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Three-dimensional models of skeletal muscle under tension and methods to induce traumatic injury: systematic review search protocol

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Abstract

Volumetric
muscle loss (VML) is defined as the significant loss of skeletal muscle as a result of traumatic injury or surgical intervention, resulting in functional and regenerative impairment. It is a considerable form of morbidity and is implicated in blast, penetrating or blunt trauma. Current research on VML is centred around models that are not specific to the injury patterns or environments usually encountered. In order to examine the effects of traumatic injury on skeletal muscle, more representative *in vitro* models are required to generate a deeper cellular picture prior to preclinical validation. Whilst *in vivo* models are invaluable, they are expensive and have a lower throughput platform for discovery research. The aim of this systematic review is to examine the types of *in vitro* muscle models that are applicable to understanding VML. We have therefore designed an inclusive search protocol to incorporate all relevant muscle models under tension and endeavour to subcategorise these depending on methods of inducing injury. “Skeletal muscle” was the major inclusion criterion, followed by “three dimensional” and “model”. The Ovid interface was used to search MEDLINE, EMBASE and Web of Science Core Collection databases to yield 4,895 eligible articles after de-duplication. As of 30/05/2024 articles are in the process of being blindly screened by two independent reviewers. Major inclusion criteria are three dimensional *in vitro* models under tension. A sub analysis will subsequently be performed to examine how injury is induced in such muscle models.

Methods

1 This systematic review was reported in compliance with the PRISMA 2020 checklist. The protocol was developed prospectively in collaboration with a research librarian (NT) at the Nuffield Department of Rheumatology and Musculoskeletal Sciences (NDORMS).

2 All databases were searched from inception until 13/03/2024. The Ovid interface was used to search MEDLINE (1946-present), EMBASE (1974-present) and Web of Science Core Collection (1900-present) databases. No date or language limits were applied. Synonyms were produced in line with elements of the research question. “Skeletal muscle” was the major inclusion criterion, followed by “three dimensional” and “model”. Synonyms for skeletal muscle included “myotube”, “slow-twitch muscle fibres” and “fast-twitch muscle fibres”. Synonyms for “three-dimensional” included “3D”, “organoid” and “lab on a chip”. Synonyms for “model” included “scaffold”, “architecture” and “platform”. Full search strategies can be found in the appendix.

Inclusion criteria

3 In vitro studies that utilised any skeletal muscle cell lines (primary or immortalised, single or multicellular) of any species cultured with an anchor system were eligible for inclusion. Models that used organic hydrogel compounds native to the human body (fibrin or collagen) were included. Where studies reported minor experimental modifications of previously reported models (with detailed methods), the most comprehensive study or studies were included.

Exclusion criteria

4 Models that did not impose axial strain or loading, self-assembly models (spheroids etc) or tissue explant models (including slice culture) were excluded. In vitro models that cultured cells on patterned surfaces (to include orientation) were also excluded, even if they used 3D systems. In vitro monolayer systems were excluded. Ex vivo perfusion systems were also excluded. Models that synthesised hydrogels using materials that were incapable of biodegradation (breakdown of organic matter into constituent elements) within humans (or human tissue) were excluded. Studies without detailed methods, opinion pieces, reviews, letters, conference abstracts, in vivo work and book chapters were excluded.

Appendix

5 EMBASE search:

	Total Records downloaded (enter this number here to update SearchReport tab):	1970		
	Search Strategy			
	Embase 1974 to present			
	1	skeletal myoblast/	596	
	2	(skeletal adj2 myoblast*).tw,kf.	2170	
	3	skeletal muscle cell line/	83	
	4	(cell* adj2 (stem or primary or satellite)).tw,kf.	624478	
	5	(myogenic or	172977	

		skeletal muscle).tw,kf.		
	6	4 and 5	11204	
	7	skeletal muscle/	144693	
	8	slow muscle fiber/	2149	
	9	fast muscle fiber/	2212	
	10	10	skeletal.tw,kf.	299053
	10			
	11	(muscle* adj2 fiber*).tw,kf.	35259	
	12	10 and 11	13999	

	13	(fast-twitch or intermediate or white or type II).tw, kf.	1117798	
	14	(red or slow-twitch or type I).tw, kf.	630013	
	15	13 or 14	1657758	
	16	11 and 15	6707	
	17	myotube*.tw,kf.	15390	
	18	(skeletal adj2 myocyte*).tw,kf.	751	

	19	(myogenic or skeletal muscle).tw,kf.	172977	
	20	(cell* adj2 c2c12).tw,kf.	6130	
	21	19 and 20	3398	
	22	1 or 2 or 3 or 6 or 7 or 8 or 9 or 12 or 16 or 17 or 18 or 21	171236	
	23	3d.tw,kf.	324905	
	24	three d.tw,kf.	638	
	25	3 dimension*.tw,kf.	38685	
	26	orga	13217	

		noid/		
	27	organoid*.tw,kf.	23541	
	28	exp lab on a chip/	11240	
	29	lab on a chip.tw,kf.	3765	
	30	organ on a chip.tw,kf.	1453	
	31	exp bioengineering/	235895	
	32	bioengineer*.tw,kf.	15596	
	33	biological engineer*.tw,kf.	1427	
	34	tissue engineer*.tw,kf.	80668	

	35	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	628442	
	36	22 and 35	3934	
	37	model*.tw,kf.	5000672	
	38	scaffold*.tw,kf.	158968	
	39	architecture*.tw,kf.	197564	
	40	platform*.tw,kf.	357571	
	41	(system or systems).tw,kf.	4417710	

	42	37 or 38 or 39 or 40 or 41	8919326	
	43	36 and 42	2505	
	44	conference*.pt.	5859448	
	45	43 not 44	1970	

6 MEDLINE search:

	Total Records downloaded (enter this number here to update SearchReport tab):	2650		
	Search Strategy			
	Medline (Ovid MEDLINE‰ Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE‰ Daily and Ovid MEDLINE‰) 1946 to present			
	1	exp Myoblasts, Skeleta	4090	

		l/		
	2	(skeletal adj2 myoblast*).tw,kf.	1795	
	3	(cell* adj2 (stem or primary or satellite)).tw,kf.	422521	
	4	(myogenic or skeletal muscle).tw,kf.	139662	
	5	3 and 4	8576	
	6	Muscle, Skeletal/	166516	
	7	Muscle Fibers, Skeletal/	17604	
	8	Muscle Fibers, Slow-Twitch/	2488	

	9	Muscle Fibers, Fast-Twitch/	3131	
	10	skeletal.tw,kf.	237495	
	11	11	(muscle* adj2 fiber*).tw,kf.	29880
	11			
	12	10 and 11	11474	
	13	(fast-twitch or intermediate or white or type II).tw,kf.	844075	
	14	(red or slow-twitch or type I).tw,kf.	493609	
	15	13 or 14	1266664	
	16	**11 and 15**	5555	
	17	myotub	12495	

		e*.tw,kf.		
	18	(skeletal adj2 myocyte*).tw,kf.	600	
	19	(myogenic or skeletal muscle).tw,kf.	139662	
	20	(cell* adj2 c2c12).tw,kf.	4658	
	21	19 and 20	2556	
	22	1 or 2 or 5 or 6 or 7 or 8 or 9 or 12 or 16 or 17 or 18 or 21	193945	
	23	3d.tw,kf.	249537	
	24	three d.tw,kf.	468	
	25	3 dimension*.tw,kf.	29970	

	26	Organoids/	13773	
	27	27	organoid*.tw,kf.	15510
	27			
	28	Lab-On-A-Chip Devices/	7533	
	29	lab on a chip.tw,kf.	3690	
	30	organ on a chip.tw,kf.	1382	
	31	exp Bioengineering/	62819	
	32	bioengineer*.tw,kf.	12040	
	33	biological engineer*.tw,kf.	432	

	34	Tissue Engineering/	45681	
	35	tissue engineer*.tw,kf.	64407	
	36	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	387881	
	37	22 and 36	3428	
	38	model*.tw,kf.	3967863	
	39	scaffold*.tw,kf.	135360	
	40	methods.fs.	4360174	
	41	architecture*.tw,kf.	172933	

	42	platform*.tw,kf.	271052	
	43	(system or systems).tw,kf.	3641694	
	44	38 or 39 or 40 or 41 or 42 or 43	10499757	
	45	37 and 44	2650	

7 Web of science search strategy:

Search Strategy

#	Search Query	Database	Results
1	"myotube OR (skeletal NEAR/2 myoblast*) OR ""skeletal muscle"" OR ""fast twitch muscle fibre*"" OR ""slow twitch muscle fibre*"" OR (skeletal NEAR/2 myocyte*) (Topic) AND 3d OR ""three dimension*"" OR ""three d"" OR organoid* OR ""lab on a chip"" OR ""organ on a chip"" OR bioengineer* OR ""tissue engineer*"" OR ""biological engineer*"" (Topic) AND model* OR scaffold* OR architecture* OR platform* OR system OR systems (Topic) "	Web of Science Core Collection	2811