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Promotion of Consistent Myelin-associated Upregulation

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HIF-1α and CXCR4 cooperatively regulate vascular growth and remodeling Our understanding of the HIF-1α and CXCR4 axis has been greatly expanded in recent years with the identification of many key signaling pathways that control growth and remodeling, and the rapid progress in understanding the molecular and cellular mechanisms. We will briefly recapitulate some of the key findings, and then give a brief overview of the central role of the HIF-1α/CXCR4 axis in vascular remodeling. The HIF-1α/CXCR4 axis: The HIF-1α/CXCR4 receptor is a heterodimer composed of CXCR4, a co-receptor, and SH2, a small Groucho receptor that is a major regulator of angiogenesis. The HIF-1α/CXCR4 receptor is a co-receptor that is expressed on both endothelial cells (EPC) and smooth muscle cells (SMC). The HIF-1α/CXCR4 receptor co-regulates the following proteins: vascular endothelial growth factor (VEGF), angiopoietin-1 (Ang-1), insulin-like growth factor-1 (IGF-1), insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (b-FGF), fibroblast growth factor (FGF-2), growth factor-binding protein 1 (GBMP) and vascular smooth muscle cell-derived factor-

1 (VSMC-1). The HIF-1α/CXCR4 receptor mediates the inhibition of the HIF-1α/CXCR4 signaling pathway during skeletal and cardiac muscle development.

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To our knowledge, the studies reviewed here are the most comprehensive studies demonstrating that vascular endothelial cells are mobilized from the bone marrow into the circulation after ischemia and that HIF-1α and VEGF-A are sufficient to transduce the HIF-1α/VEGFR2 signaling cascade in ECs. However, the study also demonstrated that HIF-1α and VEGF-A could not simultaneously activate VEGFR2 and HIF-1α/VEGFR2 signaling, whereas this was the

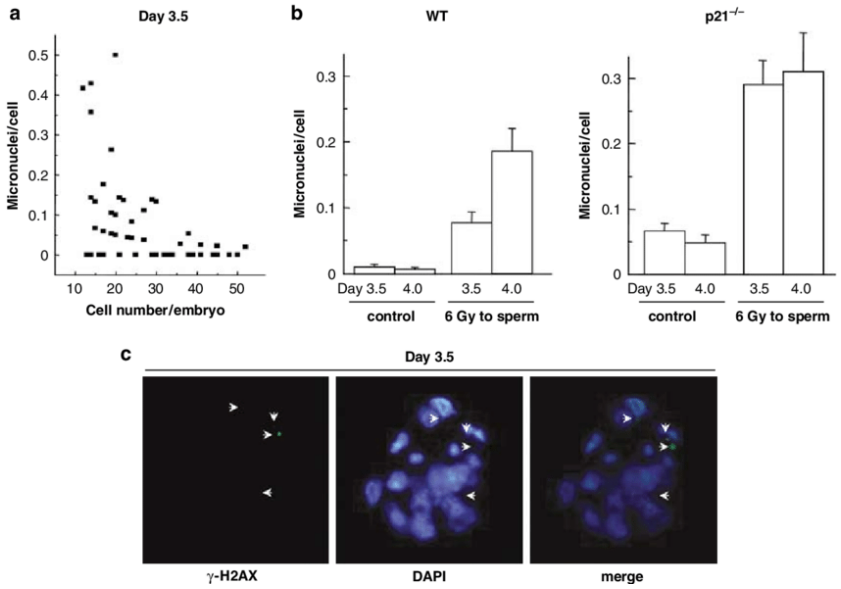

FIGURE 1 Observed Immediate Fertilization Response to Irradiation

case only in the case of HIF-1α. The authors also reported that HIF-1α/VEGFR2 signaling is required for the induction of HIF-1α and VEGFR2 in ECs (Fischer et al. (2015)), further implicating the HIF-1α/VEGFR2 signaling pathway in the regulation of endogenous HIF-1α and VEGFR2 signaling in the production of HIF-1α and VEGFR2.

This study has established that VEGF-A-dependent proteolysis of adenomatosis through VEGFR2 is sufficient to induce vascular endothelial cell proliferation and induce the recruitment of the VEGFR2 to the HIF-1α/VEGFR2 signaling domain that is required for VEGF-A-dependent adhesion and migration. The recruitment of the VEGFR2 appears to be mediated by the HIF-1α/VEGFR2 signaling cascade, which leads to the activation of VEGFR2, thereby activating the HIF-1α/VEGFR2 signaling cascade. Further supporting this notion is the findings that VEGF-A-mediated recruitment of pro-inflammatory cytokines to the ECs, in addition to HIF-1α and VEGFR2 signaling, may induce the production of VEGFR2 in ECs.

The recent report that VEGF-A mediates HIF-1α-dependent vasodilation further establishes that VEGF-A is required for vascular endothelial progenitor cell (EC) proliferation and migration. The VEGF-A-dependent angiogenesis and vasculogenesis is mediated by the VEGFR family of heparan sulfate proteoglycans (Gould et al. (2012)). HIF-1α and VEGFR2 are expressed in ECs, whereas VEGF-A is expressed in non-endothelial tissues including bone marrow vasculature (Haas et al. (2013a,b)). VEGF-A mediates the HIF-1α-dependent angiogenesis and vascularization and plays important roles in the regulation of vascular integrity, angiogenesis, and the survival of endothelial cells (Rennert et al. (2013)).

The current study presents a novel model suggesting that the HIF-1α/VEGFR2 pathway is required for HIF-1α/VEGFR2 activation in ECs by inducing the expression of VEGFR2. The HIF-1α/VEGFR2 pathway is also critical for VEGFR2 expression to promote the regulation of EC proliferation and vascularization. The authors proposed that VEGF-A-dependent recruitment of pro-inflammatory cytokines and angiogenesis by VEGFR2 in ECs may drive EC proliferation and vascularization, thereby promoting the recruitment of the VEGFR2 signaling domain.

The finding that the HIF-1α/VEGFR2 signaling cascade is required for the recruitment of neovessels and the

formation of ECs suggests that HIF-1α/VEGFR2 signaling may modulate the ability of ECs to establish and maintain vascular integrity. The authors showed that the VEGF-A/VEGFR2 signaling may influence the migration and proliferation of ECs in vitro , and the recruitment of the VEGFR2a/VEGFR2. However, HIF-driven recruitment CD34 + /CD133 + cells into the regenerated region is less efficient than HIF-driven recruitment of CD133 + /CD34 + cells in the regenerating area.

The expression of cyclin D is decreased in CD34 + /CD133 + cells. This may be due to the loss of cyclin D-regulated transcription. This effect may also occur through the influence of CD133. To evaluate the function of cyclin D-regulated transcription in the regenerating region, CD34 + /CD133 + cells were transfected with a plasmid encoding either a plasmid containing DNA encoding cyclin D or a DNA encoding a phosphorylated serine (Ser 1/Ser 3), or a plasmid containing V-Ras, a serine residue that regulates Drosophila HIF-receptor signaling (Vangestan et al., 2005). Recombined cells were detected by luciferase assays, and these transfected cells were observed on the surface of regenerating bone. Transfected cells were quantified by the percentage of transfected cells with phosphorylated Ser 7 on the surface and expressed phosphorylated Ser 7. The transfected cells were harvested and analyzed for HIF-1α and HIF-2α expression.

The HIF-2α/β isoform, which is expressed during the proliferative phase, is critical for HIF-1α/β activity (Boulware et al., 2004). The constitutive accumulation of HIF-1α is an important mechanism for regulating HIF-2α activity. HIF-2α is ubiquitously expressed in the bone marrow microenvironment where it may regulate proliferation, and the presence of this isoform in regenerating bone can suppress HIF-1α-mediated transcription (Chen et al., 2001b ; Li et al., 2004). However, the HIF-2α activity of CD34 is impaired in irradiated mice, and the absence of HIF-2α in irradiated cells may compromise the regenerative potential of the regenerating area, leading to the reduction of HIF-2α activity in this region.

The expression of cyclin D was decreased in the regenerating region in both HIF-1α/β isoform as well as in the HIF-2α/β isoform. HIF-2α/β isoform was significantly reduced in both irradiated and uninjured adult mice. The reduction of cyclin D expression in irradiated mice is likely due to the reduced expression of cyclin D in the regenerating region.

Cyclin D protein levels were significantly decreased in the regenerating region of irradiated mice. These parameters were significantly reduced in both irradiated and uninjured adult mice. The decrease in cyclin D expression was not only due to suppression of cyclin D expression, but also to suppression of HIF-1α activity, which may impair the ability of HIF-1α to induce HIF-1α transcription in the regenerating region and thereby promote HIF-1α transcription in the regenerating region.

To evaluate the role of HIF-1α in the regenerating region, CD133 + /HUVECs were transfected with a plasmid encoding either a plasmid containing V-Ras, a serine (Ser 1/Ser 3) that inhibits V-Ras signaling (Li et al., 2004), or a serine (Ser 3) that activates V-Ras (Li et al., 2001). The transfected cells were harvested and analyzed for V-Ras and HIF-1α expression. HIF-1α expression was not significantly reduced in CD133 + /HUVECs.

The expression of cyclin D was decreased in CD34 + /CD133 + cells. This may be due to the suppression of cyclin D expression in these cells. In irradiated mice, CD34 + /CD133 + cells were found in the regenerating region. The majority of CD34 + /CD133 + cells were CD133 + /CD34 + , while CD133 + /CD34 + cells were mostly in the CD133+/CD133+ fraction. However, CD34 + /CD133 + cells were also found in the regenerating region. CD133 + /CD34 + cells were significantly reduced in irradiated and uninjured adult mice.

CD133 + /CD133 + cells were transfected with a plasmid encoding either a plasmid containing V-Ras or a serine (Ser 1/Ser 3) that inhibits V-Ras signaling. At the indicated time points, the transfected cells were harvested and analyzed for cyclin D expression. The transfected cells were harvested and analyzed for HIF-1α and HIF-2α expression. HIF-1α expression was not significantly reduced in CD34 + /CD133 + / addition, in irradiated cells, the levels of pro-apoptotic factors such as CCR2, TNFα, NOS, BDNF, and IL-6 were significantly increased. In contrast, in the uninjured

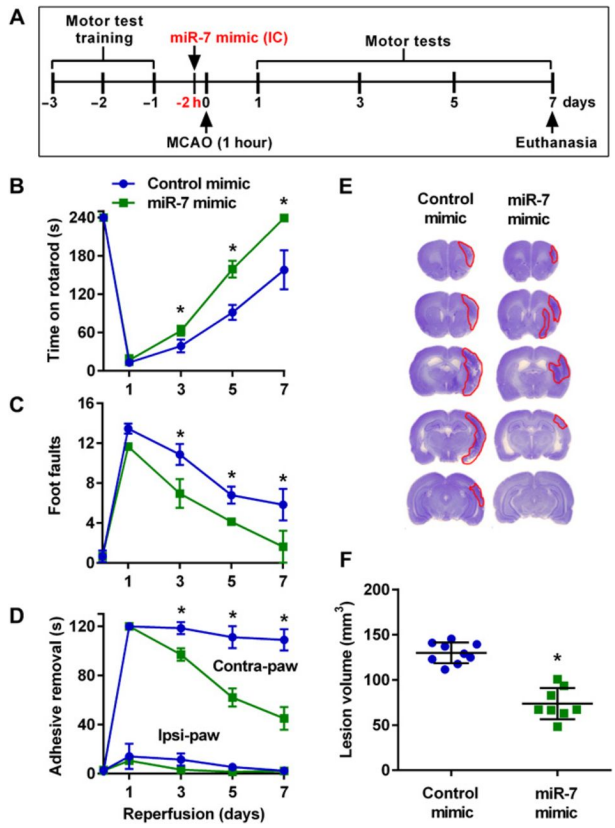

FIGURE 2 Significant Function Ischemic Recovery

mouse, the levels of pro-apoptotic factors such as CCR2, TNFα, and NOS did not change significantly. These data suggest that the level of pro-apoptotic factors in irradiated cells is critically important in the development of peripheral vascular disease in the mice, and that the changes observed in irradiated cells reflect more than just a decrease in the number of pro-apoptotic factors. Further, the lack of a reduction in pro-apoptotic factors could be due to reduced pro-inflammatory cytokine levels, which were undetectable in the uninjured brain.

To determine the role of HIF-1α in promoting apoptosis in the injured brain, we analyzed the level of apoptosis induced by HIF-1α or CCS-3 in the uninjured brain. We examined apoptosis by measuring the levels of apoptosis-associated proteins such as caspase-3, caspase-9, p38, and caspase-9. Interestingly, apoptosis-associated proteins accounted for significantly less apoptosis-associated proteins in irradiated brain than in uninjured control brains.

In this study, we have found that apoptosis-associated proteins are increased in irradiated and irradiated mouse CNS. We have also found that apoptosis-associated proteins are reduced in irradiated and irradiated brain. Although in irradiated brain, apoptosis-associated proteins were undetectable in these brain sections, apoptotic-associated proteins were significantly reduced. These data suggest that the levels of apoptotic-associated proteins are critical for the development of acute vascular disease in the brain of irradiated mice.

In the present study, we have compared the severity of peripheral and central vascular diseases in the brain of irradiated and irradiated mice and found that the latter are characterized by elevated levels of apoptotic factors

whereas peripheral vascular disease is characterized by reduced levels of apoptotic factors. We have also found that in the brain of irradiated and irradiated mice levels of apoptotic-associated proteins are reduced.

The central nervous system (CNS) is a major organ and a major source of the pro-survival factors and cytokines produced in response to brain injury. The central nervous system includes the brain, spinal cord, skeletal muscles, the nervous system of the spinal cord, and the cerebellum. The cerebrospinal fluid (CSF) is a vital tissue for survival of the CNS and is the blood supply for the CNS. The CSF is a circulating vesicle containing 3 to 4 million cells, which are released into the blood and secreted proteins, ultimately releasing cytokines and growth factors. The CSF is a major site of action in the development of neurodegeneration, and the release of cytokines is important for survival of the CNS and for the neurodegeneration in the CNS. The CSF is a major site of action in the initiation of neurodegenerative events by the release of cytokines, growth factors, and cytokines that promote neurodegeneration, including neurofibrillary tangles (NFTs) resulting from the release of pro-fibrillary tangle (PGTL).

CNS pathology is characterized by neuropathology by the progression of neurofibrillary pathology. Neurofibrillary pathology is a major pathological feature of the CNS and is the most common cause of death in patients with peripheral neuropathy (PNS) (Pittenger and Rudnicki, 2007). Patients often present with acute peripheral neuropathy or in the last decade of the decade as a result of a variety of factors, including an underlying neurodegenerative disorder, peripheral arterial disease, myocardial infarction, cerebrovascular disease, and ischemia/reperfusion injury (Illingworth and Rudnicki, 2010 ; Pittenger et al., 2007). The neurofibrillary pathology is a major cause of peripheral vascular disease (PVD), neuropathic pain, and stroke. The pathogenesis of these diseases is mediated by the production of neurofibrillary tangles (PFTs) and PGP-2 (pigmented cells), which are the structural elements of the arteriole wall and connective tissue of the peripheral vessels (Pittenger et al., 2005). PFTs are not only responsible for the development of peripheral vascular disease but also contribute to its pathogenesis (Pittenger et al., 2005). PFTs, which are produced by the piaocytes, are associated with the formation of PVD, and PGP-2, which is produced by the endothelial cells, are responsible for the progression of PVD. PVD and PFR. The progression is driven by the production of CNS develops, maintains and remodels, and regulates the functions of the central nervous system (CNS) in a variety of ways (e.g., CNS plasticity, neurogenesis, growth of new neurons, axonal sprouting). However, the cellular and molecular mechanisms that mediate the processes of CNS plasticity and growth are still under active investigation (e.g., in the context of stroke). The importance of brain-computer interfaces (BCI) for the neurocognitive recovery following brain injury has been demonstrated in a number of studies (reviewed in (Cherney et al. (2013)), see also (Cherney et al. (2013)). Although the effects of BCI on brain function in young adult patients were not studied in this review, the effects of BCI on the brain in aged patients are probably well described. In summary, BCI is a novel toolkit for patients, clinicians and researchers to study neurological deficits following brain injury. The impact of BCI on clinical effectiveness is likely to reach a high level of significance for improving BCI-based BCI-guided interventions.

One of the main findings from these studies is that the number of newly synthesized β-catenin-expressing cells is significantly increased in the subventricular zone of the rat brain after a 2-hour TBI compared to the control rats. The number of β-catenin-positive cells in the subventricular zone of the rat brain after a 2-hour TBI was also significantly increased compared to the control rats. These results are consistent with the concept that the increase in the number of β-catenin-positive cells with the TBI may reflect the effects of the TBI on the expression of the transcription factor c-Met.

In the absence of a conditioned environment, β-catenin-dependent transcription is not restricted to the subventricular zone of the rat brain and many other brain regions. However, several other brain regions also begin to express β-catenin after the TBI, and some of these cells are able to form new β-catenin-expressing cells. In a study recently published by Chen et al. Similar to the findings in rats, a similar effect was observed in the subventricular zone of the rat brain after a 2-hour TBI. These results are in agreement with our data and have been shown to be specific to the

subventricular zone of the brain in rats.

In addition to the expression of β-catenin, some other gene transcription factors including MyoD, Myogenin, myogenin, and myogenin are also upregulated in the subventricular zone of the rat brain after a 2-hour TBI. In addition to these genes, MyoD was upregulated in the subventricular zone of the rat brain after a 2-hour TBI. Myogenin and myogenin have been implicated in the expression of several genes involved in the regulation of cell cycle dynamics and apoptosis. The increase in the number of myogenin-expressing cells in the subventricular zone of the rat brain after a 2-hour TBI is also consistent with the increase in the number of β-catenin-positive cells in the subventricular zone of the rat brain after a 2-hour TBI.

Another factor that may be important to the increase in the number of β-catenin-positive cells in the subventricular zone of the rat brain after a 2-hour TBI is the stimulation of the transcription factor Casp1. Casp1 is a protein involved in the regulation of cell proliferation and differentiation.

Following a 2-hour TBI, cells are actively proliferating, and the number of newly synthesized β-catenin-expressing cells increases. Therefore, the number of newly synthesized β-catenin-expressing cells in the subventricular zone of the rat brain after a 2-hour TBI could be directly related to the number of new β-catenin-positive cells in the subventricular zone of the rat brain after a 2-hour TBI. One of the main features of the increase in the number of β-catenin-positive cells in the subventricular zone of the rat brain after the TBI is the stimulation of the transcription factor Casp1. Casp1 is a protein involved in the regulation of cell proliferation and differentiation. Casp1 has been implicated in the growth of retinal ganglion cells, as well as a new cells have been 44], we found that the expression of a transcription factor, SHH3, was downregulated in the spinal cord in the sham-operated animals, whereas the expression of MRL-SNARE, a marker of the MRL-Gsa-Skeletal muscle lineage, increased over time. However, we could not study the effects of MRL-SNARE on the expression of this gene following SCI. Therefore, to determine the effects of MRL-SNARE on locomotor recovery, we compared the expression levels of a number of genes in the spinal cord and the spinal cord contralateral to the injury. We found that a number of genes were significantly upregulated in the spinal cord of the mice subjected to the SCI, such as a number of genes, such as BMP4, which promotes axonal outgrowth and is required for locomotor recovery, RAS, which is a marker of the regenerating fibers, and PTH 1-34, which is required for muscle atrophy (Gould et al. (2012); Smith et al. (2014)). Interestingly, a number of genes with expression profiles similar to those of SHH3 were upregulated in the spinal cord. These genes include WNT1, Notch, and the transcription factor SCF4. Interestingly, MRL-SNARE was downregulated in the spinal cord, while MRL-SNARE protein was elevated in the contralateral spinal cord. These data provide supporting evidence implicating SCF4 and MRL-SNARE as transcriptional regulators of SCF4. We also found that MRL-SNARE and MRL-APC expression profiles were upregulated in the spinal cord, but remained downregulated in the contralateral spinal cord. These data indicate that MRL-SNARE and MRL-APC are not solely responsible for the upregulation of MRL-SNARE in the spinal cord of the injured mice.

The upregulation of MRL-SNARE in the spinal cord was associated with an increased expression of MUNE3, a marker for MRL-derived muscle fibers (Gould et al. (2012)). These data suggest that MUNE3 levels are an important determinant of the effect of MRL-SNARE on SCF4 expression, or MUNE3 signaling may be involved in the induction of SCF4 in the spinal cord of the injured mice.

In the present study, we used the mouse SCF4 as a model to examine the effects of SCF4-induced upregulation of MRL-SNARE, with a focus on the effects on the spinal cord of downregulation of MUNE3. MUNE3 is one of the known MUNE factors, since it is expressed primarily by satellite cells in the adult muscle (Lukens et al. (2013)), (Liu et al. (2012)). This effect of MUNE3 is likely to be important for the induction of SCF4 expression and upregulation of MUNE3, because MUNE3 was upregulated in the spinal cord. This is consistent with previous studies showing that MUNE3 upregulation is associated with axonal sprouting and muscle atrophy in the spinal cord (Gould et al. (2012)

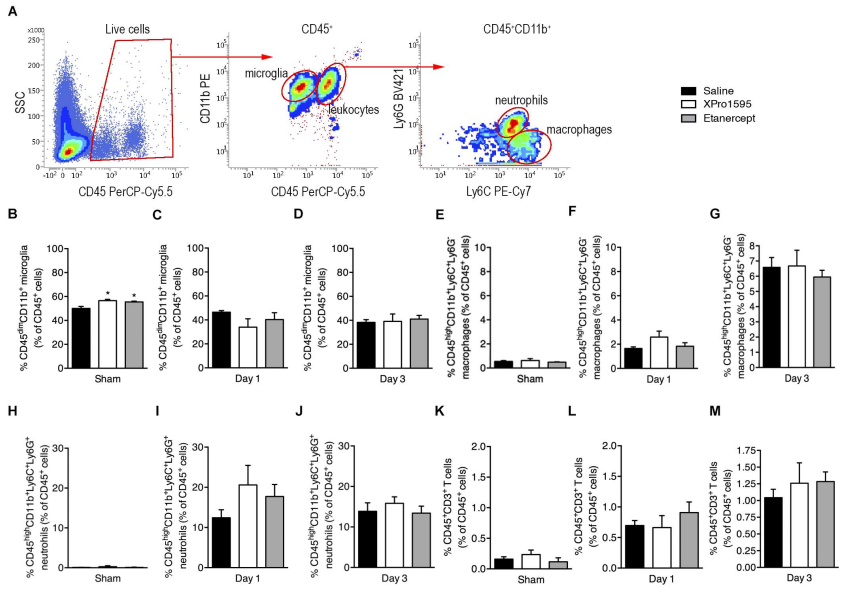

FIGURE 3 Significant Functional Contralateral TMS/Efluor Recovery

). The mechanisms by which MUNE3 upregulation is associated with muscle atrophy in the spinal cord are not fully understood. As in the spinal cord, upregulation of MUNE3 has been shown to promote axonal growth in both the spinal cord and the spinal cord contralateral to the injury (Gould et al. (2012)). Therefore, a potential mechanism by which MUNE3 upregulation promotes muscle atrophy in the spinal cord involves a parallel upregulation of MUNE3.

The upregulation of MUNE3 in the spinal cord is consistent with previous studies showing that MUNE3 is required in skeletal muscle to maintain the normal growth rate of the spinal cord and promote muscle regeneration (Liu et al. (2012)). Previous studies have also shown that upregulation of MUNE3 is associated with axonal growth (Rae et al. (2014)). Thus, we expect that upregulation of MUNE3 in the spinal cord is associated with a parallel upregulation of MUNE3, and that these results may help explain the upregulation of MUNE3 in the cervical spinal cord.

The upregulation of MUNE3 in the spinal cord is a direct result of MUNE3 transcriptional activity; this transcriptional activation represents a potential mechanism by which an MUNE3-mediated mechanism could be mediated. MUNE3 was first identified in the embryonic spinal cord (Gould et al. (2012)). Recent studies have reported that MUNE3 promotes axonal growth through a variety of mechanisms, including by promoting myelin formation, inducing migration of myelin-associated myelin, and inducing myelination (Gould et al. (2012); Li et al. (2014); Bai et al. (2012a,b); Smith et al. (2014); Liu et al. (2012)). MUNE3 is also involved in myelin repair by stimulating myelination and myelin migration (Bai et al. (2012a,b)), (Walker et al. (2015); Bai et al. (2012b)). In the spinal cord, MUNE3 regulates the activity of MUNE1, which has been shown to be the direct inhibitory to MUNE3 (Lukens et al. (2013)). MUNE3 has been shown to promote axonal sprouting, and myelination in the spinal , the high level of expression observed in the spinal cords of all mice strains is likely to be due to the fact that MRL mice show similar increases in the expression of these genes compared to controls. Furthermore, a single SCI model in the MRL mice results in a decrease in the expression of the SCN 1 gene, suggesting that the decrease in SCN 1 expression is due to SCN deficiency. These data provide strong evidence that the decrease in SCN 1 expression in the spinal cords of MRL-SNARE mice may be due to a defect in SCN 2 generation, which results in a reduction in the expression of SCN 1 .

Mice have lower resting levels of pro-MHC, and lower levels of MHC 7 compared to controls. Our data suggest that the expression of the two MHC genes in the spinal cord is decreased in MRL-SNARE mice, suggesting that these mice are different from controls. The decrease in SCN is also associated with a decrease in the expression of the anti-MHC gene, MHC 7. Mice subjected to SCI in the MRL-SNARE mice showed a 50% reduction in SCN expression, compared to wild type littermates. These data also suggest that the decrease in SCN is due to a reduction in the expression of pro-MHC, suggesting that changes in pro-MHC levels may be involved in the decrease in SCN level. This reduction in SCN level may contribute to some of the differences in histopathology between MRL and control groups. For example, the increase in the expression of the pro-MHC gene in MRL-SNARE mice occurs mainly in the lumbar region, a region that is associated with a reduction in inflammatory and degenerative diseases (Li et al. (2014)). Previous studies in SCI models in mice have shown that SCN is a central regulator of a number of processes (Hashmi et al. (2011); Borlongan et al. (2012)). Therefore, we decided to compare the expression of pro-MHC and anti-MHC in the spinal cord of these MRL-SNARE animals and their respective wild type littermates. The results showed that SCN, as a central regulator of SCN, is a significant contributor to the decrease in SCN levels observed in the spinal cords of MRL-SNARE mice.

The analysis of RNA isolated from SCI-induced spinal cord in mice, compared to control cords, demonstrated that expression of pro-MHC, anti-MHC and anti-MHC 7 were all decreased in spinal cords of MRL-SNARE mice compared to control cords. Furthermore, the decreases in SCN mRNA levels were more evident in spinal cords of MRL-SNARE mice compared to wild type littermates, suggesting that these changes may contribute to the decrease in SCN levels observed in this group. The ability of stroke to restore function and the consequent ability of stroke to reverse the course of the disease are central to the investigation of therapeutic interventions for the treatment of cerebral ischemia. Although the mechanisms of cerebral ischemia recovery following stroke are unknown, there are several basic concepts for stroke and stroke therapy related its therapeutic outcomes. First, the recovery follow-ing ischemic stroke is associated with an initial burst of growth in blood flow. In addition, a substantial fraction of post-ischemic stroke is associated with significant recovery of brain activity and function. Second, following ischemic stroke, there is an initial influx of extracellular matrix molecules, leading to the release of their expression. Third, the extracellular matrix released with ischemia increases in concentration and leads to the stabilization of the extracellular matrix released with ischemia, leading to the release of matrix-degrading peptides such as MMP-7 and ADAMTS-7. In addition, extracellular matrix molecules can promote the release of MMP-7 and ADAMTS-7, as well as matrix metalloproteinase 2 (MMP-2) and the proteolytic cleavage of MMP-2 and MMP-7, respectively. Finally, the extracellular matrix released with ischemia is associated with increased proliferation of neuroblasts and neuronal progenitors and secondary astrocytes [7 – 9]. The effect of stroke is a combination of growth and activation of neurogenesis, promoting plasticity, and regulating neuroinflammation (Auletta et al. (2013)). The mechanisms of therapeutic effectiveness of stroke remain unknown.

The ischemic stroke results in brain damage (i.e., death) followed by a neuroprotective response (i.e., restoration of neurotransmitter and other neurotransmitters and signaling molecules) leading to a recovery in brain function (i.e., enhanced recovery of function and recovery of ischemic state). The recovery is associated with the recovery of brain function. Cerebellar function is significantly improved following a stroke, which in turn leads to functional recovery (Noble et al. (2011)). Following a stroke, ischemic stroke can result in the ischemia The role of the TGF-β superfamily in recovery after stroke is not well delineated. The TGF-β signaling pathway is activated in the brain after traumatic brain injury, a condition known to be associated with neurogenesis, and several recent studies show that this pathway is involved in stroke recovery (Li et al. (2014); Borlongan et al. (2012); Drago et al. (2014)). The activation of this pathway is the result of the activation of a TGF-β-regulated microglia pro-inflammatory system, an important factor in the activation of TGF-β signaling cascades after ischemic stroke (Li et al. (2014); Hayakawa et al. (2013)). Fol-

lowing ischemic stroke, a large series of intracellular events are mediated by TGF-β signaling cascades, which include activation of the canonical TGF-β signaling pathway, activation of the p38 mitogen-activated protein kinase pathway, expression of the fibroblast growth factor receptor-γ (FGF-R), and activation of the growth and differentiation signal transduction pathway.

An additional aspect of functional recovery is that patients regain the ability to use their arm, which can be used to evaluate the ability of the brain to repair or replace itself. To accomplish this, functional recovery of the upper arm is achieved by increasing strength and/or strength conditioning during recovery from the most severe of the injuries. The ability to perform these tasks may also be improved with the increased strength of the upper arm (Paleville et al. (2012)).

Two different methods to assess functional recovery are the application of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDC-3F). TMS and TDC-3F are commonly used to assess functional recovery, but it is also commonly used to assess recovery after stroke (Jiang et al. (2014); Plane et al. (2010)). The TMS technique has been used in the clinic to assess functional recovery after ischemic stroke (Yousuf et al. (2015)). However, the TDC-3F technique was used only with ischemic stroke, which has been shown to provide a much better recovery of the upper arm.

Another way to evaluate functional recovery is to determine functional recovery after stroke. This technique is a method that has been used to assess functional recovery after ischemic stroke (Paleville et al. (2012)). The technique has been used to assess functional recovery after stroke due to a variety of injuries (Paleville et al. (2012)). One of the main goals of the stroke trials is to determine whether stroke improves functional recovery after stroke. After a stroke, a significant number of patients recover from the most severe behavioral impairment at the injury site (Yousuf et al. (2015)).

One of the more widely-used studies to evaluate functional recovery after stroke is the application of transcranial magnetic stimulation (tDCS) to rats (Paleville et al. (2012)). TMS/eFluor ® is commonly used to assess functional recovery after ischemic stroke. This study used an animal model after stroke to evaluate the effect of tDCS on functional recovery (Jiang et al. (2014); Soleman et al. (2010)). TMS/eFluor ® was applied to the hindlimb muscles of the rat and the tester noted that tDCS had a significant effect on functional recovery.

The use of neuroimaging to assess functional recovery after a stroke has been extensively studied. Studies using in vitro models including studies of limb muscles in vitro (Paleville et al. (2012)) and in vivo in vivo (Paleville et al. (2012)) are ongoing. Tissue collected from the hindlimbs of the rats after stroke, as well as the brains of the brains of the injured rats, were subjected to histological analysis to determine the extent of axonal density and connectivity to the striatum. The extent of the axonal density was determined using an EPI camera, which was used to measure the density of the axons that were present. Due to the large volume of the tissue, the density measurements were limited in size. However, the tissue density was representative of the density of the intact axons that were regenerated after injury.

An important goal of neuroimaging is to understand the mechanisms that promote recovery after stroke and assess its effects on functional recovery. In the present study, we investigated the effects of tDCS on functional recovery after ischemic stroke.

There was a significant improvement in functional recovery after a stroke in the ischemic leg of the rat (Figure 2-B). No significant change in functional recovery was observed in the ischemic contralateral limb in the ischemic leg of the same animals treated with TMS/eFluor ® (Figure 3). Similarly, there was a significant improvement in functional recovery after stroke in the ischemic contralateral limb of the same rat treated with TMS/eFluor ® (Figure 4). These results suggest that TMS/eFluor ® improves functional recovery after stroke.

The ability of the ischemic penumbra to be significantly improved after stroke was verified by the presence of

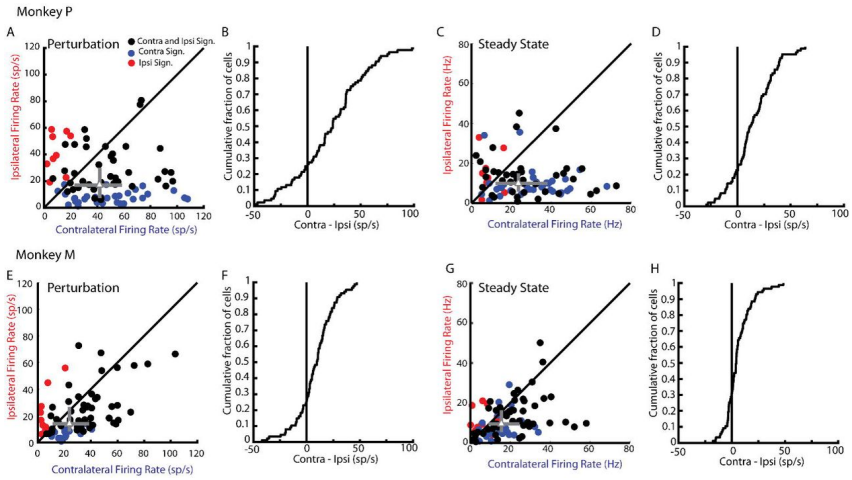

FIGURE 4 Significant Contralateral Improvement

neuronal excitability. The lesion site did not appear to be significantly compromised. The lesion site appeared to be significantly reduced in the injured with TMS alone. The ischemia also showed a significant reduction in the animal-based stroke trial is also being done in the form of an open-label, phase II trial in stroke patients that will evaluate the effects of tDCS, including the effects of tDCS, on functional recovery (Pantoja et al. (2012)).

In addition to potential effects on the cardiovascular system, it has been shown that tDCS may have an important effect on the immune system, since it may reduce inflammatory cytokines (Herrmann et al. (2011); Auletta et al. (2013)). Tissue-type inflammatory cytokines are important to maintain homeostasis of the nervous system. Tissue-type inflammatory cytokines include interleukin (IL)-1β, tumor necrosis factor α (TNFα), and interleukin (IL)-10 (Noble et al. (2011)).

Tissue-type inflammatory cytokines are primarily produced by monocytes as part of a macrophage-induced inflammatory response. Tissue-type cytokines are known to be regulated by several mechanisms including inflammatory chemokines, inflammatory monocytes, and immune cell-associated mediators, thereby modulating their secretion. Tissue-type cytokines can have effects on cells including proliferation, migration, migration, and death (Li et al. (2014)). Tissue-type cytokine release is regulated by inflammatory monocytes (Ranganathan et al. (2013)).

Tissue-type inflammatory cytokines exhibit striking changes in their expression patterns. For example, in the first week after stroke, most tissue-type cytokines show a trend towards downregulation. The downregulation seen in the first week after stroke correlates with the increase in inflammatory cytokines, which is also accompanied by an increase in cytokine secretion. In addition, the upregulation of cytokines that are either associated with or closely associated with stroke is seen in patients with stroke. For example, the upregulation of cytokines that signal to T cell function is seen in patients with stroke (Hashmi et al. (2011)).

It has been reported that stimulation with tDCS can induce the release of many cytokines in the form of chemokines associated with the inflammation/inflammatory response [15 – 17]. A recent study showed that in patients with stroke, tDCS increased the expression of key cytokines in the brain, in a dose-dependent manner (Hayakawa et al. (2013)). In a study of stroke patients, tDCS increased the levels of cytokines, chemokines and chemokines associated with the inflammation/inflammatory response, such as interleukin-10 (IL-10) (Hayakawa et al. (2013)). In the current study, cell-type specific cell-type specific cytokines were released and the upregulation of cytokines was seen

following stimulation.

Tissue-type cytokines are produced by macrophages, and these cytokines are thought to be important for promoting the inflammatory response. The release of TNFα is an important process for the stimulation of macrophage production. TNFα, which in turn stimulates the production of IL-10 (Fischer et al. (2015)), also stimulates the production of IL-10 (Fischer et al. (2015)). In addition, stimulation of macrophages with TNFα led to downregulation of the inflammatory cytokine, IFN-γ and to a decrease in the expression of several inflammatory molecules that are associated with the inflammatory response (Fischer et al. (2015)).

Tissue-type cytokines are produced by immune cells, and cytokines are released and released by immune cells. For example, TNFα released from the erythroventus muscle stimulates the production of IL-10, IL-4, and IL-12 in macrophages (Paleville et al. (2012)). Similarly, stimulation of immune cells with TNFα led to downregulation of IL-4 and IL-12 in macrophages (Paleville et al. (2012)).

Tissue-type cytokines may be produced by immune cells such as macrophages (Bryers et al. (2013)), the neutrophils (Mancl et al. (2014)), the T lymphocytes (Lukens et al. (2013)), or macrophages (Lukens et al. (2013)). Tissue-type cytokines can be produced in a manner similar to cytokines released by other cell types including neutrophils, macrophages, and immune cells. The release of proinflammatory cytokines, such as IL-1β and TNF-α, is a key process for the stimulation of macrophage production. The release of IL-6 is another process that activates the production of proinflammatory cytokines. Tissue-type cytokines have been shown to be released by immune cells such as T cells (Bryers et al. (2013)). Tissue-type cytokine release is regulated by inflammatory monocytes (Ranganathan et al. (2013)).

In order to study tDCS-induced changes in macrophage production, subjects were stimulated with a single 30-second period of stimulation. After 1 week, the levels of cytokines were measured on day 1, 2, and 4. Tissue-type cytokines, IL-1β and TNF-α, were measured on day 5 and day 14 following the last stimulation.

The stimulation of macrophages is an important aspect of the study. In principle, stimulation with macrophages can be an important process to stimulation of macrophage production, since macrophages produce cytokines. In the synovium, the cytokines are increased by the synovitis and cause a decrease in the local metabolism of the cytokines and chemokines.

Skeletal microenvironments within the bone marrow are composed of numerous matrix constituents that play important regulatory roles in regulating bone homeostasis. Each tissue-type-derived cytokine, from inflammatory monocytes to osteoclast-forming cells, is involved in the regulation of a subset of interstitial homeostasis-modulating cytokines and chemokines, such as TNF-α, IL-1β, and MCP-1 (Rennert et al. (2013)).

Liver injury induces inflammation and apoptosis, both of which can lead to bone destruction (Figure 1). The expression of inflammatory and apoptotic molecules is increased in the blood of the murine embryo and is associated with the development of osteosarcomas (Gould et al. (2012)) (Figure 1). The expression of inflammatory mediators is increased in the blood of the murine embryo; these include monocyte chemotactic protein-1 (MCP-1), interleukin 1 (IL-1), and tumor necrosis factor-α (TNF-α), and keratinocytes are also increased. A decrease in the expression of inflammatory molecules is observed in murine bone marrow following exposure to irradiation, a response that is dependent on the location of inflammatory cells within the marrow (Pantoja et al. (2012)). The response is observed in mice that are irradiated immediately after fertilization and in the embryo within the first three days (Figure 1). The increase in cytokine expression in the blood is accompanied by a decrease in expression of IL-3, a cytokine that is expressed in the bone marrow. The decrease in IL-3 expression in the blood and the absence of IL-3 in the marrow, correlates with the presence of apoptosis in murine bone marrow (Li et al. (2014)). The decrease in IL-3 expression in the marrow correlates with the presence of osteomas that are present in the murine marrow as well as the presence of osteosarcomas. A decrease in the expression of IL-1β in the marrow correlates with the presence of osteomas that

are present in the murine marrow. This decrease in IL-1β in the marrow is associated with the absence of apoptosis in the murine marrow.

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references

Fischer, J A, Zelinka, Christopher, Gallina, Donika, et al. Reactive microglia and macrophage facilitate the formation of Müller glia-derived retinal progenitors. Glia 2015;p. 1608–1628.

Gould, W T, Oppenheim, W R. Motor Neuron Trophic Factors: Therapeutic Use in ALS? Brain research reviews 2012;p. 187–198.

Haas, L T, Lloyd, G P, Yang, Tung H, et al. Exercise Training and Peripheral Arterial Disease. Comprehensive Physiology 2013;p. 2933–3017.

Rennert, C R, Sorkin, Michael, Garg, K R, et al. Stem cell recruitment after injury: lessons for regeneraPve medicine. Regeneraive medicine 2013;p. 833–850.

Cherney, R L, Harvey, L R, BabbiV, M E, et al. Epidural corPcal sPmulaPon and aphasia therapy. Aphasiology 2013;p. 1192–1217.

Gould, W T, Oppenheim, W R. Motor Neuron Trophic Factors: TherapeuPc Use in ALS? Brain research reviews 2012;p. 165–171.

Smith, M G, Onifer, M S. ConstrucPon of pathways to promote axon growth within the adult central nervous system. Brain research bullePn 2014;p. 300–305.

Lukens, R J, Vogel, Peter, Johnson, R G, et al. RIP1-driven autoinflammaPon targets IL-1 independently of inflammasomes and RIP3. Nature 2013;p. 224–227.

Liu, Huaqing, Shubayev, Veronica. Matrix metalloproteinase-9 controls proliferaPon of NG2+ progenitor cells immediately after spinal cord injury. Experimental neurology 2012;p. 236–246.

Rae M, A P, Porter, E B. The Perineuronal Net Component of the Extracellular Matrix in PlasPcity and Epilepsy. Neurochemistry internaPonal 2014;p. 963–972.

Li, Jun, Parker, BreV, Martyn, Colin, et al. 'text': 'The Gene and Its Related Diseases', 'italic': 'PMP22'. Molecular neurobiology 2014;p. 673–698.

Bai, Lianhua, Lennon, P D, Caplan, I A, et al. Hepatocyte growth factor mediates MSCs sPmulated funcPonal recovery in animal models of MS. Nature neuroscience 2012;p. 862–870.

Walker, L C, Xu, Ming X. PTEN inhibitor bisperoxovanadium protects oligodendrocytes and myelin and prevents neuronal atrophy in adult rats following cervical hemicontusive spinal cord injury. Neuroscience letters 2015;p. 64–68.

Li, Yi, Liu, Zhongwu, Xin, Hongqi, et al. The Role of Astrocytes in MediaSng Exogenous Cell-Based RestoraSve Therapy for Stroke. Glia 2014;p. 238–238.

Hashmi, T J, Huang, Ying Y, Osmani, Z B, et al. Role of Low-Level Laser Therapy in NeurorehabilitaSon. PM R : the journal of injury, funcSon, and rehabilitaSon 2011;p. 292–305.

Borlongan, V C, Glover, E L, Tajiri, Naoki, et al. The Great MigraSon of Bone Marrow-Derived Stem Cells Toward the Ischemic Brain: TherapeuSc ImplicaSons for Stroke and Other Neurological Disorders. Progress in neurobiology 2012;p. 213–228.

Aule`a, J J, Bartholomew, M A, Maziarz, T R, et al. The potenSal of mesenchymal stromal cells as a novel cellular therapy for mulSple sclerosis. Immunotherapy 2013;p. 529–547.

Noble, W P, Liang, Jiurong, Jiang, Dianhua. Hyaluronan as an Immune Regulator in Human Diseases. Physiological reviews 2011;p. 221–264.

Drago, Denise, Cossetti, Chiara, Iraci, Nunzio, et al. The stem cell secretome and its role in brain repair. Biochimie 2014;p. 2271–2285.

Li, Hongmei, Gonnella, Patricia, Safavi, Farinaz, et al. Low dose zymosan ameliorates both chronic and relapsing Experimental Autoimmune Encephalomyelitis. Journal of neuroimmunology 2014;p. 28–38.

Hayakawa, Kazuhide, Qiu, Jianhua, Lo, H E. Biphasic actions of HMGB1 signaling in inflammation and recovery after stroke. Annals of the New York Academy of Sciences 2013;p. 50–57.

Paleville TD, L DG, Kay M, B W, Folz, J R, et al. Respiratory Motor Control Disrupted by Spinal Cord Injury: Mechanisms, Evaluation, and Restoration. Translational stroke research 2012;p. 463–473.

Jiang, Yuqiu, Williams, Tja P, Martin, H J. Rapid and persistent impairments of the forelimb motor representations following cervical deafferentation in rats. The European journal of neuroscience 2014;p. 165–172.

Plane, M J, Whitney, T J, Schallert, Tim, et al. Retinoic Acid and Environmental Enrichment Alter Subventricular Zone and Striatal Neurogenesis after Stroke. Experimental neurology 2010;p. 125–134.

Yousuf, Seema, Atif, Fahim, Sayeed, Iqbal, et al. Progesterone in transient ischemic stroke: a dose–response study. Psychopharmacology 2015;p. 3313–3323.

Paleville TD, L DG, Kay M, B W, Folz, J R, et al. Respiratory Motor Control Disrupted by Spinal Cord Injury: Mechanisms, Evaluation, and Restoration. Translational stroke research 2012;p. 463–473.

Soleman, Sara, Yip, Ping, Leasure, Leigh J, et al. Sustained sensorimotor impairments after endothelin-1 induced focal cerebral ischemia (stroke) in aged rats. Experimental neurology 2010;p. 13–24.

Pantoja S, R D, Isenberg, S J, Roberts, D D. Therapeutic Targeting of CD47 to Modulate Tissue Responses to Ischemia and Radiation. Journal of genetic syndrome gene therapy 2012;p. 382–393.

Herrmann, L J, Abarbanell, M A, Weil, R B, et al. Gender Dimorphisms in Progenitor and Stem Cell Function in Cardiovascular Disease. Journal of cardiovascular translational research 2011;p. 103–113.

Ranganathan, Vilapakkam P, Jayakumar, Calpurnia, Mohamed, Riyaz, et al. Netrin-1 regulates the inflammatory response of neutrophils and macrophages, and suppresses ischemic acute kidney injury by inhibiting COX-2 mediated PGE2 production. Kidney international 2013;p. 1087–1098.

Hayakawa, Kazuhide, Qiu, Jianhua, Lo, H E. Biphasic actions of HMGB1 signaling in inflammation and recovery after stroke. Annals of the New York Academy of Sciences 2013;p. 50–57.

Fischer, J A, Zelinka, Christopher, Gallina, Donika, et al. Reactive microglia and macrophage facilitate the formation of Müller glia-derived retinal progenitors. Glia 2015;p. 1608–1628.

Bryers, D J, Giachelli, M C, Ratner, D B. Engineering Biomaterials to Integrate and Heal: The Biocompatibility Paradigm Shifts. Biotechnology and bioengineering 2013;p. 1898–1911.

Mancl, A K, Kirsner, S R, Ajdic, Dragana. Wound biofilms: lessons learned from oral biofilms. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society 2014;p. 352–362.

Lukens, R J, Vogel, Peter, Johnson, R G, et al. RIP1-driven autoinflammation targets IL-1 independently of inflammasomes and RIP3. Nature 2013;p. 224–227.

Ranganathan, Vilapakkam P, Jayakumar, Calpurnia, Mohamed, Riyaz, et al. Netrin-1 regulates the inflammatory response of neutrophils and macrophages, and suppresses ischemic acute kidney injury by inhibiting COX-2 mediated PGE2 production. Kidney international 2013;p. 1087–1098.