

Table S1: A summary of microRNAs (miRNAs) associated with pathways related to physical frailty in humans

MiRNA	Function in physical/cognitive domains	Direction of regulation	References
miR-1	Promoter of skeletal muscle differentiation and regeneration	Decreased in muscle impairment Increased after acute exercise	[72] [73]
miR-9 (miR-9-1, miR-9-2, and miR-9-3)	Inhibitor of Skeletal Muscle Satellite Cell Proliferation	Decreased after acute exercise	[73,74,75]
miR10a-5p miR10a-3p	Inhibitor of myogenic differentiation Negative Regulator ossification	Increased in osteoporosis Increased in muscle loss	[76] [68]
miR-19a/b	Inflammatory responses, muscle cell apoptosis; fat-free mass metabolism	Increased in sarcopenia	[77,78]
miR-21	Muscle atrophy following denervation; muscle regeneration; myogenic differentiation of satellite cells; inflamm-miR; mitomiR	Increased in sarcopenia Increased levels led to fewer and smaller myotubes in satellite cells	[67] [79]
miR-21-5p	Osteogenic differentiation	Decreased in osteoporosis Increased in osteoporosis	[80] [81,82]
miR-22-3p	Smooth muscle cell differentiation; Regulation of endothelial cell proliferation	Increased in osteoporosis	[76]
miR-23a-3p	Inhibitor of myogenic differentiation	Increased in osteoporosis; Increased in muscle impairment; Decreased after acute exercise	[81] [72] [73]
miR-24-3p	Inhibitor of myogenic differentiation	Increased in osteoporosis;	[81]
miR-26a	Promoter of myogenic differentiation	Increased in skeletal muscle regeneration after injury	[83]
miR-27a	Satellite cell proliferation; Promoter of myoblast differentiation; mitomiR	Overexpression in muscle prevents diabetes-induced muscle cachexia	[84]

miR-29b	Myotube formation; myoblast proliferation; mitomiR	Increased in muscle atrophy cellular models	[85]
miR-30a-3	Skeletal muscle protein turnover and atrophy	Increased in muscle atrophy cellular models	[86]
miR-31	Regulation of myogenic transcription factors; mitomiR	Decreased after acute exercise	[73]
miR-34a/c	Muscle protein synthesis; targeting of cell senescence factors; mitomiR Myoblast proliferation and differentiation	Increased in sarcopenia Increased during myogenesis in muscle cellular model	[84] [87]
miR92a-3p	Oxidative stress; endothelial dysfunction; mitomiR	Increased in physical decline	[68]
miR-93	Inhibitor of myogenic differentiation	Increased in osteoporosis	[81]
miR-100-5p	Inhibitor of myogenic differentiation	Increased in osteoporosis	[81]
miR-122a-5p	Inhibitor of myogenic differentiation	Increased in osteoporosis	[81,82]
miR-124	Inhibitor of myogenic differentiation; inflamm-miR	Increased in osteoporosis	[72]
miR-125b	Inhibitor of myogenic differentiation	Increased in osteoporosis Decreased in muscle impairment	[72,81,82]
miR-133a/b	Satellite cell proliferation; Myoblast differentiation	Decreased in sarcopenic patients; Increased in osteoporosis Decreased in osteoporosis and muscle impairment; Increased after acute exercise High levels protective for muscle atrophy	[80,88,89,90] [72,76]; [73] [91]
miR-139-5p	Myogenic differentiation; cell growth	Decreased in osteogenic differentiation in human mesenchymal cells	[92]
miR-142-3p	Osteoblast differentiation	Increased in osteoblast differentiation in human mesenchymal cells	[93]
miR-142-5p	Muscle homeostasis	Down-regulated in frailty subjects	[69]

miR-143-3p	Inhibitor of myogenic differentiation	Upregulated in hypertrophic response in human skeletal muscle	[94]
miR-146a	Promoter of satellite cell differentiation; inflamm-miR	Dysregulated in muscle disorders; Increased in osteoarthritic patients; Down-regulated in sarcopenia	[95 (and references therein)] [89]
miR-148a-3p	Inhibitor of myogenic differentiation	Increased in osteoporosis	[81]
miR-151a	Cell proliferation; mitomiR	High levels protective for muscle atrophy	[91]
miR-155	Inhibitor of myogenic differentiation; inflamm-miR; mitomiR	Increased in aged muscle cells; Down-regulated in sarcopenia	[96] [89]
miR-181 (miR-181a-miR-181b-miR-181c)	Myogenic differentiation; inflamm-miR; mitomiR	Decreased in aged muscle; Overexpression in osteogenesis Increased after acute exercise	[97] [51] [73]
miR185-3p	Cell migration; angiogenesis; regulation of LDL clearance	Increased in physical decline	[68]
miR-186	Muscle differentiation, development and muscular atrophy	Increased levels decrease myogenin expression in primary muscle cells;	[98]
miR-187	Promoter of myogenic differentiation	Decreased in osteoporosis	[99]
miR-194-3p miR-194-5p	Muscle atrophy; lipid accumulation in skeletal muscle cells; myogenic differentiation	Increased in muscle loss; Increased in osteoporosis	[68] [100]
miR-195	Control of satellite cell quiescence; mitomiR	Overexpression of miR-195/497 enhances myogenesis	[101]
miR-203a-3p	Skeletal muscle protein turnover and atrophy	Increased in muscle atrophy cellular models Increased levels correlate with muscle mass index and intramuscular adipose tissue content	[86] [102]
miR-206	Myoblast differentiation and regeneration	Decreased in muscle impairment; High levels protective for muscle atrophy	[67,72,91]

miR-208a/b	Promoter of myogenic differentiation; specification of muscle fibres	Increased levels in response to endurance exercise in healthy men; Down-regulated in sarcopenia	[103] [89]
miR-210	Inflamm-miR; overexpression protects from muscular damage	Down-regulated in sarcopenia	[89]
miR-222	Differentiation of skeletal muscle cells	Down-regulated in sarcopenia	[89]
miR-326	Cell proliferation and apoptosis	Increased in muscle loss	[68]
miR-328	Promoter of myogenic differentiation	Decreased in osteoporosis; Down-regulated in sarcopenia	[76] [89]
miR-422a	Regulation of cell growth and proliferation	Increased in osteoporosis	[104]
miR424a-5p	Regulation of cell growth and proliferation	Increased in muscle wasting	[105]
miR-431	Myogenic differentiation and muscle regeneration	Decreased levels in aged myoblast	[106]
miR-449b-5p	Cell cycle control and differentiation	Increased levels in old muscle samples	[51, 78]
miR-486	Myoblast differentiation; muscle atrophy	Decreased in muscle impairments	[72,95]
miR-489	Control of satellite cell quiescence	Overexpression suppresses muscle regeneration	[107]
miR-497	Control of satellite cell quiescence	Overexpression enhances myogenesis in cellular models	[101]
miR-499	Biomarker of muscle atrophy; mitomiR	Down-regulated in sarcopenia	[89]
miR-503	Promoter of myogenic differentiation	Induced during muscle differentiation in cellular models	[108]
miR-518f	Inhibitor of myogenic differentiation	Increased in osteoporosis	[99]
miR-532-5p	Osteoblast differentiation	Increased in physical frailty; Decreased in osteogenic cell model	[68] [109]
miR-675	Myogenic differentiation	Increased in low muscle mass	[110]
miR-760	Inhibitor of proliferation and differentiation in myoblasts	Increased in muscle loss	[68]
miR-874	Osteogenic differentiation	Decreased in osteoporosis	[111]