Review

Journey into Bone Models: A Review

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Supplementary material

Table S1: Overview on scaffold-based bone models published between 2007 and 2017

Scaffold	Application in vitro / in vivo	Results	Field of application	References
TCP or CaP-based scaffolds				
β-TCP	monkey MSCs/ monkeys	β-TCP/MSC showed better bone regeneration compared to β-TCP	in vitro model and BTE application	[1]
HA/TCP	human osteoblasts / -	adhesion, proliferation, osteogenesis	in vitro model	[2]
apatite-TCP, HA	mouse calvarial cells / -	homogeneous loading, enhancing its mechanical strength, cells grow and differentiate as osteoblasts in a reproducible manner	in vitro system to analyze bone cell function and bone-targeting molecules under load	[3,4]
mPCL/TCP	sheep MPC and OB/ sheep	higher bone formation with MPCs, allogenic cells induced no acute or delayed immunological response	in vitro model and BTE application	[5,6]
TCP-BG/PLL		high amount of carbonate apatite, better bioactivity properties compare to PLL	in vitro model and BTE application	[7,8]
PLG/TCP/Icariin	MC3T3-E1 osteoblastic cells (Subclone 14, CRL-2594) / SAON rabbit	superior biodegradability, biocompatibility, and osteogenic ability compared to PLG/TCP	in vitro model and BTE application focused on SAON	[9]
CHS/CaP, CHS/CaP/Pg	murine MSCs / male albino Wistar rats	Pigeonite enhances bioactivity, biomineralization and osteoblast differentiation	in vitro model and BTE application	[10]
CDHA, biphasic CaP (80:20 HA:β-TCP), β-TCP	rat MSCs / canine	CDHA: accelerated bone formation and new ectopic bone replaced scaffold; CaP: bone deposited on the surface	in vitro model and BTE application	[11]

Table S1. *Cont.*

Scaffold	Application in vitro / in vivo	**Table 1.** *Cont.*	Field of application
Natural polymer-based scaffolds			
collagen loaded with secretome biotherapeutic	rat MSCs, rat calvarial osteoprogenitor cells / rat	enhanced migration, proliferation, new bone volume, connectivity, and angiogenesis	beneficial effects for bone healing in vivo	[12]
collagen/β-TCP, collagen	rat MSCs / -	collagen/β-TCP > collagen: osteogenesis, attached cell number, expression of osteogenic markers	in vitro model and BTE application	[13,14]
fibrin glue scaffold	equine MSCs / mouse	osteogenic differentiation capacity	in vitro model and BTE application	[15]
CHS, PGel, CS-PGel	- / rat	*in vivo* bone regeneration: CHS < CHS-PGel < PGel	in vitro model and BTE application	[16–19]
recombinant human BMP-2-loaded gelatin/nano-HA/fibrin	human MSCs / rabbit	osteogenic capability	in vitro and in vivo: growth-factor delivery carrier and a 3D matrix	[20]
recombinant human BMP-2-loaded CHS/ collagen	- / rabbit	biocompatibility, bone formation, appropriate degradation	Scaffold-mediated drug delivery for BTE, treating segmental bone defects	[21,22]
CHS/nano-HA/SF	MSCs / rabbit	in vitro: biocompatibility, no toxicity, cell adhesion and proliferation; in vivo: new bone	in vitro model and BTE application to repair segmental defect	[23,24]
substance-doped HA	MG63 human osteoblasts cells	Lithium promote osteoblast activity; degradation rate of LiHA < HA	in vitro model and BTE application	[25–27]
HA/alumina scaffold	- / canine	scaffold with a 3mm passage formed new bone compared to the scaffold without a passage	in vitro model and BTE application	[28]
CHS/ β-1,3-glucan /HA	human AT- and marrow-derived MSCs / -	both cells proliferate and differentiate, bone marrow-derived spread better and attached stronger	in vitro model and BTE application	[29–31]
nano-HA/polyamide 66	rat MSCs / -	sufficient proliferation and differentiation greatly improve through perfusion culture conditions	in vitro model and BTE application	[32]
TGF-β1-SF-CHS, SF-CHS	rabbit MSCs / rabbit	TGF-β1-SF-CHS: biocompatibility, enhance osteoconductivity and bone formation	in vitro model and BTE application	[33]
ASA scaffold, ASA/β-TCP scaffold	canine MSCs / canine	higher bone formation with ASA scaffold compared to ASA/β-TCP	in vitro model and BTE application	[34]
Calcium-Infiltrated HA	HUVECs / -	calcium release at the surface, promoted a hematopoietic lineage direction of HUVECs	in vivo-like scaffold for hematopoietic BTE	[35]

Synthetic polymer-based scaffolds

PLG-mediated minicircle DNA (MC) delivery	Skull-derived osteoblasts transfected with BMP-2 / mice	higher osteocalcin expression and mineralization	Scaffold-mediated gene delivery for BTE, treating long bone defects	[36]
PCL/PLG, PCL/PLG/duck beak, PCL/PLG/TCP	- / rabbit	bone formation: PCL/PLG < PCL/PLG/TCP < PCL/PLG/duck beak	in vitro model and BTE application	[37]
polydopamine-coated PLG-[Asp-PEG]	rat MSCs / rat	could more efficiently promote osteogenic differentiation *in vitro*	-	[38]
PLG/PEG with incorporated BMP-2	human MSCs / mouse	osteogenesis, bone formation	in vitro model and BTE application	[39,40]
(30:70% *w*/*w*) SPCL, SPCL-Si	- / rat	SPCL-Si: significant higher bone formation	in vitro model and BTE application	[41]
nano-HA/PLG, PLGA	rabbit MSCs / rabbit	Viability and proliferation rate, bone formation rate: nano-HA/PLGA > PLGA	in vitro model and BTE application	[27,42,43]
(60:40) PCL/HA, PCL	canine MSCs / canine	bone regeneration, seeded with MSCs enhance the amount of bone ingrowth	in vitro model and BTE application	[39,44–48]

Table S2: Summary of bioreactors suitable for bone models

Scaffold	Cells	Vascularisation	Mech. load	Perfusion	Reference
physiologic matrix (explant)	multiple (whole bone explant)	yes (explant)	yes	yes	[49]
hydroxyapatite ceramic	human MSCs, HSCs	no	no	yes	[50]
hydroxyapatite ceramic	human MSCs (primary isolates)	no	no	yes	[51]
trabecular bone (bovine), 3D CNC milled	human MSCs (primary isolates)	no	no	yes	[52]
poly (L-lactide-co-caprolactone)	human MSCs (primary isolates)	no	no	yes	[53]
polyurethane	Fibroblasts (commercial, ATCC)	no	yes	no	[54]
commercial animal derived collagen scaffold, NiTi scaffold	human MSCs (primary isolates)	no	yes	yes	[55]
hydroxyapatite ceramic	human MSCs and stromal vascular fraction cells (both primary isolates)	yes	no	yes	[56]
hydroxyapatite ceramic	whole mononuclear fraction isolated from bone marrow (primary isolate, commercial)	no	no	yes	[57]
collagen scaffold	fibroblasts (primary isolates)	no	yes	yes	[58]
acellular bone matrix (bovine)	human MSCs (primary isolates)	no	yes	yes	[59]
fibrin	human MSCs (primary isolates)	no	yes	yes	[60]

Table S3: Summary of microfluidic bone models

Scaffold	Cells	Mech. load	Vascularisation	Perfusion	Chip material	Reference
collagen and fibrinogen hydrogel	hMSC, hMSC-OB (primary isolates), HUVECs (commercial, transfected primary cells)	no	yes	yes	PMMA	[61]
fibrin with hydroxy apatite NPs	HUVECs (undisclosed)	no	yes	yes	PDMS	[62]
none	hMSCs (commercial, primary isolates)	yes (stretchin)	no	yes	PDMS, PMMA, glass	[63]
demineralized bone powder	animal, bone-inducing material is pellettet and subcutanously implanted for host cell ingrowth	no	yes	yes	PDMS	[64]
ceramic, hydroxyapatite coated zirconium oxide	hMSC, HSPCs (primary isolates)	no	no	yes	PDMS, glass	[65]
Hydroxyapatite beads (20-25 μm in size)	MLO-A5 (post-osteoblast/pre-osteocyte cell line), hOB (primary isolate)	yes (shear)	no	yes	PDMS	[66]

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