes may undergo remodeling, leading to that portion of the heart thickening or losing membrane potential (Nas 2021).

Interestingly, *Streptococcus mitis*, *Staphylococcus aureus*, or *Streptococcus faecalis* infection in the left ventricle resulted in 19% mortality after one week, which elevated to 82% the following week (Santoro and Levison 1978). This study may have mimicked left-sided heart failure in rats. Additionally, N-(3-oxododecanoyl)-L-homoserine lactone (3-oxo-C12-HSL) from *Pseudomonas aeruginosa* leads to bradycardia (Gardiner *et al.* 2001). Arrhythmia is associated with heart failure due to disturbed heart activity. A study demonstrated using *Bacillus anthracis* and *E. coli* that the circulatory shock-associated lethality in rats is independent of inflammatory cytokines (Cui *et al.* 2006). Besides, *E. coli* lipopolysaccharide impedes the mean arterial pressure in rats resulting in hypotension (Thiemermann and Vane 1990). Another study supports these findings using *Bacillus anthracis*, wherein both

heart rate and mean arterial pressure was reduced (Cui *et al.* 2005).

K. pneumonia infection in rats also modulated mean arterial pressure (Dong *et al.* 2012). Reduced mean arterial pressure indicates a change in the cardiac output and vascular resistance (Guyton *et al.* 1959). This event affects the microcirculation, which is also evident during sepsis (Hamzaoui and Shi 2020). Supporting evidence shows that sepsis in rats directs toward microvascular dysfunction affecting capillary pressure and density of perfused capillary (Armour *et al.* 2001).

Smooth muscle degeneration

While studies show that lipopolysaccharide from *E. coli* impeded aortic smooth muscle vaso-contractility (Takahashi *et al.* 2003). Other studies suggest that this implication on the vascular smooth muscle resulted from nitric oxide-mediated signaling pathway (Yang *et al.* 2005). Another study revealed that bacterial lipopolysaccharide curbed ∝-actin expression in the vascular smooth muscle cells (Sandbo *et al.* 2007). Meanwhile, in rats infected with *Chlamydia pneumoniae*, phosphatidylinositol 3-kinase activated the Ras-associated C3 botulinum toxin substrate 1, allowing vascular smooth muscle cells to relocate and contribute to atherosclerosis (Zhang *et al.* 2014).

Campylobacter jejuni infection in rats resulted in a reduced interstitial cell of Cajal (ICC) density in the deep muscular plexus of the intestine (Jee *et al.* 2010). The ICC is an integral part of the alimentary canal prompting intestinal motility. Reduced ICC may lead to impaired smooth muscle contractility.

A study suggests that chronic *E. coli* infection in rats triggers a compensatory response in the gastrointestinal tract through increased protein synthesis to compensate for the marked drop in protein production in the skeletal muscle (Breuillé *et al.* 1998). According to another study, enterohaemorrhagic *E. coli* containing phage-encoded Shiga toxin permeates the intestinal mucosa through the Paneth cells' globotriaosylceramides, impeding the release of chemokines that mitigate inflammation (Croxen and Finlay 2010). In the same way, phage-encoded Shiga toxin did not prevent the synthesis of protein intra-cellularly (Croxen and Finlay 2010). Conversely, an earlier experiment reported elevation in the cytokine levels after E. coli infection, which apparently recruits interleukin-lβ (IL- 1β) and tumor necrosis factor-∝ (TNF-∝), and lipopolysaccharide and interacts immediately with the voltage-gated calcium channels of the vascular smooth muscle cell (Wilkinson *et al.* 1996).

Trichinella spiralis infection in rats induced contractile tension in the longitudinal smooth muscle of the jejunum, which varies with calcium levels (Vermillion and Collins 1988). Likewise, the presence of an enteric parasite, *Nippostrongylus brasiliensis*, altered the calcium-dependent contraction in the jejunum of infected rats (Fox-Robichaud and Collins 1986).

B. Mice (*M. musculus*)

A typical laboratory mouse comes from the Muridae family, with Murinae as a subfamily. Mice have been an integral part of various disease studies in humans due to their genetic similarity. In fact, 85% of the transcripts of mice are similar to humans (Modrek and Lee 2003). Hence, several disease phenotypes were developed using mice associated with digestive, immune, nervous, skeletal, and cardiovascular systems (Higgins and Jacobsen 2003). The main characteristic of a mouse model replicating a human disease can be traced to the disease's origin, where a workable method for inducing the model can be used. Similarly, the indications of post-induction symptoms are comparable to how the actual disease manifests (Rydell-Törmänen and Johnson 2019).

The recently humanized mouse model has been used widely to depict human diseases through xenografting human tumors in mice. Eventually, the mouse who received the transplanted cell or tissue produced an antigen-specific immune response that recapitulates the human tumor origin (Meraz *et al.* 2019). Additionally, several drug interventions have been applied to this model, which targets a specific tumor type (Yin *et al.* 2020). Aside from transplanting tissues, the advent of CRISPR-Cas-9 expanded the utilization of animal models to apprehend biological basis and molecular mechanisms underlying genetic diseases (Ahmad and Amiji 2018). Indeed, there are several mouse models developed for rare metabolic diseases, cardiomyopathies, albinism, and sensorineural hearing loss (Murillo-Cuesta *et al.* 2020).

Skeletal muscle degeneration

There are about 47 genes in mice recently reported to increase skeletal muscle mass, such as the over-expression of *Ski, Fst, Acvr2b, Akt1, Rheb, Igf1, Pappa, Ppard, Fstl3, Ucn3, Mcu, June, Gprasp1, Mmp9, Dgkz, Ppargc1a, Ltbp4, Bmpr1a, Crtc2, Xiao, Adrb2, Asb15, Cast, Eif2b5, Tpt1, Nr4a1, Gnas, Pld1, Camkk1, and Yap1; whereas knockout or knockdown of Mstn, Klf10, Ikbkb, Atgr1a, Ncor1, Grb10, Smad4, Dgat1, Thra, Bdkrb2, Nr3c1, Crim, Inhba, Tp53inp2, Inhbb, Nol3, Esr1* resulted to muscle hypertrophy (Verbrugge *et al.* 2018). In a study conducted, exogenous follistatin supplementation decreased the frequency of

E. coli K1 sepsis-related death in mice, suggesting a potential connection between Fst expression and skeletal mass (Dieelberg *et al.* 2012). Meanwhile, Fast and activin comprise the activin/FS-system, which evokes the inflammatory response during infection, implying the possible role of activin receptor type 2B (Acvr2b) in PAMD (Ebert *et al.* 2010). It only warrants further investigation of these genes to provide scientific evidence on their response against various pathogens.

A study involving the muscular pathology of Leishmania-infected mice revealed that protein degradation during muscular injury is an early response to stimulus-inducing atrophy (Ahmed *et al.* 2010). The plight of comparing empirical data from mice models with one Leishmania strain to others, despite genetic similarity or pathophysiology, has been brought up in some papers due to various factors, including the mice's genotype and parasite's quantity, genetic make-up, inoculation route, etc. (Loeuillet *et al.* 2016). Despite these challenges, other discoveries might help to understand how severe muscle tissue inflammation leads to myofiber loss and consequent muscular atrophy (Silva-Almeida *et al.* 2010). Chronically, severe inflammation of the nerve infection site and muscular atrophy were consistently observed (Calura *et al.* 2008). Aside, evidence shows that interleukin-6 is secreted by skeletal muscle in mice after bacterial infection. Studies have shown that interleukin-6 leads to skeletal muscle atrophy and muscle wasting due to myofibrillar protein loss (Haddad *et al.* 2005, Belizario *et al.* 2016).

Another study investigating the muscle strength of *Trichinella spiralis*-infected mice was shown to diminish muscle strength after 1 to 48 weeks of post-administration of the pathogen (Park *et al.* 2018). Additionally, the cytokines of the infected mice were upregulated during the early stages of infection, with maintained nuclear infiltration during the early to chronic stages of infection (Park *et al.* 2018). There was a decrease in IL-5 and IL-6 after the initial infection, whereas IL-10, IL-25, TGF-∝, and TGF-β were maintained (Park *et al.* 2018).

Optical imaging reveals that intravenous injection of *S. aureus* and *E. coli* in mice targets the thigh muscle of the animal (Leevy *et al.* 2006). Similarly, a photodynamic study suggests that *S. aureus* localizes in soft tissue (Gad *et al.* 2004).

Pseudomonas aeruginosa causes pulmonary infection in mice and weakens the diaphragmatic muscle by disrupting calcium homeostasis (Divangahi *et al.* 2009). Another study further revealed that 2-amino acetophenone is detected in the lungs during *Pseudomonas aeruginosa* infection (Bandyopadhaya *et al.* 2019). This compound alters reactive oxygen species homeostasis, disturbing muscle contractions and other skeletal muscle functions in mice (Bandyopadhaya *et al.* 2019).

Moreover, studies suggest that LPS primarily from gram-negative bacteria disrupt muscle protein synthesis in mice by inhibiting the mammalian target of rapamycin (mTOR) activity (Lang *et al.* 2010, Svanberg *et al.* 2000). Interestingly, studies have revealed that the toll-like receptor gene Tlr4 is crucial for the release of pro-inflammatory cytokines induced by the bacterial LPS in mice and that its knockdown may cause endotoxin intolerance (Munford 2010). There were pieces of

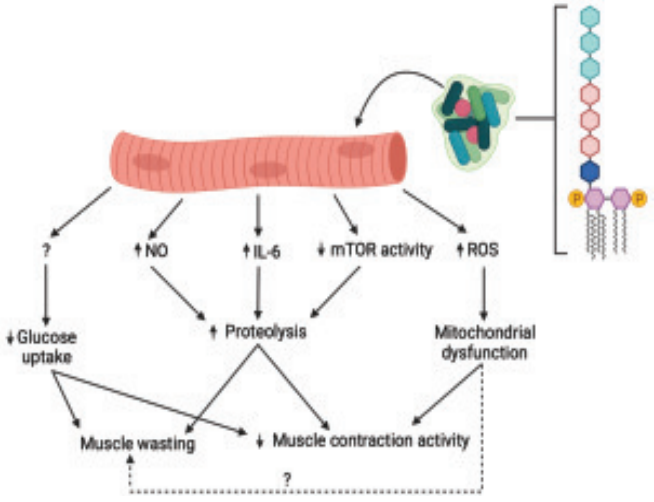

Fig. 1. Proposed therapeutic targets for PAMD in skeletal muscles. (Solid arrow line depicts evidence-based mechanism, whereas dashed arrow line represents unknown mechanism).

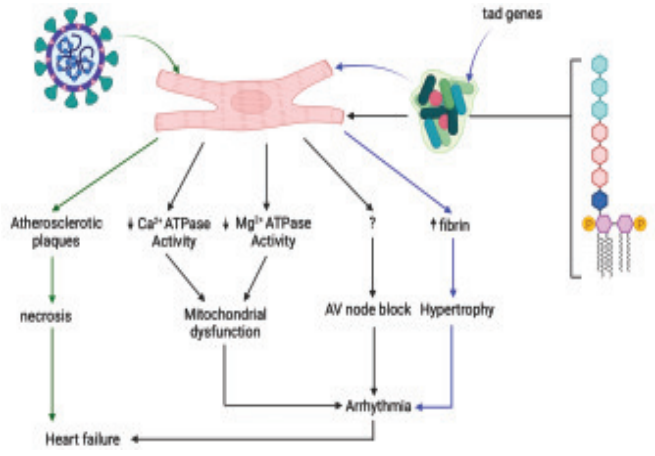

Fig. 2. Proposed therapeutic targets for PAMD in cardiac muscles. (Black arrows are associated with bacterial endotoxins; whereas blue arrows denotes association with *tad* genes. Virus-mediated pathway is represented by the green arrows).

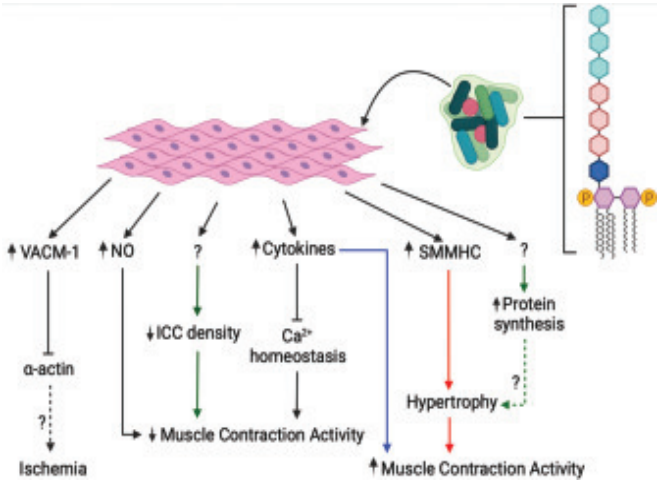

Fig. 3. Proposed therapeutic targets for PAMD in smooth muscles. (Solid arrow line depicts evidence-based mechanism, whereas dashed arrow line represents hypothesized mechanism).

evidence that demonstrated a reduction in lean body mass and gastrocnemius weight in mice (Lang *et al.* 2010). Aside from weight, impaired protein synthesis affects the fast- and slow-twitch muscles (Vary and Kimball 1992). Aside, LPS also induces inducible nitric oxide synthase and diminishes microvascular reactivity of the skeletal muscle endothelial cells in mice (Wu *et al.* 2003).

Furthermore, bacterial infections attenuated the bioenergetics of the skeletal muscle in mice. A study on *Porphyromonas gingivalis* infected soleus displayed an impaired glucose uptake (Watanabe *et al.* 2021). Additionally, *Pseudomonas aeruginosa* induces mitochondrial dysfunction in skeletal muscle (Tzika *et al.* 2013). The disruption of glucose transport and the electron transport chain reduces the energy produced and consumed by the skeletal muscle.

Cardiac muscle degeneration

In mice, *Chlamydia pneumoniae*, *Chlamydia psittaci*, and *Chlamydia trachomatis* were found to cause peri-vascular inflammation, fibrotic alterations, and blood vessel blockage in the heart (Bachmaier *et al.* 1999). Similarly, a study has reported that *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerealla forsythia*, and *Fusobacterium nucleatum* cause atherosclerosis in infected mice (Chukkapalli *et al.* 2015). Perivascular inflammation, fibrotic alterations, blood vessel blockage, and atherosclerosis are important causes of heart failure, leading to impaired heart activity, such as arrhythmia. The obstruction in the middle cerebral artery mimics the intraluminal suture MCAo model in mice to demonstrate ischemic stroke in humans (Fluri *et al.* 2015). Previously a study associated atrial fibrosis with an increased risk of thromboembolism in stroke patients, which may be recapitulated in embolic stroke models and embolic clot models in mice (Fonseca *et al.* 2018, Fluri *et al.* 2015).

Evidence shows that bacterial infection or *Candida albicans* blocks the atrioventricular node resulting in bradycardia (Fairchild *et al.* 2011). Further, bacterial endotoxins attenuate heart variability in mice during sepsis (Fairchild *et al.* 2009).

Moreover, cytomegalovirus in mice results in the formation of atherosclerotic plaques, which may cause the cardiac muscle to die (Berencsi *et al.* 1998). Also, the toxin pneumolysin secreted by *Streptococcus pneumoniae* induces microscopic lesions on the myocardium of mice (Brown *et al.* 2014). This paper suggests that the adverse effect of this microlesion compromises the heart function due to the scarring, which may eventually lead to a hypertrophic heart (Brown *et al.* 2014). A study has shown that the risk of ischemic stroke advances with hypertrophic cardiomyopathy accompanied by atrial fibrillation, which mouse models of embolic stroke and embolic clots may mimic (Fauchier *et al.* 2022, Fluri *et al.* 2015).

Smooth muscle degeneration

Streptococcus pneumoniae infection in mice results in an aberrant airway smooth muscle due to the elevation of smooth-muscle-myosin-heavy-chain (SMMHC) contractile proteins (Peng *et al.* 2019). This event leads to structural changes in airway smooth muscle, such as hypertrophy or hyperplasia, resulting in hyper-responsiveness (Busse 2010, Peng *et al.* 2019).

Another study demonstrated that *E. coli* infection in the uterus induced interleukin-1∝, interleukin-1β, tumor necrosis factor-∝, and cyclooxygenase-2 affecting smooth muscle contractility (Hirsch *et al.* 1995). This incident accounted for numerous cases of pre-term delivery during the said infection.

C. Rabbit (*Oryctolagus cuniculus*)

One of the most common rabbit species used in the lab comes from the genus *Oryctolagus*. Generally, rabbits belong to the family Leporidae, order Lagomorpha. Unlike mice and rats, the intermediate size of rabbits makes them easier to dissect during histological experiments (Pogwizd and Bers 2008). Rabbits are a popular model for molecular immunology; however, they are also used to study skin, heart, and neurological diseases (Pogwizd and Bers 2008, Esteves *et al.* 2018, Nas 2020b).

Primarily due to their extensive antibody repertoire, rabbits have been used to study immunological problems and develop immunological approaches for over a generation (Mage *et al.* 2019). They also have a complementary paratope collection; monoclonal antibodies that are specific for the same antigen cross-react with murine antigens frequently, which can hasten pre-clinical safety tests in mouse models of human disease (Webber *et al.* 2017). Furthermore, the Food and Drug Administration has approved rabbit monoclonal antibodies for diagnosing human illnesses through immune-histochemistry (Mage *et al.* 2019).

Skeletal muscle degeneration

There are different mechanisms by which a pathogen induces skeletal muscle degeneration in rabbits, but an earlier study suggests that the disruption of normal metabolism plays a pivotal role (Guckian 1973). In this study, hypoglycemia and elevated amino acid levels were detected after the *Diplococcus pneumoniae* infection in rabbits (Guckian 1973). Energy deficit has long been considered a factor for membrane dysfunction during sepsis (Illner and Shires 1981). Evidence shows that *Escherichia coli*(*E. coli*) infection in rabbits induces loss of membrane potential, hypotension, and lesion in the skeletal muscle tissues (Illner and Shires 1981). Another study supports that *E. coli* LPS was involved in the skeletal muscle's mitochondrial dysfunction (Trumbeckaite *et al.* 2001). A recent study illustrated that pannexin-1 (Panx-1) channel inhibition modulates the clearance of intracellular ATP against *E. coli* lipopolysaccharides (LPS-induced inflammatory response, cellular energy depletion, and organ damage in the rabbit's skeletal muscle (He *et al.* 2018). These previous findings lead toward LPS-induced dysregulation of ATP generation and consumption in the skeletal muscle.

Another study demonstrated muscle trauma through the *Staphylococcus aureus*-induced muscle contamination affecting the injured skeletal muscle (Eardley *et al.* 2012). Additionally, diphtheria toxin from *Corynebacterium*-induced dystrophic lesion in the rabbit's diaphragm and gastrocnemius (Senay *et al.* 1958). This damage was accompanied by necrotic tissue, reduction of isometric tetanus tension, and fatigue resembling muscular dystrophy (Senay *et al.* 1958). In a recent study in rabbit skeletal muscle, diphtheria toxin reduces protein synthesis by polymerizing monomeric G-actin to F-actin, which modulates ADP-ribosyltransferase activity and promotes the breakdown of the cytoskeleton (Unlu *et al.* 2013).

Cardiac muscle degeneration

It has long been reported that *Streptococcus viridians* (*S. viridans*) infection in rabbits leads to cardiomyopathy by attenuating the calcium ATPase and magnesium ATPase activity in the sarcolemma and myofibril, respectively (Tomlinson *et al.* 1976). This cardiomyopathic heart has impaired mitochondrial respiration and phosphorylation (Tomlinson *et al.* 1976). The electrocardiogram of the infected rabbit's heart displayed a high QRS amplitude and flat T wave, which is associated with the depression of intraventricular pressure velocity (Tomlinson and Dhalla 1976). Similarly, *Streptococcus* infection with pharyngeal origin damaged the cardiac muscle through necrosis and impeded collagen supply (Morse *et al.* 1955). Another study reported that *Streptococcus* adheres to the arteriole's sarcolemma of the rabbit's cardiac muscle (Zabriskie and Freimer 1966). This dated proofs are reinforced by recent findings where the genetic residues of *S. viridans* and *S. mutans* were traced in the thrombotic materials of patients with myocardial infarction, suggesting its role in plaque formation (Piñón-Esteban *et al.* 2020).

Staphylococcus aureus infection damaged the elastic laminae of the rabbit's aorta, which eventually leads to a myocardial lesion (Ferguson *et al.* 1986). *S. aureus* DNA traces were also identified in thrombotic materials of patients with myocardial infarction, indicating possible contribution to endodontic infection prior to myocardial infarction (Piñón-Esteban *et al.* 2020).

Additionally, *E. coli* LPS reduces pyruvate, octanoyl-carnitine, succinate, and complex I + III activity in the mitochondrial respiratory chain, which alters cardiac function leading to coronary vascular resistance (Trumbeckaite *et al.* 2001).

An early study reported that *Streptococcus viridans*, *Pseudomonas pseudoalkaligenes*, and *Staphylococcus epidermidis* induced endocarditis in rabbits following infection and mitral valve lesion (Imataka *et al.* 1993). A rabbit with polymicrobial sepsis reveals that it is not only the mitral valve that is damaged during infection but also the interventricular septum, atrium, and ventricles (Tumer *et al.* 2019).

Moreover, rabbits infected with coronavirus exhibited multifocal myocardial degeneration, evident from the surviving population (Small *et al.* 1979). Likewise, rabbits infected with coxsackievirus developed myocardial necrosis (Pogwizd and Bers 2008).

Smooth muscle degeneration

Studies suggest that bacterial infection affects the normal physiological function of the urinary bladder's smooth muscle and mucosa (Hypolite *et al.* 1993, Birder *et al.*2012). Besides, *E. coli* infections in rabbits were observed to have a firm adherence to the bladder, resulting in overdistension and ischemia, which can be eased by antimicrobial coating on urinary catheters (Ruggieri *et al.* 1986; Tailly *et al.* 2021). During an *E. coli*-induced bladder infection, the RhoA/Rho-kinase pathway has also been associated with modulating calcium sensitization, smooth muscle myosin light chain phosphatase activity, and CPI-17 phosphorylation (Zhang *et al.* 2011). Evidence shows that ischemia leads to high-energy phosphate degradation in the smooth muscle of the rabbit's bladder (Levin *et al.* 1996). Contrastingly, a study reported that *S. aureus* and *E. coli* adherence in the submucosa matrix of the bladder is modest, suggesting probable inherent antibacterial activity in this area (Meng *et al.* 2015).

Similarly, a report demonstrated that lipopolysaccharide from *E. coli* impaired the contraction and relaxation of cavernous smooth muscle in rabbits (Kim *et al.* 1999). Recent studies support that stimulating the RhoA/Rho-kinase pathway is implicated in the endothelin 1-induced contraction of the cavernous smooth muscles (Zhang *et al.* 2011).

Another study observed that an atherosclerotic lesion in the vascular smooth muscle of rabbits resulted in the expression of vascular adhesion cell molecule-1, which impeded the á-actin expression (Li *et al.* 1993). Likewise, the introduction of lipopolysaccharide from *E. coli* exhibited similar effects on vascular smooth muscle cells (Li *et al.* 1993). Vascular smooth muscles in damaged vessels may generate ROS or through leukocyte recruitment, which amplifies inflammatory response and cellular proliferation (Miyahara *et al.* 2013). The bradykinin B1 receptor is upregulated during inflammation and injury, and LPS potentiates its sensitivity to its agonists, increasing its responsiveness and influencing vascular contractions (Marceau *et al.* 2010).

Further, histological reports suggest that *Chlamydia pneumoniae* infection in rabbits also leads to atherosclerotic lesions with *Chlamydia* particles found inside the lesion (Khoshbayan *et al.* 2021). *C. pneumoniae* elevates cytokine production, aggravating oxidative stress in the vascular tissues culminating in the migration and proliferation of vascular smooth muscle, endothelial dysfunction, platelet activation, and atherosclerotic plaques deposits (Di Pietro *et al.* 2013). Rabbits infected with *C. pneumoniae* also displayed bronchiolitis, where the smooth muscle is constricted (Fong *et al.* 1997, Moazed *et al.* 1996). Besides, lesions were observed in the smooth muscle tissues indicated by spindle cell proliferation (Fong *et al.* 1997).

THERAPEUTIC TARGETS IN PAMD

Having discussed the three mammalian models for PAMD, we amalgamated current knowledge on how the different pathogens cause muscular dysfunction in mammals. We proposed different therapeutic targets to expound the present understanding and insight into pathogen-associated muscle degeneration.

In the skeletal muscle, the endotoxin of bacteria, such as LPS, has been found to elevate NO, IL-6, mTOR activity, and ROS, as shown in Fig. 1. The changes in NO, IL-6, and mTOR lead to protein breakdown in the skeletal tissues, which affected muscular contraction and degradation (Wu *et al.* 2003, Goodman 1994, Lang *et al.* 2010). Meanwhile, the disruption of ROS homeostasis leads to mitochondrial dysfunction, which also affects muscular contraction (Bandyopadhaya *et al.* 2019). However, there are still gaps in this proposed mechanism that warrants further investigation, namely the mechanism of how the bacterial endotoxins reduced glucose uptake and the relationship of mitochondrial dysfunction to muscle wasting.

Unlike the skeletal muscle, studies in the cardiac muscle identified another factor from the bacteria, tad genes that potentially result in muscle degeneration (Schreiner *et al.* 2013). Similarly, the introduction of the virus appears to have also caused cardiac muscle degeneration. We proposed different mechanisms for how these different factors lead to a degenerative heart muscle, as shown in Fig. 2. Bacterial endotoxin (black arrow line) impedes Ca^{2+} and Mg^{2+} ATPase activity, which results in mitochondrial dysfunction (Tomlinson *et al.* 1976). The energy for cardiac muscle contraction relies on mitochondrial activity; hence, arrhythmia may arise when mitochondrial activity is depleted. Interestingly, it is still unclear how the bacterial endotoxin blocks the heart's pacemaker, AV node, resulting in arrhythmia.

On the other hand, tad genes (blue arrow line) enable the bacteria to adhere to the surface of the cardiac muscle in the presence or absence of a lesion, which upregulates fibrin expression, causing hypertrophy (Schreiner *et al.* 2013). A thickened cardiac muscle may lead to impaired contractile activity, which reflects arrhythmia.

Interestingly, viral infection contributes to plaque formation in the heart (green arrow line), making the involved tissues undergo necrosis (Small *et al.* 1979,

Pogwizd and Bers 2008). Necrotic heart tissues and arrhythmias are associated with heart failure.

Lastly, the effects of bacterial infection in smooth muscle vary and appear to be contradictory to different tissues, as shown in Fig. 3. For instance, bacterial infection promotes proteolysis in skeletal muscle, whereas in some intestinal smooth muscle (green arrow line), protein synthesis is elevated (Breuillé *et al.* 1998). However, the mechanism for this protein catabolism remains elusive. Also, we hypothesized that the build-up of protein may also be associated with smooth muscle hypertrophy, which still needs further investigation.

Moreover, the effect of bacteria on muscle contraction activity appears to vary in different smooth muscle tissues. The hyper-responsiveness of the smooth muscle in the respiratory tract (red arrow line) is associated with the hypertrophied muscle due to elevated smooth muscle myosin protein (SMMHC) (Peng *et al.* 2019). Similarly, some cytokines in the urinary tract (blue arrow line) increased smooth muscle contractile activity (Hirsch *et al.* 1995). Conversely, high NO and various cytokines lead to reduced vascular smooth muscle (black arrow line) contraction (Yang *et al.* 2002, Wilkinson *et al.* 1996). Likewise, bacteria diminished ICC density in the intestines (green arrow line) in an unknown mechanism, which causes impeded motility.

Furthermore, bacterial endotoxin may have caused VACM-1 upregulation inhibiting the expression of actin. It is still unclear how diminished actin leads to ischemia (Li *et al.* 1993).

CONCLUSION

This paper reviewed empirical studies related to pathogen-associated muscle degeneration in three standard animal models: rats, mice, and rabbits. Evidence shows that muscle degeneration occurs in skeletal, cardiac, and smooth muscle tissues. Pathogen-associated skeletal muscle degeneration is marked by muscle wasting and reduced contractile activity caused by endotoxin, promoting muscle protein degradation, mitochondrial dysfunction, and carbohydrate depletion. Consequently, these bacterial endotoxins, tad genes, and viral toxins cause lesions, mitochondrial disruption, and hypertrophic tissues in cardiac tissues, which eventually leads to arrhythmia and heart failure. Lastly, the effect of bacterial endotoxin on smooth muscle depends on the tissues. Increased muscle contraction is observed in the urinary tract, respiratory tract, and gastrointestinal tract after infection. Contrastingly, reduced contractile activity was observed in the vascular smooth muscle. Knowing these distinct different physiological changes and potential therapeutic targets in the different tissues after infection may provide novel insight for future studies into pathogen-associated muscle degeneration.

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