Duchenne and Becker muscular dystrophy (DMD/BMD) comprise a spectrum of devastating X-linked muscle wasting disease accounting for over 80% of all cases of muscular dystrophy (Bushby et al., 2010a). In DMD, boys are diagnosed as toddlers and most are wheelchair bound by age 15. Death often occurs by age 20 from respiratory complications or cardiomyopathy. More patients survive to age 30 due to home ventilation and corticosteroids, which can prolong ambulation by 2–3 years, reduce risk of scoliosis, and mitigate pulmonary and cardiac decline in the second decade (Bushby et al., 2010a,b). Despite this demonstrated efficacy, more than 25% of boys with DMD are not treated with corticosteroids due to intolerable side-effects or lack of response (Bushby et al., 2010a,b). In BMD, the disease is milder and more clinically heterogenous than DMD. Muscle weakness often is first noticed in adolescence or young adulthood. Cardiac decline in BMD patients may surpass skeletal muscle decline, with death from cardiomyopathy often occurring before age 60 (Bushby et al., 2010a). There is a clear need for additional therapeutic strategies to manage the clinical challenges of DMD/BMD.

More than 25 years have passed since mutations in the DMD gene were discovered to cause DMD/BMD (Monaco et al., 1986; Koenig et al., 1987). Mutations resulting in the absence of a functional dystrophin protein cause DMD, whereas mutations resulting in a reduced amount or shortened dystrophin protein cause BMD. Dystrophin is a large (427 kDa) sub-sarcolemmal protein that provides a physical link between the intracellular actin cytoskeleton and the extracellular matrix (Blake et al., 2002). Loss of dystrophin destabilizes the sarcolemma, rendering the muscle fibers susceptible to injury during contraction (Petrof et al., 1993). Repeated cycles of necrosis followed by regeneration lead to satellite cell depletion and gradual replacement of muscle by fat and connective tissue, manifesting clinically as progressive muscle wasting and weakness (Blake et al., 2002). Dystrophin also is a scaffolding protein that localizes other structural and signaling proteins to the sarcolemma, forming a highly organized multimeric dystrophin-associated glycoprotein complex (DGC) (Blake et al., 2002). Dystrophin deficiency disrupts the DGC, resulting in the absence, downregulation, or mislocalization of the dystrophin-associated proteins. Thus, numerous pathogenetic mechanisms are likely activated in dystrophin-deficient muscle in response to disruption of the sarcolemmal DGC. Identifying the key mechanistic link(s) between loss of dystrophin and the clinical phenotype of DMD/BMD has been a major focus of research efforts with the ultimate goal of discovering new therapeutic targets to slow or prevent the dystrophic process.

THE VASCULAR HYPOTHESIS OF DMD
One putative mechanism that has received increased attention recently is muscle ischemia. One of the earliest histological changes seen in dystrophic muscle, even before the onset of significant muscle weakness, is the appearance of small random groups of muscle fibers at the same stage of necrosis or regeneration surrounded by histologically normal muscle fibers (Engel, 1967). In the pre-dystrophin era, it was proposed that this characteristic focal necrosis might reflect local microvascular ischemia. The idea was that vascular insufficiency at the level of the microcirculation caused selective infarction of only those muscle fibers supplied by the obstructed blood vessels, while nearby fibers...
supplied by unobstructed vessels were not affected (Bramwell, 1925; Demos and Escoffier, 1957; Cazzato, 1968). Initial experimental support for this vascular hypothesis came from studies performed more than 40 years ago in which the characteristic focal lesions of DMD muscle were reproduced in the muscles of healthy animals by occlusion of intramuscular arterioles with dextran beads, or by functional ischemia induced by a combination of arterial ligation and vasoconstrictor injection (Hathaway et al., 1970; Mendell et al., 1971, 1972). However, subsequent morphological studies did not reveal any fixed anatomical abnormalities in the skeletal muscle microcirculation of DMD patients, with the exception of replication of the capillary basal lamina (Jerusalem et al., 1974; Musch et al., 1975; Koehler, 1977; Leinonen et al., 1979). In addition, findings from studies of skeletal muscle blood flow in DMD patients were equivocal, indicating that blood flow to resting muscle was decreased, increased, or normal (Demos, 1961; Emery and Schelling, 1965; Kapuscinska et al., 1970; Paulson et al., 1974; Bradley et al., 1975; Leinonen et al., 1979). The lack of any identifiable cause of muscle ischemia in DMD patients diminished enthusiasm for the vascular hypothesis.

**FUNCTIONAL MUSCLE ISCHEMIA DUE TO LOSS OF SARCOLEMMAL nNOSµ**

It was not until after the discovery of dystrophin and the DGC that the vascular hypothesis re-emerged. Among the dystrophin-associated proteins is neuronal nitric oxide synthase µ (nNOSµ), a muscle-specific splice variant of NOS, which is recruited to the sarcolemma by two independent interactions involving its PDZ (post-synaptic density 95, discs large, and zonula occludens-1) domain. The nNOSµ PDZ β-finger interacts with the PDZ domain of the adaptor protein α-syntrophin, which binds to dystrophin's C-terminal domain, while the nNOSµ PDZ groove interacts with spectrin-like repeats 16 and 17 (R16/17) within dystrophin's rod domain (Brennan et al., 1995; Chang et al., 1996; Lai et al., 2009, 2013). Dystrophin deficiency causes nNOSµ to be misplaced from the sarcolemma to the cytosol where it is associated with reduced muscle perfusion and increased focal constriction of muscle microvessels (Kobayashi et al., 2008). The exaggerated fatigue response in the mdx mice appears to be due to the loss of sarcolemmal nNOSµ, as excessive fatigue also is observed in nNOS null mice and in wild type mice treated with a NOS-specific inhibitor (Kobayashi et al., 2008). Reduced NO signaling also contributes to contraction-induced injury of dystrophin-deficient muscle. Mdx muscle exhibits progressive damage post-contraction that can be alleviated by treatment with a NO donor (Asai et al., 2007). Thus, the updated version of the vascular hypothesis of DMD suggests that the nNOSµ-NO pathway could be considered as a potential new drug target to slow disease progression in DMD/BMD patients.

Collectively, these observations in numerous mouse models and in DMD/BMD patients have advanced the concept that NO produced by sarcolemmal nNOSµ helps to regulate blood flow in active muscle by blunting the potentially deleterious effect of sympathetic activation during exercise. The loss of this protective mechanism may leave dystrophin-deficient skeletal muscle vulnerable to recurrent bouts of ischemia, thereby promoting muscle fatigue and exacerbating use-dependent muscle injury (Rando, 2001; Asai et al., 2007). Consistent with this hypothesis, mdx mice display an exaggerated exercise-induced fatigue response that is associated with reduced muscle perfusion and increased NO signaling also contributes to contraction-induced injury of dystrophin-deficient muscle. Mdx muscle exhibits progressive damage post-contraction that can be alleviated by treatment with a NO donor (Asai et al., 2007). Thus, the updated version of the vascular hypothesis of DMD suggests that the nNOSµ-NO pathway could be considered as a potential new drug target to slow disease progression in DMD/BMD patients.

However, many questions remain about the nature of the ischemic stimulus and the long term effects of ischemia on dystrophic muscle. For example, vasoconstrictor responses to activation of sympathetic nerves are reduced in the resting cremaster muscles of mdx mice (Bagher et al., 2011), suggesting that there may be less sympathetic vasoconstriction to oppose during exercise. While this does not appear to be the case in the forearm muscles of DMD/BMD patients (Sander et al., 2000; Martin et al., 2012), studies of other muscles including locomotor muscles are warranted. Whether other metabolic vasodilator pathways independent of nNOSµ-NO (e.g., H⁺, K⁺, ATP) are impaired and contribute to functional ischemia has yet to be explored in dystrophic muscle. Also unknown is if functional ischemia manifests primarily as maldistribution of blood flow within the active muscles or as reduced total muscle blood flow. Compensatory mechanisms such as angiogenesis that are engaged to counteract muscle ischemia appear to be robust in young mdx mice (Straino
Thomas Muscle ischemia in muscular dystrophy

FIGURE 1 | Left panel, in healthy muscle, nNOSµ is localized to the sarcolemma by association with the rod domain of dystrophin and the PDZ domain of α-syntrophin (syn). During muscle contraction, some of the nNOSµ-derived nitric oxide (NO) diffuses to the nearby microvessels where it increases cGMP and attenuates norepinephrine (NE)-mediated vasoconstriction. This NO-mediated functional sympatholysis optimizes blood flow in the working muscles. Right panel, in dystrophic muscle, nNOSµ is reduced in amount and mislocalized from the sarcolemma to the cytosol. Less NO is generated during muscle contraction, resulting in unrestrained sympathetic vasoconstriction and transient functional muscle ischemia, which may exacerbate injury of the diseased muscle fibers. Genetic and pharmacologic interventions targeting different aspects of nNOSµ-NO signaling that alleviate functional muscle ischemia in preclinical studies are shown. sGC, soluble guanylyl cyclase; DG, dystroglycan; PDE, phosphodiesterase.

et al., 2004), but impaired in older mdx mice (Palladino et al., 2013), suggesting that the impact of muscle ischemia on disease progression may vary over time.

RESTORING nNOSµ-NO SIGNALING TO ALLEVIATE MUSCLE ISCHEMIA

In the absence of dystrophin, nNOSµ is both reduced in content and misplaced from the sarcolemma to the cytosol (Brenman et al., 1995; Chang et al., 1996; Chao et al., 1996; Torelli et al., 2004; Kobayashi et al., 2008). Feasible approaches to improve NO signaling in dystrophic muscle have therefore focused largely on providing exogenous NO, restoring normal levels and sarcolemmal localization of nNOSµ, or enhancing effects of residual cytosolic nNOSµ. Multiple genetic and pharmacologic strategies that boost nNOSµ-NO signaling have been shown to ameliorate many features of the dystrophic phenotype—at least in the mdx mouse. These strategies include genetic overexpression of NOS isoforms in muscle (Wehling et al., 2001; Tidball and Wehling-Henricks, 2004; Wehling-Henricks et al., 2005; Colussi et al., 2008), expression of dystrophin mini-genes that restore sarcolemmal nNOSµ (Lai et al., 2009, 2013), supplementation with the NOS substrate L-arginine to increase endogenous NO production from cytosolic nNOSµ (Barton et al., 2005; Voisin et al., 2005; Archer et al., 2006; Hnia et al., 2008; Guerron et al., 2010), treatment with NO-donating drugs (Marques et al., 2005; Brunelli et al., 2007; Benabdellah et al., 2009; Mizunoya et al., 2011; Sciorati et al., 2011; Thomas et al., 2012), and phosphodiesterase 5A (PDE5A) inhibition to prolong the half-life of cGMP arising from the residual NO generated by cytosolic nNOSµ (Asai et al., 2007; Kobayashi et al., 2008).

There is evidence to suggest that some of the beneficial effects of boosting nNOSµ-NO signaling in dystrophin-deficient muscle are likely due to correction of the abnormal vascular phenotype of functional muscle ischemia. In the mdx mouse, PDE5A inhibitors have been shown to ameliorate muscle ischemia, muscle injury, and muscle fatigue after a brief bout of downhill exercise (Kobayashi et al., 2008). In this seminal study by Kobayashi and colleagues, the effect was dramatic and immediate and was seen with two different PDE5A inhibitors, tadalafil and sildenafil. Acute tadalafil treatment has also been shown to reduce contraction-induced injury in mdx mice, while chronic treatment begun in utero improves muscle morphology, attenuates sarcolemmal damage, and reduces muscle fibrosis (Asai et al., 2007). Chronic sildenafil treatment has been shown to improve cardiac dynamics in mdx mice and to rescue dystrophic skeletal muscle and prolong survival in a zebrafish model of DMD (Khairallah et al., 2008; Adamo et al., 2010; Kawahara et al., 2011).

PDE5A inhibitors have proven to be safe and effective not only for patients with erectile dysfunction but also for those with pulmonary hypertension (Ravipati et al., 2007). Given the encouraging findings of pre-clinical studies in the mdx mouse, Martin and colleagues recently tested the translational potential of PDE5A inhibition to benefit patients with muscular dystrophy (Martin et al., 2012). They showed that treatment with a single dose of tadalafil rescued the abnormal vascular phenotype in the muscle of patients with BMD, fully restoring NO-dependent modulation of reflex sympathetic vasoconstriction in the exercising muscles. Tadalafil alleviated microvascular ischemia and fully restored muscle blood flow regulation in 8 of the 9 BMD patients studied (Martin et al., 2012). This finding is consistent with the hypothesis that PDE5A inhibition boosts a residual
NO-cGMP signal arising from nNOS\textsubscript{µ} misplaced to the cytosol of dystrophin-deficient muscle. It is not clear why one patient did not respond to tadalafil, but conceivably some patients with DMD/BMD might have such a low level of residual muscle nNOS\textsubscript{µ} that the NO-cGMP signal is insufficient for the PDE5A inhibitor to boost. For such patients, NO-donating drugs could offer an alternative approach to restore NO signaling.

The use of NO-donating drugs in muscular dystrophy was first suggested in 2005 when Voisin and colleagues showed that 6 weeks of daily molsidomine treatment of mdx mice increased muscle utrophin, reduced creatine kinase, and reduced muscle necrosis (Voisin et al., 2005). Despite the beneficial effects observed in this short-term study, molsidomine may not be the best choice for long-term NO replacement in dystrophic muscle because the drug is metabolized to SIN-1 in the liver, which decomposes into NO and superoxide that can combine to form the damaging free radical peroxynitrite (Singh et al., 1999). Over time, this could be detrimental as dystrophin-deficient muscle cells are highly sensitive to free radical injury (Rando, 2002). Furthermore, unlike the PDE5A inhibitors, acute treatment with molsidomine did not reduce exercise-induced fatigue in mdx mice (Kobayashi et al., 2008).

Another class of NO-donating drug that has shown potential in pre-clinical mdx mouse studies is the cyclooxygenase (COX)-inhibiting NO donor (CINOD) that combines a standard COX inhibitor with a NO-donating moiety to produce dual pharmacological action (Keeble and Moore, 2002; Wallace et al., 2009). Chronic treatment (6–12 months) of mdx and α-sarcoglycan null mice with the CINOD HCT 1026, a NO-donating flurbiprofen, has been shown to improve muscle morphology and reduce muscle necrosis, inflammation, and fatigue (Brunelli et al., 2007). Similar effects have been observed in α-sarcoglycan null mice treated with NCX 320, a NO-donating ibuprofen (Sciorati et al., 2011). Improved muscle blood flow may contribute to the beneficial effects of these drugs as short-term treatment for as little as 1 month with HCT 1026 reverses functional muscle ischemia in mdx mice (Thomas et al., 2012). Importantly, the effect of HCT 1026 to prevent functional muscle ischemia does not abate with prolonged treatment, negating the concern that tolerance to the drug might develop with chronic use (Thomas et al., 2012). This is a potential drawback for some commonly used NO donors such as the organic nitrates (e.g., nitroglycerin), which lose vasodilator potency during continuous exposure (Munzel et al., 2005). Translational studies to determine if CINODs ameliorate functional muscle ischemia have yet to be carried out in patients with DMD/BMD. However, an initial 12-month pilot study has shown that co-administration of the NO donor isosorbide dinitrate and COX inhibitor ibuprofen is safe and well-tolerated in adult dystrophic patients (D’Angelo et al., 2012).

While boosting nNOS\textsubscript{µ}-NO signaling appears to be an effective means to normalize muscle blood flow regulation in the mdx mouse, it is likely to have additional mechanistic influences as well. NO derived from nNOS\textsubscript{µ} has been shown to regulate force generation, muscle mass, fatigue, muscle repair from injury, oxidative stress, and inflammation (Stamler and Meissner, 2001; Powers and Jackson, 2008). Thus, boosting NO signaling may improve DMD/BMD by a variety of mechanisms that include:

(a) improving muscle blood flow and oxygen delivery (Thomas et al., 1998; Sander et al., 2000; Asai et al., 2007; Kobayashi et al., 2008; Martin et al., 2012); (b) decreasing muscle inflammation (Brunelli et al., 2007; Lai et al., 2009; Sciorati et al., 2011); (c) inhibiting histone deacetylase (HDAC) activity (Colussi et al., 2008; Cacchiarelli et al., 2010); (d) reducing muscle fibrosis (Asai et al., 2007; Guerron et al., 2010); (e) enhancing satellite cell activation during muscle repair (Anderson, 2000; Brunelli et al., 2007); (f) upregulating muscle utrophin—a dystrophin homolog with functional similarities (Voisin et al., 2005; Hnia et al., 2008); and (g) ameliorating cardiac dysfunction (Khairallah et al., 2008; Adano et al., 2010). Although the majority of studies to date have reported favorable effects of boosting NO signaling in dystrophic muscle, further careful analysis of the long-term effects of these strategies is necessary as several studies have shown detrimental effects of mislocalized NO signaling in skeletal muscle. Increased cytosolic nNOS\textsubscript{µ} is postulated to mediate disuse muscle atrophy in normal mouse muscle by non-hemodynamic mechanisms (e.g., involving Foxo transcription factors) (Suzuki et al., 2007) and to reduce force production in dystrophic mouse muscle by hypernitrrosylation of ryanodine receptors (Li et al., 2011).

**SUMMARY**

Recent findings from preclinical studies in the mdx mouse and clinical studies in DMD/BMD patients have led to renewed interest in the vascular hypothesis of muscular dystrophy. The refined hypothesis now provides a molecular mechanism, loss of sarcolemmal nNOS\textsubscript{µ} and reduced paracrine NO signaling to the muscle microvasculature, to explain the occurrence of functional muscle ischemia in dystrophin-deficient muscle. Strategies to restore nNOS\textsubscript{µ}-NO signaling in dystrophic muscle that alleviate functional muscle ischemia include dystrophin minigene therapy, PDE5A inhibition, and NO-donating drugs. The initial reports showing largely beneficial effects of restoring NO signaling in dystrophic mouse muscle suggest that reducing muscle ischemia may allow DMD/BMD patients to perform more work with less muscle injury and fatigue, thereby slowing disease progression and improving quality of life.

**ACKNOWLEDGMENTS**

The author is supported by funding from the NIH (R01-AR056221) and Department of Defense (W81XWH-12-1-0256).

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Conflict of Interest Statement: The author has received funding and research materials from Nixco Research Institute, which is the source of one of the drugs (HCT 1026) discussed in the article.