The soft touch to muscle building


Aging unavoidably results in progressive decline of muscle strength, ultimately leading to compromised quality of life for the elderly. There are no pharmacological therapies currently available to prevent muscle wasting and the economic burden is expected to only keep increasing along with projected lengthening in life expectancy. Muscle stem cells (MuSCs), also referred to as satellite stem cells, are tissue-specific stem cells dedicated to the repair of muscle tissue and a target cell-type for muscle regenerative medicine. Several reports have attributed loss of MuSC regenerative capacity to changes in the aged systemic and local muscle micro-environments and not to intrinsic defects in the aging MuSC pool. A recent report by Cosgrove and co-workers [1] provides compelling evidence contrary to this position and not only demonstrates that aged MuSC have a cell autonomous reduction in muscle regeneration, but also identify a potential molecular pathway underlying this decline in muscle function and even propose an exciting biomaterial MuSC ex vivo culture system to enhance muscle regeneration in aged patients.

It is important to highlight from the onset that all these findings have been derived from mouse models and next-step experimentation with human muscle tissue is still pending. Using FACS, the authors purified MuSCs with a predefined CD45−CD31−CD11b Sca1−CD34+Integrin α7+ phenotype from young and aged transgenic mice expressing GFP and firefly luciferase, and used these cells to conduct limiting-dilution transplantation experiments in immunodeficient NOD/SCID recipients in order to measure muscle engraftment levels. No difference in engraftment was observed between young versus aged MuSC when 100 cells were transplanted. Only when as few as ten cells from each group were delivered into primary recipients did it become apparent that aged MuSCs engrafted at significantly lower frequency than young cells, suggesting a reduced functional capacity, which was also carried over into secondary recipients receiving tissue explants from primary recipients. By employing the highly sensitive NOD/SCID transplantation assay, the authors were thus able to resolve an unappreciated cell autonomous intrinsic defect.

The intrinsic defect was tracked to an upregulation in the cell-cycle inhibitors, p16^Ink4a and p21^Cip1, both classically associated with cell senescence. Further digging revealed the stress-related pathway, p38α/β MAPK signaling, was active in greater proportion in MuSCs from aged (25%) versus young (2%) recipients and suggested that therapeutic targeting of this pathway may overcome the intrinsic defect identified in aged cells. The authors utilized SB202190, a pharmacological inhibitor of p38α/β signaling in addition to siRNA targeting, to demonstrate a reduction in cell cycle arrest in cultured progeny of aged MuSCs. The authors proceeded to extend these findings to a previously described ex vivo culture system using a soft (12 kPa) polyethylene glycol hydrogel [2] and demonstrated the synergistic...
effect of combining this soft biophysical substrate with the biochemical inhibition of SB202190 to enhance aged MuSC engraftment to levels similar to that observed with young MuSCs.

These findings are remarkable and provocative. By utilizing an ex vivo culture system using an elasticity-tuned biomaterial along with pharmacological inhibition of p38α/β signaling, the authors claim to induce MuSC self-renewal in vitro and restore the in vivo regenerative potential of aged MuSCs, thereby providing a viable therapeutic strategy to improve muscle function in the elderly. To further enforce this point, the authors transplanted ex vivo-expanded MuSCs into notexin-injured muscle of aged mice and measured the recovery in muscle function by recording twitch force. A dramatic restoration in muscle function, with twitch force levels reaching that of young mice, was observed following transplantation of ex vivo-cultured MuSCs.

If indeed this novel ex vivo culture strategy can restore the regenerative capacity of human MuSCs, then such a therapeutic strategy provides a compelling new way to treat muscle wasting in the elderly and address a major health crisis. Furthermore, the collaborative approach employed by the authors, including biomaterials, stem cells and pharmacology, clearly shows that regenerative medicine needs to fully embrace multidisciplinary research and demonstrates that softening the boundaries between various scientific disciplines is the key to accelerate progress in regenerative medicine.

– Written by Eleftherios Sachlos

Chemokine and integrins’ role in multiple sclerosis model


The common neurological disorder, multiple sclerosis (MS), is associated with demyelination and remyelination episodes that affect the CNS. The etiology of MS is unknown, but has a strong immunological component such that it is classified as an autoimmune disorder. Infiltrating leukocytes into the brain and inflammation is thought to be responsible for damage to neurons and oligodendrocytes. Current therapies prevent the leukocyte infiltration by blocking adhesion molecules such as integrins (anti-VLA4), which will reduce the relapse rate and progression. The effects of the anti-VLA4 therapy are thought to be due to mobilization of the hematopoietic progenitor cells, which may also be regulated by chemokine SDF1/CXCL12 and its receptor CXCR4. These interactions have been described previously, but the implications for MS are described in a recent paper by Banisadr et al. [3].

Remyelination is key in remitting phase of MS. This occurs spontaneously in the beginning course of the disease, however, trails off as time goes by. These researchers determined SDF-1/CXCL12 are upregulated in the brain during inflammation and are key factors in regulating the migration of oligodendrocyte progenitor cells (OPCs) to demyelinating regions in the mouse model of MS, known as experimental autoimmune encephalomyelitis (EAE). Chemokines in the brain are upregulated by many ways, one of which may be the effect of inflammatory cytokines produced by leukocytes. This manuscript, in the Journal of Neuroimmune Pharmacology, thought that inhibiting the inflammatory cell influx into the brain by anti-VLA4 may inhibit downstream upregulation of chemokines.

The researchers induced a relapsing–remitting form of MS by proteolipid protein infusion. Animals treated with anti-VLA4 antibodies prior to induction using proteolipid protein had a delayed onset and less severe clinical signs than those treated with control IgG. Animals treated with anti-VLA4 after the peak of the acute phase of the disease had similar disease onset and severity. Animals treated with control antibodies and anti-VLA4 had a similar pattern of disease.

The concerted effort by blocking integrins and chemokine expression was then studied. The researchers utilized a SDF-1-RFP/CXCR4-GFP-expressing mouse. Naive mice treated with anti-VLA4 did not show a difference in the expression of chemokines or receptors. Preclinical treatment of EAE mice with anti-VLA-4 antibody reduced the expression of CXCR4 and SDF-1 in the subventricular zone, corpus callosum and the cerebellum. Similar expression patterns were shown in mice treated with anti-VLA-4 antibodies at the acute phase of the disease. Expression of the chemokine and receptor remained similar to control in the spinal cords of the EAE mice. This was further confirmed using ELISA. The cells expressing CXCR4 were determined to be Olig-1 positive, indicative of an OPC. CXCR4 was also upregulated in CD68-expressing macrophages in EAE mouse brain and SDF-1/CXCL12 expression was in GFAP-positive astrocytes and IBA1-positive microglia. OPC expression was similar in animals treated with anti-VLA-4 preclinically or at the acute phase of disease.

The researchers in this current study found a link between a common therapy to treat MS, Tysabri and chemokines. The inhibition of the VLA-4 causes a reduction in the expression of the chemokine, SDF-1/CXCL12, which may be beneficial in
the recruitment of OPCs to areas of demyelination. The reduction in chemokines may be detrimental to the long-term repair of the demyelinating injury produced by the autoimmune disorder. Further studies need to be performed looking at the long-term effects of the current therapies that have been found to ‘stop working’ over time in patients.

– Written by Amber Kerstetter-Fogle

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References