TGF-β family signaling in endothelial cells and angiogenesis

Ma, J.

Abbreviations

ADME	absorption, distribution, metabolism and excretion
ALK1	Activin receptor-like kinase 1
ALK2	Activin receptor-like kinase 2
ALK3	Activin receptor-like kinase 3
ALK5	Activin receptor-like kinase 5
ALK6	Activin receptor-like kinase 6
AMD	Age-related macular degeneration
AMH	Anti-müllerian hormone
AMHRII	AMH type II receptor
ANOVA	A two-way analysis of variance
AS	Atherosclerosis
ATCC	American Type Culture Collection
AV	Atrioventricular
BAECs	Bovine aortic endothelial cells
BCA	Bicinchoninic acid
bHLH	Basic helix–loop–helix
BMBL	Biosafety in Microbiological and Biomedical Laboratory
BMP	Bone morphogenetic protein
BMPRI	BMP type I receptor
BMPRII	BMP type II receptor
BOECs	Blood outgrowth endothelial cells
BPE	Bovine Pituitary Extract
BRE Luc	BMP responsive element luciferase
BSA	Bovine serum albumin
caALK2	Constitutively active forms of ALK2
CAD	Coronary artery disease
CAFs	Cancer-associated fibroblasts
Cas9	CRIRSPR-associated protein
CCM	Cerebral cavernous malformation
CD31/PECAM-1	Platelet/endothelial cell adhesion molecule-1
CRISPR	Clustered regularly interspaced short palindromic repeats
CTMs	Cardiac tissue mimetics
DAPI	4′,6-diamidino-2-phenylindole
DLAV	Dorsal longitudinal anastomotic vessel
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl sulfoxide
DoC	Duct of Cuvier
dpf	Days post-fertilization
dpi	Days post-injection
EB	Elution buffer
ECFC-ECs	Human endothelial colony forming cell-derived ECs
ECM	Extracellular matrix
ECs	Endothelial cells
EDTA	Ethylenediaminetetraacetic acid

EGF	Epidermal growth factor
EMT	Epithelial-to-mesenchymal transition
EndMT	Endothelial-to-mesenchymal transition
EndMT-TFs	EndMT transcription factors
End-MyoT	Endothelial-to-myofibroblast transition
ER	Estrogen receptor
ERK	Extracellular-signal-regulated kinase
F-actin	Filamentous actin
FBS	Fetal bovine serum
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FOP	Fibrodysplasia ossificans progressiva
FSP-1	fibronectin and fibroblast-specific protein-1
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GDF	Growth differentiation factor
GS	Glycine-serine-rich
HAoECs	Heart aortic ECs
HCMECs	Human cutaneous microvascular ECs
HFD	High-fat diet
HGF	Hepatocyte growth factor
HMECs	Human dermal microvascular endothelial cells
HMGA1	High Mobility Group AT-hook 1
HMVECs	Human dermal microvascular endothelial cells
hpf	Hours post-fertilization
hpi	Hours post-injection
HRP	Horseradish peroxidase
HUVECs	Human umbilical vein endothelial cells
HVEC	Human vascular endothelial cell
IB	Immunoblotting
IC_{50}	Half-maximum inhibitory concentration
ICIs	Immune checkpoint inhibitors
ID	Inhibitor of DNA binding
IF	Immunofluorescence
IL	Inflammatory interleukin
IPH	Idiopathic portal hypertension
ISV	Intra segmental vessel
JNK	Jun amino-terminal kinase
kDa	kilodalton
LAP	latency-associated peptide
LB	Lysogeny broth
LCMS	liquid chromatography mass spectrometry
MAECs	Mouse aortic endothelial cells
MAPK	MAP kinase
MCECs	Mouse cardiac endothelial cells
MESECs	Mouse embryonic stem cell-derived ECs
MET	Mesenchymal-to-endothelial transition

MKL	Modulator magakaryoblastic leukemia
mPAP	Mean pulmonary artery pressure
MS-1	Murine pancreatic microvascular endothelial cell
MSCs	Mesenchymal multipotent cells
NHEJ	Non-homologous end joining
NT	Non-targeting
NTRK1	Neurotrophic receptor tyrosine Kinase 1
PAECs	Pulmonary artery ECs
PAH	Pulmonary arterial hypertension
PAI1	Plasminogen activator inhibitor-1
PBS	Phosphate-buffered saline
PDGF	Platelet-derived growth factor
PDX	Patient-derived xenograft
PEI	Polyethyleneimine
PI3K	Phosphoinositide 3-kinases
PVDF	Polyvinylidene difluoride
RFP	Red fluorescent protein
RIPA	Radioimmunoprecipitation assay
RIPF	Radiation-induced pulmonary fibrosis
rPAECs	Rat pulmonary arterial endothelial cells
RVSP	Right ventricular systolic pressure
SDS-PAGE	Sodium dodecyl sulphate polyacrylamide gel electrophoresis
sgRNA	Single guide RNA
shRNA	Short hairpin RNA
SIV	Subintestinal vessel
SM22α	Smooth muscle protein 22α
SMAD	Sma and Mad related protein
SMCs	Smooth muscle cells
SRPK1	Serine-arginine protein kinase 1
STAT	Signal transducer and activator of transcription
TβRI	TGF-β type I receptor
TβRII	TGF-β type II receptor
TAK1	TGF-β activated kinase 1
TBST	Tris-buffered saline with Tween 20
TGFβR	TGF-β receptor
TGFβ	Transforming growth factor-β
TIE1	Tyrosine kinase with immunoglobulin-like and EGF-like domains 1
TIE2	Tyrosine kinase with immunoglobulin-like and EGF-like domains 2
TMJD	Temporal mandibular joint disorder
TNF	Tumor necrosis factor
TRAF6	TNF-receptor associated factor 6
VE-Cadherin	Vascular endothelial-Cadherin
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
vWF	Von Willebrand Factor
α-SMA	α-smooth muscle actin

List of publications

1. **Ma J**, Ren J, Thorikay M, van Dinther M, Sanchez-Duffhues G, Caradec J, Benderitter P, Hoflack J, Ten Dijke P. Inhibiting endothelial cell function in normal and tumour angiogenesis using BMP type I receptor macrocyclic kinase inhibitors. Cancers. 2021 13: 2951.
2. **Ma J**, van der Zon G, Gonçalves MA, van Dinther M, Thorikay M, Sanchez-Duffhues G, Ten Dijke P. TGF-β-Induced Endothelial to Mesenchymal Transition Is Determined by a Balance Between SNAIL and ID Factors. Frontiers in Cell and Developmental Biology. 2021 Feb 12;9:182.
3. **Ma J**, van der Zon G, Sanchez-Duffhues G, Ten Dijke P. TGF-β-mediated Endothelial to Mesenchymal Transition (EndMT) and the Functional Assessment of EndMT Effectors using CRISPR/Cas9 Gene Editing. Journal of Visualized Experiments: Jove. 2021 Feb 26(168).
4. Li C*****, **Ma J***, Groenewoud A, Ren J, Liu S, B. Snaar-Jagalska E, Ten Dijke P. "Establishment of Embryonic Zebrafish Xenograft Assays to Investigate TGF-β Family Signaling in Human Breast Cancer Progression." Methods in Molecular Biology (MiMB). (2021). *These authors contributed equally
5. **Ma J**, Sanchez-Duffhues G, Goumans MJ, Ten Dijke P. TGF-β-induced endothelial to mesenchymal transition in disease and tissue engineering. Frontiers in Cell and Developmental Biology. 2020, 8: 260.
6. **Ma J**, Kang K, Zhang Y, Yi Q, Gu Z. Detachable polyzwitterion-coated ternary nanoparticles based on peptide dendritic carbon dots for efficient drug delivery in cancer therapy. ACS Applied Materials & Interfaces. 2018 Nov 26;10(50):43923-35.
7. **Ma J**, Kang K, Yi Q, Zhang Z, Gu Z. Multiple pH responsive zwitterionic micelles for stealth delivery of anticancer drugs. RSC Advances. 2016;6(69):64778-90.
8. Yi Q, **Ma J**, Kang K, Gu Z. Bioreducible nanocapsules for folic acid-assisted targeting and effective tumor-specific chemotherapy. International Journal of Nanomedicine. 2018;13:653.
9. Yi Q, **Ma J**, Kang K, Gu Z. Dual cellular stimuli-responsive hydrogel nanocapsules for delivery of anticancer drugs. Journal of Materials Chemistry B. 2016;4(28):4922-33.
10. Kang K, **Ma J**, Yi Q, Gu Z. Localized drug release and effective chemotherapy by hyperthermia-governed bubble-generating hybrid nanocapsule system. Nanomedicine. 2017 Dec;12(24):2763-83.
11. Li L, Ugalde AP, Scheele CL, Dieter SM, Nagel R, **Ma J**, Pataskar A, Korkmaz G, Elkon R, Chien MP, You L. A comprehensive enhancer screen identifies TRAM2 as a key and novel mediator of YAP oncogenesis. Genome Biology. 2021 Dec;22(1):1-28.

Curriculum Vita

Jin Ma was born on 11st of November 1991 in Shanxi province, China. From 1th September 2010, she started her bachelor study in pharmacy at the College of pharmacy in Lanzhou University, China. She obtained her bachelor degree in June 2014. From 1st September 2014, Jin started her master study in Pharmacy at National Engineering Research Center for Biomaterials, Sichuan University, China. During her master internship, under the supervision of Prof. Zhongwei Gu and Dr. Qiangying Yi, she investigated multiple pH responsive zwitterionic micelles for stealth delivery of anticancer drugs and peptide dendrimers functionalized zwitterionic drug nanocarriers for stimuli-responsive cancer theranostics. She obtained her master degree in June 2017. From September 2017, Jin started her PhD study funded by a CSC scholarship at the Department of Cell and Chemical Biology, Leiden University Medical Center, the Netherlands. During her PhD, she studied TGF-β signaling in endothelial cells and angiogenesis under the supervision of Prof. Peter ten Dijke. She focused on obtaining new insights of the underlying mechanisms that govern TGF-β-induced endothelial to mesenchymal transition. Besides, she identified two novel BMP type I receptor macrocyclic kinase inhibitors for inhibiting endothelial cell function in normal and tumor angiogenesis.

Acknowledgements

After four years exciting PhD study, I'm very proud to show the results of my research in this booklet. With the encouragement and support from all the colleagues, friends and family, I could really enjoy and accomplish this adventure.

First and foremost, I am extremely grateful to my supervisor Prof. Peter ten Dijke, who showed me the beauty of cell biology, especially TGF-β signaling, with his immense knowledge and plentiful experience. Thanks for guiding me with patience and encouragement which helped me through my academic research, especially the first two tough years.

Next, I want to express my heartfelt gratitude to my co-promotor Dr. Gonzalo Sanchez-Duffhues. Thanks for our discussions and your practical advices for my projects, especially thanks for reading through all my manuscripts and the thesis booklet, and coming up with very valuable feedback. Your support made each story more attractive. I also want to express my appreciation to my co-advisors Dr. David Baker and Dr. Paul Geurink. Thanks for your very helpful questions and comments, which inspired me into extra thinking about my projects. Thanks Prof. Manuel A. F. V. Gonçalves for helping me to edit and critically revise the EndMT manuscript, and also for professional support in the CRISPR/CAS9 filed. Thanks to my collaborators Dr. Pascal Benderitter and Dr. Josselin Caradec.

It's my pleasure to be a member of the TGF-β family. Thanks Maarten, Midory, Gerard and Sharon for their daily lab organization and technical assistance. Thanks Laila for your generous help and advices during my PhD study. Thanks Sijia and Jiang for sharing valuable experience and giving me a lot of valuable suggestions for my research. Thanks Maureen, Catalina, Prasanna, Maarten, Yongsheng, Yifan, Chloé, Yuanzhuo and Abhishek for very useful discussions and support. Many thanks to Dr. Christopher John Hipolito for giving me encouragement and advices. Many thanks to Xinxin, Chao and Haijiang. Special thanks our PhD team: Jing, Dieuwke, Chuannan for always ready to help each other both in research and in daily life. What a pleasure to take the PhD adventure together with you!

Thanks to everyone in our CCB department. Thanks Julia for arranging the meetings, rooms and documents for different tasks. Thanks Willem for helping me figure out any possible problems with my computer. Thanks Annelies, Lennard and Karien for your help on taking amazing images and videos using the microscope. Also thanks to Hans, Martijn, Steve, Qian, Yuqing, Jing Liu, Jin Gan, Yufeng, Ben, Kseniya and Diana.

Thanks to my best Chinese friends in Leiden: Xueying, Jing, Nannan, Wan and Lingling. I will remember our memorable moments in this beautiful land.

Last, I would like to express my special thanks to my families and my boyfriend, who are always fill my heart with love and are always supportive for my decisions.

I never know what is going to happen and who I am going to meet in the future, but I will enjoy the journey.