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Thrombosis and fibrosis: mutually inclusive targets to combat in COVID-19

Mehmet Agirbasli

Published Online: 17 December 2021

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Published Online: 13 January 2022

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Preview Abstract

Future Science OA - Editorial Advisory Board

Senior Editors

Ian A Blair, University of Pennsylvania, USA

Dr. Blair received his Ph.D. in Organic Chemistry in 1971 from Imperial College of Science and Technology, London, under the mentorship of the 1969 Nobel Laureate, Sir Derek H.R. Barton. He was appointed as the A.N. Richards Professor of Pharmacology at University of Pennsylvania in 1997 and Director of a new Center for Cancer Pharmacology. In 2002, Dr. Blair was appointed as Vice-Chair of the Department of Systems Pharmacology and Translational Therapeutics. In 2014, he became Director of the NIEHS-funded Penn Superfund Research and Training Program Center. Dr. Blair is an expert in the use of mass spectrometric methods for the structural elucidation and quantification of endogenous biomolecules. His current research is involved with the development of biomarkers in order to establish genetic/phenotype correlations and to assess the interaction between genes and exposure to environmental chemicals. He is particularly interested in the regulation of cellular oxidative stress and how this underpins mechanisms involved in carcinogenesis, cardiovascular disease, and neurodegeneration. Dr. Blair discovered electron capture atmospheric pressure chemical ionization, a technique that makes it possible to conduct high sensitivity quantitative analyses of chiral biomolecules. He is a Fellow of the American Association for the Advancement of Science and the American Association of Pharmaceutical Scientists. He received the 2011 Eastern Analytical Award for Outstanding Achievements in Mass Spectrometry. Dr. Blair is on the editorial boards of the Molecular and Cellular Proteomics, Journal of Lipid Research, and Chemical Research in Toxicology. He has published 329-refereed manuscripts, they have been cited 13,970 times, and he has an h-index of 59. Read more about his work here.

Editorial Board

Cardiology

Vasilios Athyros, Aristotle University of Thessaloniki, Greece

Dr. V.G. Athyros studied medicine and was trained in Internal Medicine in the Aristotle University of Thessaloniki, Greece. He founded the Atherosclerosis and Metabolic Syndrome Outpatient Clinics in 1990 and he remains the Head of these clinics. He has performed more than 426 studies, and has 282 entries in PubMed, 342 in Scopus, 340 in Google Scholar, and 330 in ResearchGate covering lipoprotein metabolism, atherogenisity and clinical properties of plasma lipids and lipoproteins, in therapeutic interventions in all kinds of high-risk patients including those with dyslipidemia, obesity, diabetes, arterial hypertension, chronic kidney disease, non-alcoholic fatty liver disease and the metabolic syndrome, both in primary and secondary cardiovascular disease prevention. Dr. Athyros is a Faculty member at the School of Medicine, Aristotle University of Thessaloniki, Greece with a joint position in the Clinic of Internal Medicine at the University (HippoKration) Hospital. Furthermore, Dr. Athyros has been a member of the Advisory Board of the Hellenic Society of Lipidology since 1995 and of the Hellenic (Greek) Atherosclerosis Society (HAS) since 2002. He has been elected as Vice-President (2008-2010) and as a President (2010-2012) of HAS, while he continues to be a member of the Advisory Board of HAS today. For 12 years he was responsible for Scientific Programming and Research Planning of HAS. Since 2013 he has been the Vice-President in the Hellenic (Greek) Society for Medical Education.

Catherine Martel, Université de Montréal, Canada - section social media editor

Catherine obtained her PhD from the Université de Montréal, and pursued a postdoctoral fellowship first at Mount Sinai School of Medicine in New York, then at Washington University School of Medicine in St. Louis, Missouri, and obtained the Junior Investigator Award for Women from the Arteriosclerosis, Thrombosisand Vascular Biology (ATVB) council of the American Heart Association. Her postdoctoral work is certainly groundbreaking and brings forward new considerations in the field: she discovered that the lymphatic vessel route, the network that runs in parallel with the blood vessels, is critical for removing cholesterol from multiple tissues, including the aortic wall. In 2013, Dr. Martel joined the ATVB's Early Career Committee in 2013, eager to bring a Canadian perspective to the group and get involved in council activities. Since 2014, Dr. Catherine Martel has been an Assistant professor at the Department of Medicine at the Université de Montréal, and a research scientist at the Montreal Heart Institute. Her research program now focuses on characterizing the physiopathologic role of the lymphatics in the initiation, progression and regression of atherosclerosis. Basic and translational research will allow her team to identify the causes of lymphatic dysfunction, and eventually target potential therapeutic strategies aiming at improving lymphatic function at the different levels of the atherothrombotic disease. You can follow Catherine's lab at @LaboMartel_ICM. Catherine joined the Future Science OAboard via our Young Ambassador panel. We interviewed Cath about her time as an early career researcher, and what advice she has for others. You can read the full interview here.

Italo Porto, University of Genova, Italy

Dr. Porto graduated in medicine in 1998 from at the Catholic University of the Sacred Heart, Gemelli Hospital in Rome, Italy, where he also finished his General Medicine and Cardiology residency in 2002. He was then Clinical and Interventional Fellow at the John Radcliffe Hospital Oxford (UK), where his research resulted in several high-level scientific publications. His PhD was awarded by Catholic University of the Sacred Heart, Rome in 2006. Following this, he held positions at the Gemelli Hospital, San Donato Hospital and the Catholic University. He moved back to his mother hospital (Gemelli Hospital Catholic University of the Sacred Heart) in November 2014 as Senior Interventional Cardiologist. The focus of his research is mainly integrative, at the edge between basic and clinical science in the cath lab.His current H-index is 36, with more than 4400 citations received.

Kjell Sakariassen, KellSa s.a.s, Italy

Kjell gained his Ph.D. in Medical Physiology from the University Hospital of Utrecht in 1984. He underwent post-doctoral studies in arterial thrombosis and vascular inflammation/arteriosclerosis at Roche, Basel and University of Washington, Seattle from 1984—1987. Between 1987 and 2004 he held, sequentially, the positions of Research Scientist at Roche; Group Leader at the Biotechnology Center of Oslo, University of Oslo; Head of Discovery at Nycomed, Oslo; Professor of Physiology at University of Oslo; Head of Pharmacology, Pharmacia and Biovitrum, Stockholm and Uppsala; and World-Wide Head of Pharmacology and Early Safety Evaluation at Serono Int., Ivrea, Geneva and Boston. He is currently CEO and Managing Director of KellSa s.a.s., Biella (2004—present), and KellSa Diagnostics GmbH, Basel, (2012—present). He was a member of Scientific and Cardiovascular Boards of Evolva SA, Basel (2007—2013), and is currently a member of the National Swedish Board of the SciLifeLab Drug Discovery and Development Platform, Stockholm and Uppsala (2014—present). His professional expertise particularly lies in research and development of cardiovascular, bleeding and inflammatory disorders, including diagnostics. You can follow Kjell on Twitter at @SakariassenS.

Jaap Jan Zwaginga, Leiden University Medical Center, The Netherlands

After his PhD on uremic bleeding at the medical school at University Utrecht in 1989, Jaap Jan became an MD in 1991. Following subsequent positions at the University Hospital Utrecht; and the Academic Medical Centre in Amsterdam in combination with Sanquin Amsterdam, he is currently a haematologist, transfusion specialist and professor in Transfusion Medicine at the Leiden University Medical Center in the Netherlands. He is, moreover, head of the Centre for Stem cell Therapy at the LUMC and a clinical JACIE inspector. Finally, he is Clinical and Laboratory manager of the Sanquin-LUMC Jon J van Rood Research Center for Clinical transfusion medicine. With over 125 publications, he has been principle or co-investigator for several project grants and clinical studies. His current research interests surround evidence-based transfusion medicine, and regenerative and immunomodulatory cell therapies.

Dermatology

Kavita Beri, Young Ambassador panel, Jersey Shore University Medical Center, USA -section social media editor

Michael H Gold, Tennessee Clinical Research Center, Gold Skin Care Center, Nashville, TN, USA

Dr. Michael H. Gold is the founder & medical director of Gold Skin Care Center, Advanced Aesthetics Medical Spa, The Laser & Rejuvenation Center, and Tennessee Clinical Research Center in Nashville, TN. He is a board-certified dermatologist and dermatologic surgeon and oversees the various facets of the center's operations. Dr. Gold has earned worldwide recognition for providing patients with leading-edge technological advances in dermatology and aesthetic skin care. He plays an integral role in the development of new pharmaceutical products and medical devices through his clinical research and has authored over 300 published scientific articles, 28 textbook chapters. In addition, Dr. Gold helped establish the Tennessee Society for Laser Medicine and Surgery (TSLMS). He also helped start two international groups: the Dermatologic Aesthetic Surgery International League (DASIL) and 5-Continent-Congress (5CC), one of the world's leading conferences on Dermatologic and Aesthetic Surgery.

Adam J Friedman, George Washington School of Medicine and Health Sciences, Washington, DC, USA

Having undergone undergraduate training at the University of Pennsylvania, Adam Friedman graduated with Distinction in Dermatologic Research from the Albert Einstein College of Medicine (NY, USA). He then went on to complete his internship at New York Hospital Queens, before returning to Einstein for his dermatology residency, where he was appointed Chief Resident. He served as the Director of Dermatologic Research at Einstein for five years, and is currently the Residency Program Director and Director of Translational Research in the Department of Dermatology at The George Washington University School of Medicine & Health Sciences. His broad interests cover medical and pediatric dermatology, and research utilizing nanotechnology for dermatological treatment. He has published numerous articles and textbooks, and received multiple awards. He also serves on various committees and advisory boards, and regularly appears in the media discussing his field. Adam led a special focus issue on nitric oxide in medical applications, which you can read here.

Microbiology & Infectious Disease

Dayle Daines, Old Dominion University, USA

Dr. Daines obtained a B.Sc. at the University of Calgary and her Master's and Ph.D. degrees at the University of Rochester School of Medicine and Dentistry in the Department of Microbiology & Immunology (USA). She has worked in research institutes, government laboratories, and academic institutions and is currently an Assistant Professor in the Department of Biological Sciences at Old Dominion University. Her research focuses on bacterial pathogenesis and molecular mechanisms of host-pathogen interactions, particularly those that involve persistence and growth arrest. Another related area of interest is the characterization of novel drug targets and the discovery of new therapeutic compounds.

Medicinal Chemistry, Pharmacology & Drug Discovery

George Baillie, University of Glasgow, UK

George Baillie is a Professor and PI within the Institute of Cardiovascular and Medical Sciences at the University of Glasgow (UK). His research over the last 15 years has examined many aspects of the cAMP signaling pathway in disease and he has published over 140 papers on the subject. His major discovery was that phosphodiesterases are "compartmentalized", and it is their location within cells that direct their function. The Baillie/Houslay lab was the first to discover a specific function for a single isoform of PDE4 (namely PDE4D5 with beta-arrestin desensitizes the beta2-adrenergic receptor). His lab has since gone on to ascribe functions to several other PDE4 isoforms and these discoveries have been published in Science, Nature, PNAS, EMBO, Molecular Cell and Current Biology. Professor Baillie is founder and director of Sannox Therapeutics, a spin-out venture within University of Glasgow. You can follow George on Twitter at @qbma25. Read more about his work here.

Jürgen Bajorath,University of Bonn, Germany

Jürgen Bajorath received his diploma and PhD degrees (1988) in biochemistry from the Free University in West-Berlin, Germany. He was a postdoc with Arnie Hagler at Biosym Technologies in San Diego. From 1990-2004, Jürgen held various positions in academia and the pharmaceutical industry in Seattle including 7 years at the Bristol-Myers Squibb Pharmaceutical Research Institute. In 1995, he became an Affiliate Professor at the University of Washington. In 2004, Jürgen was appointed Professor and Chair of the newly formed Department of Life Science Informatics at the University of Bonn. He also continues to be an Affiliate Professor at the University of Washington. Jürgen is a member of a number of editorial and scientific advisory boards and an editor of the Journal of Medicinal Chemistry. His research focuses on chemoinformatics, the development and application of computational methods for pharmaceutical research, and drug discovery. Jürgen has more than 550 publications and 25 patents.

Hugo Cerecetto, Universidad de la República, Uruguay

Hugo Cerecetto is Professor of Chemistry in the Nuclear Research Centre at School of Sciences, University of the Republic (Uruguay) working on the research and development of new therapeutic agents. Dr. Cerecetto's research interests are tropical diseases and cancer. He has been a researcher in the different stages of Drug Discovery and Development Platform involving design and synthesis of new bio-active agents, in vitro and in vivo biological studies, QSAR, and pre-clinical assays (studies of mutagenicity, stability, metabolism, and formulation). The developed hits, leads and drugs belong mainly to anti-T. cruzi agents, selective hypoxic cytotoxins and theragnostic agents for tumoral hypoxia.

X Margeret Liu, The University of Alabama, USA

Dr. X. Margaret Liu obtained her Ph.D. degree in 2005 in the Department of Chemical and Biomolecular Engineering at The Ohio State University. She had worked as Sr. scientist and team leader in biopharmaceutical and biotechnology industries for six and a half years. In January, 2012, she joined academic research as an assistant professor in the Department of Chemical and Biological Engineering at The University of Alabama. Dr. Liu's research focuses on the improvement of biopharmaceuticals production by host cell engineering and integrated process development, and the development of next-generation bioenergy and biochemical using rational metabolic cell-process engineering facilitated with systems biology.

Bioengineering, Drug Delivery & Nanotechnology

Raj Bawa,Bawa Biotech LLC, PRI at Albany College of Pharmacy; Guanine, Inc., USA

Raj Bawa, MS, PhD, MD ('22) is president of Bawa Biotech LLC (founded 2002), a biotech/pharma consultancy and patent law firm based in Ashburn, Virginia, USA. Trained as a microbiologist and biochemist, he is an inventor, entrepreneur, professor, and registered patent agent licensed to practice before the US Patent & Trademark Office. He is currently a scientific advisor to Teva Pharmaceutical Industries, Ltd. (Israel), a visiting research scholar at the Pharmaceutical Research Institute of Albany College of Pharmacy (Albany, NY), and vice president/chief IP officer at Guanine, Inc. (Rensselaer, NY). Currently, he is also a medical student and will receive the MD degree in 2022. He has served as a principal investigator in the past, most recently as a principal investigator of a CDC grant to develop an assay for carbapenemase-resistant bacteria. He was an adjunct professor at Rensselaer Polytechnic Institute in Troy, NY from 1998-2018, where he received his doctoral degree in three years (biophysics/biochemistry). In the 1990s, Dr. Bawa held various positions at the US Patent & Trademark Office, including primary examiner from 1996-2002. Presently, he is a life member of Sigma Xi, co-chair of the nanotech and precision medicine committees of the American Bar Association and founding director of the American Society for Nanomedicine (founded 2008). He has authored over 100 publications, co-edited 7 texts, and serves on the editorial boards of numerous peer-reviewed journals, including serving as an associate editor of Nanomedicine (Elsevier). Some of Dr. Bawa's awards include the Innovations Prize from the Institution of Mechanical Engineers, London, UK; Appreciation Award from the Undersecretary of Commerce, Washington, DC; Key Award from Rensselaer's Office of Alumni Relations; and Lifetime Achievement Award from the American Society for Nanomedicine.

Marianna Foldvari, University of Waterloo, Canada

Dr. Marianna Foldvari is a Professor of Pharmaceutical Sciences at the University of Waterloo's School of Pharmacy in Canada. She is an internationally recognized expert in nanomedicine. Her interests include pharmaceutical nanotechnology and drug delivery system design for dermatology, neurodegenerative disorders such as glaucoma, and autoimmune diseases. Current investigations include novel materials, mechanisms and pathways that enable the discovery and invention of needle-free administration methods of medicines (dermal, transdermal, transmucosal, ocular, oral and intranasal), especially proteins and nucleic acids.

John G Hardy, Lancaster University, UK

Dr. Hardy received his Ph.D. in Chemistry from the University of York in 2007. He enjoyed postdoctoral fellowships in France, Germany, Northern Ireland and the USA, working with the Nobel Laureate Jean-Marie Lehn (Strasbourg), Thomas Scheibel (Bayreuth), Colin McCoy (Belfast), David Kaplan (Tufts) and Christine Schmidt (Austin, Texas and Gainesville, Florida). He is currently a Lecturer (Assistant Professor) in the Department of Chemistry and Materials Science Institute at Lancaster University. His current research focus is the development of materials that respond to electricity, light and magnetism and their application for biomedical applications (such as drug delivery, or tissue engineering and regenerative medicine). You can follow his lab at @JGHardyLab.

Ali Khademhosseini, Terasaki Institute, USA

Ali Khademhosseini is Professor of Medicine at Harvard Medical School and Director of the Biomaterials Innovation Research Center at Brigham and Women's Hospital. He is also a faculty at the Harvard-MIT Division of Health Sciences and Technology as well as an Associate Faculty at the Wyss Institute for Biologically Inspired Engineering and a Junior PI at Japan's World Premier International-Advanced Institute for Materials Research at Tohoku University where he directs a satellite laboratory. He is recognized as a leader in combining micro- and nano-engineering approaches with advanced biomaterials for regenerative medicine applications. In particular, his laboratory has pioneered numerous technologies and materials for controlling the architecture and function of engineered vascularized tissues. He has authored over 450 journal papers (H-index = 80, >23,000 citations) and 50 books/chapters. In addition, he has delivered 250+ invited/keynote lectures. Dr. Khademhosseini's interdisciplinary research has been recognized by over 30 major national and international awards. He is a recipient of the Presidential Early Career Award for Scientists and Engineers, the highest honor given by the US government for early career investigators. He is also a fellow of the American Institute of Medical and Biological Engineering (AIMBE), the Royal Society of Chemistry (RSC), Fellow of the Biomaterials Sciences and Engineering (FBSE) and the American Association for the Advancement of Science (AAAS). Currently he serves on the editorial board of numerous leading journals. He received his Ph.D. in bioengineering from MIT (2005), and MASc (2001) and BASc (1999) degrees from University of Toronto both in chemical engineering. Read more here.

Jae-Young Lee, Gwangju Institute of Science and Technology, Republic of Korea

Dr. Jae-Young Lee is an assistant professor of School of Materials Science and Engineering, Gwangju Institute of Science and Technology (GIST), Republic of Korea. Dr. Lee received B.S. and M.S. degrees in Chemical Technology from Seoul National University in 1997 and 1999, respectively. He worked as a research manager in LG Life Science Ltd from 1999 to 2005. He received his Ph.D. from The University of Texas at Austin in 2010. He studied his postdoctoral research at University of California Berkeley with an American Heart Association (AHA) postdoctoral fellowship. He joined GIST in 2012. His current research focuses on the development of functional biomaterials that can improve biomaterial-cell interactions for various uses. His research interests include designs of surface modification of implantable bio-electrodes, tissue engineering scaffolds, and nano-biomaterials for therapeutic applications.

Didier Letourneur, CNRS, France

Didier is Research Director at CNRS. In 2002, he founded a research structure focused on the use of biomedical polymers for 3D structures and contrast agents for vascular imaging. Since 2005, he has led the team of Cardiovascular Bioengineering at Inserm-X Bichat hospital - University Paris Nord and Paris Diderot (France). He is now the Director of the Laboratory for Vascular Translational Science (LVTS–Inserm U1148) with about 160 persons. He is actively involved in several regional, national and European projects. Since 2013, he has been the European coordinator of "NanoAthero", a large scale NMP FP7 program on imaging and treatment of cardiovascular diseases with nanotechnologies. The author of 118 international publications and inventor of 15 patents, he has won several prizes: "Coup d'Elan for Research" Foundation Bettencourt 2001, Diderot Innovation Award 2009 CNRS-University Paris 7, Cardiovascular Innovation Award 2011 from the Medical Research Foundation, and OSEO/BPI emergence 2012 & Creation-Dev 2013 for start-up creation "IMMATIS". He has more than 90 invited lectures and seminars and is the co-organizer of several national and international conferences and two Inserm training workshops for regenerative medicine. He is the vice-chairman for Regenerative Medicine at the European Technology Platform for Nanomedicine and President of BIOMAT, French Society for Biomaterials.

Niren Murthy, University of California at Berkeley, USA

XiuJun (James) Li, University of Texas at El Paso (UTEP), USA

XiuJun (James) Li received his Ph.D. in bioanalytical chemistry in 2008 from Simon Fraser University, Canada, and then moved to University of California Berkeley and Harvard University for his postdoctoral research from 2009 to 2011, as a NSERC Postdoctoral Fellow. Currently, he is a tenure-track Assistant Professor in the Department of Chemistry at University of Texas at El Paso (UTEP), USA. His current research interest is centered on bioanalysis and bioengineering using microfluidic lab-on-a-chip and nanosensing. Dr. Li is the recipient of UT STARS Award in 2012, UTEP Outstanding Performance Award in 2014, and the 2014 Bioanalysis Young Investigator Award.

Oncology

Lev Berstein, Petrov Research Institute of Oncology, St. Petersburg, Russia

Lev is Chief of Laboratory of Oncoendocrinology at Petrov Research Institute of Oncology, St. Petersburg, Russia. His main scientific interests include mechanisms of hormonal carcinogenesis, studying of risk factors of hormone-associated tumors and new approaches to prevention and treatment of the latter. He received several international distinctions (including UICC Translational Cancer Research Fellowship), serves as a Member of Council of Russian Endocrine Association, at editorial boards of two national journals and as a reviewer for Future Oncology, J. Cancer Res. Clin. Oncol., Mol. Cell. Endocrinology, Cancer Epidemiology, Biomarkers & Prevention and others. In his bibliography are 7 monographs, 16 chapters and more than a hundred papers in peer-reviewed journals. He graduated as MD at Tartu University in Estonia and received his PhD and DMS degrees from Cancer Endocrinology at Petrov Institute in St.Petersburg.

Carlo Buonerba, Cancer Center of Excellence of Basilicata (CROB), Italy

Dr Carlo Buonerba studied electronic engineering before earning his medical degree, summa cum laude, at University Federico II of Naples in 2009. He is an active clinical researcher and medical writer. He has served as co-investigator in 7 prospective trials and has authored more than 60 papers, with an h index of 13. He is also an entrepreneur having founded and become the CEO of two companies that provide scientific editorial assistance and develop medical software. Genitourinary cancer and thymic epithelial tumors comprise his main fields of research.

Liang Cheng, Indiana University School of Medicine, USA

Dr. Liang Cheng is Professor of Pathology and Urology at Indiana University School of Medicine, Indianapolis, Indiana, USA. Currently, he is Chief of the Genitourinary Pathology Service, Director of the Urologic Pathology Fellowship, and Director of Molecular Diagnostics and Molecular Pathology Laboratories. Dr. Cheng has published over 600 peer-reviewed articles in high-impact scientific journals. His published work has been cited more than 21,000 times (h-index: 75). He is also the author and editor of several textbooks, including Bladder Pathology, Urologic Surgical Pathology, Essentials of Anatomic Pathology, Molecular Genetic Pathology , Atlas of Genitourinary Pathology, Molecular Surgical Pathology , Renal Tumors, and Atlas of Anatomic Pathology.

John Greenman, University of Hull, UK

John is a tumour immunologist with extensive experience of developing lab on a chip technology for analysing tumour biopsies. He has published over 150 peer-reviewed publications and his immunobiology group works closely with clinicians, chemists and engineers. The majority of this research work has focused on tumours of the Head & Neck region, identifying novel markers of progression or treatment response. He gained his PhD at the Tenovus Cancer Research Institute (Southampton University), and worked as a postdoc at the Dunn School of Pathology in Oxford before moving to Hull in 1995; he was awarded his Professorship in 2009. He was made Heart Research UK's researcher of the year in 2012 for his work on heart on a chip. He is currently Head of the School of Life Sciences.

Simon Lo, University of Washington School of Medicine - Radiation Oncology, Seattle, WA, USA

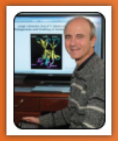
Dr. Lo is Professor of Radiation Oncology and Vice Chair for Strategic Planning of Department of Radiation Oncology. Previously, he was a Professor of Radiation Oncology and Director of Neurologic Radiation Oncology and Gamma Knife Radiosurgery at University Hospitals Seidman Cancer Center, Case Western Reserve University. He has served previously on the faculty at the Indiana University Cancer Center and Arthur G. James Cancer Hospital, Ohio State University. Dr. Lo's research interest is in delivering stereotactic radiation to all body sites as well as neurologic radiation oncology. He is the Chair of the American College of Radiology Appropriateness Criteria Bone Metastasis Expert Panel and Member of the American Society for Radiation Oncology Bone and Brain Metastasis Taskforce. His collaborative work on radiobiologic modeling for ablative radiation dose range with his colleagues at Ohio State University has been recognized internationally. He has published 170 peer-reviewed publications and over 50 book chapters and has edited or co-edited 4 textbooks, including a comprehensive textbook in stereotactic body radiation therapy, which has had 36,000 chapter downloads and is available in most medical libraries worldwide. Dr. Lo has lectured in national and international meetings and at a number of prestigious medical schools as a visiting professor. He is the Radiation Oncology Track Chair for the Radiological Society of North America refresher courses and the President-Elect of the Council of Affiliated Regional Radiation Oncology Societies (CARROS) of American College of Radiology. He is a member of the CNS/Pediatric Committee of the American Board of Radiology. He is currently a Fellow of American College of Radiology.

Srdjan Saso, Imperial College London, UK

Dr Saso qualified in 2007 from Imperial College, School of Medicine. He went on to complete basic training in Northwick Park and St. Mary's Hospitals before being appointed, in 2009, to the North West Thames Deanery Obstetrics and Gynecology program. In 2011 he became a member of the Royal College of Surgeons. He completed his PhD at Imperial College London in 2014, which focused on aspects of fertility preservation and uterine transplantation. In addition to his clinical appointments, he worked on the application of statistical methodology to review various aspects of surgical practice, holding an Honorary Clinical Research Fellowship in the Department of Biosurgery and Surgical Technology at Imperial College under the supervision of Professor Thanos Athanasiou and Lord Ara Darzi.

J Richard Smith, West London Gynaecological Cancer Centre, UK

J Richard Smith trained as a doctor at the University of Glasgow and in London, obtaining his MRCOG in 1988 and graduating with an MD in 1992, covering cervical cancer, immunity and infection. Subsequently lecturing at Charing Cross and Westminster Medical School, he went on to become Director of Gynaecology at Chelsea and Westminster Hospital and visiting associate professor at NYU Medical Centre in New York. He has been based at the West London Gynaecological Cancer Centre, Queen Charlotte's & Chelsea Hospital, Imperial College London for the last 6 years. He is also an adjunct associate professor at NYU Medical Centre. With an interest in doctor/patient communication, he is the series editor for the Patient Pictures book series. He is also editor of the Atlas of Gynaecological Oncological surgery (4th edition; 2016). He has written over 20 books and also has over 130 peer review publications, plus 50 others. Mr Smith has, for the past 15 years, been involved with the UK Uterine Transplantation research team, and is currently its leader. He is also interested in fertility-sparing surgery for women with cancer.



Dimiter Dimitrov, University of Pittsburgh, USA

Dr. Dimitrov joined the National Cancer Institute of the National Institutes of Health, USA, in 1990 where he is senior investigator and appointed at the senior biomedical research service. His research group includes molecular biologists who are experts in display/screening/libraries methodologies, antibody engineering, protein biochemistry, structural and computational biology. His major long-term goal is the development of clinically useful therapeutics and vaccines based on human monoclonal antibodies including engineered antibody domains. He has authored and coauthored more than 360 articles cited about 15,000 times, and is inventor or coinventor of more than 50 inventions, patent applications or patents.

Ajay Goel, City of Hope, CA, USA

Ajay earned his PhD degree from Panjab University, Chandigarh, India in 1996. After a brief tenure at University of Virginia, Charlottesville, Dr. Goel joined University of California San Diego in 1998 for a post-doctoral training fellowship in a gastrointestinal cancer research lab. In 2001, he became Assistant Professor at the School of Medicine, UCSD, La Jolla. He moved to Baylor in 2003 and is now at the City of Hope in Duarte. Dr. Goel's primary research is focused on gastrointestinal cancer pathogenesis and its prevention. A significant focus of his research lab is Cancer Epigenetics, and he is very interested in developing disease biomarkers for the early detection of various gastrointestinal malignancies. He has published almost 180 scientific articles in peer reviewed international journals and several book chapters. He is also a primary inventor on more than 11 patents aimed at developing various biomarkers for the diagnosis, prognosis and prediction of gastrointestinal cancers. Dr. Goel is a member of the American Association for Cancer Research (AACR) and the American Gastroenterology Association (AGA) and is on the international editorial boards of several journals.

Neurology

Breno Satler Diniz, CAMH and University of Toronto, Canada

Dr. Diniz graduated in Medicine at the Federal University of Minas Gerais (2003). He completed a Medical Residency in Psychiatry and Geriatric Psychiatry at the Institute of Psychiatry, Hospital das Clinicas, Faculty of Medicine, USP (2007) and earned his PhD from the Department of Psychiatry, Faculty of Medicine, USP (2011). He completed a Postdoctoral Fellow in Geriatric Psychiatry and Neurosciences at the Department of Psychiatry, University of Pittsburgh, USA (2012). His areas of research interest are: depression in the elderly neurobiology of neuropsychiatric disorders, biomarkers in geriatric depression and cognitive impairment, translational research in psychiatry and neurosciences. You can follow Breno on Twitter at @BrenoSatler.

Immunology

Vito Sabato, University of Antwerp and Antwerp University Hospital, Belgium

Vito was educated at Università Cattolica del Sacro Cuore (Rome, Italy) were he obtained his MD degree and subsequently his certificate as Specialis in Allergology and Clinical Immunology. He is currently Senior Staff Member at the Department of Immunology, Allergology and Rheumatology of Antwerp University Hospital. His activity is mainly focused on flow-assisted analysis of basophils, role of inhibitory receptors in tempering IgE-mediated disease and clonal mast cell-mediated diseases.

Frank Staal, Leiden University Medical Center, The Netherlands

Frank was educated at Utrecht University Medical School, The Netherlands were he obtained his B.Sc. and M.Sc. degrees, both cum laude. He moved to the USA to obtain a Ph.D. degree in Genetics from Stanford University under the guidance of the late Leonard Herzenberg. He moved back to Holland to work with Hergen Spits in Amsterdam and Hans Clevers in Utrecht, after which he started his own lab at Erasmus MC, Rotterdam. Currently he is full professor of Molecular Stem Cell Biology at Leiden University Medical Center. His research focuses on molecular regulation of immature T lymphocyte development and hematopoietic stem cell biology. Besides basic aspects of transcriptional regulation and cell signaling in mouse and human, this knowledge is applied to diagnosis and gene therapy applications of primary human immunodeficiencies as well as to abnormal lymphoid development in acute lymphoblastic leukemias. Translational research leading to novel diagnostic and therapeutic tools is an integral part of his research activities.

Regenerative Medicine

Chris Mason, University College London, UK

Dr. Chris Mason is Professor of Regenerative Medicine Bioprocessing in the Advanced Centre for Biochemical Engineering, University College London working on the clinical translation and commercialization of cell and gene therapies, and tissue-engineered products. He has a multidisciplinary track record, spanning therapeutics, medical devices and information technology, in discovery, clinical medicine, bioprocessing, regulation, healthcare economics, reimbursement and business. His current responsibilities include: Senior Editor of "Regenerative Medicine" journal, Chair of the BioIndustry Association (BIA) Regenerative Medicine and Cell Therapy Industry Group, Founder and Chief Executive Officer of the London Regenerative Medicine Network, and Trustee of the UK Stem Cell Foundation. Dr. Mason is on a number of national and international committees, working groups and initiatives related to the academic, clinical translation and commercialization of advanced therapies including the UK-Israel Science Council, UK Regenerative Medicine Expert Group, the Scientific Advisory Panel of the UK Cell Therapy Catapult, and the Strategic Advisory Board of the Canadian Centre for the Commercialization of Regenerative Medicine. Dr. Mason is a general spokesperson for the regenerative medicine sector including frequent newspaper, radio and TV interviews, plus on social media via Twitter at @Prof_ChrisMason.

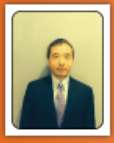
Biochemistry & Biomarkers

Pablo Moscato, University of Newcastle, Australia

Australian Research Council Future Fellow Prof. Pablo Moscato was born in 1964 in La Plata, Argentina. He obtained his BSc. of Physics at University of La Plata, and he defended his PhD at UNICAMP, Brazil. While at the California Institute of Technology Concurrent Computation Program (1988-89) he developed in collaboration with Michael Norman a methodology called "memetic algorithms" which is now widely used around the world. He is the founding co-director of the Priority Research Centre for Bioinformatics, Biomarker Discovery and Information-based Medicine (2006-) and the founding director of the Newcastle Bioinformatics Initiative (2002-2006) of The University of Newcastle. He is also Chief Investigator of the Australian Research Council Centre in Bioinformatics. He has been working in Evolutionary Computation for 25 years, and in heuristic methods for Operations Research problems since 1985. His work and ideas have been highly influential in a large number of scientific and technological fields and his manuscripts have been highly cited. He is one of Australia's most cited computer scientists. In the past seven years he has introduced a unifying hallmark of cancer progression based on the changes of information theory quantifiers, developed a novel mathematical model and an associated solution procedure based on combinatorial optimization techniques to identify drug combinations for cancer therapeutics. He has also identified proteomic signatures to predict years in advance the clinical symptoms of Alzheimer's Disease among other `firsts'. You can follow Pablo on Facebook and read more about his work here.

Nate Snyder,Drexel University, USA

Dr. Snyder is an Assistant Professor at Drexel University in Philadelphia, PA. Nathaniel studied Biochemistry at the University of Maryland and trained at the National Institutes of Health. His Ph.D. thesis in Pharmacology at the University of Pennsylvania concerned analytical measurements of low abundance biological molecules using liquid chromatography-mass spectrometry (LC-MS). Also completed at the University of Pennsylvania, Dr. Snyder's MPH work investigated non-invasive biomarkers of asbestos exposure. Nathaniel has published over 60 peer-reviewed articles and presented academic works on analytical chemistry, metabolism, inflammation, and environmental exposure assessment.



Naidong Weng, Janssen Research & Development, USA

Dr. Weng is Scientific Director, Janssen Fellow, and Head of Bioanalytical Chemistry and Pharmacokinetics, Janssen Research & Development, Johnson and Johnson. He has 97 peer-reviewed journal publications, 10 book chapters, over 100 posters and over 25 podium presentations. He also co-edited one book on bioanalysis (Eliminating bottlenecks for efficient bioanalysis: practices and applications in drug discovery and development, 2014) and one Special Focus Issue of Bioanalysis on Bioanalytical Laboratory Structure and Management (2014). He has been teaching short courses on DMPK at ASMS since 2011. He serves on the editorial advisory boards for three international scientific journals as well as on various scientific/organizational committees, most recently as the chairman for CPSA Shanghai 2013 and CPSA USA 2015. He also serves as a reviewer for (bio)analytical journals and has reviewed over 100 submitted manuscripts.

Ian Wilson, Imperial College London, UK

Ian studied biochemistry at the University of Manchester Institute of Science and Technology (UK), obtained a PhD at Keele University (UK) and then worked in Pharma finally as a Senior Principal Scientist in DMPK for AstraZeneca. Now at Imperial College (London, UK) he is author, or co-author, of some 490 publications, and has received awards in separation and analytical science from the Royal Society of Chemistry, the Chromatographic Society and the Belgian Society of Pharmaceutical Sciences. His research is directed towards the development of hyphenated techniques in chromatography and their application to problems in drug metabolism, toxicology and metabonomics.

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Yang bertandatangan di bawah ini :

Nama	: Dr. Santi Martini, dr. M.Kes
NIP	: 196609271997022001
Pangkat/Golongan	: Pembina / Gol. (IV/a)
Jabatan	: Dekan

Dengan ini menerangkan bahwa :

Nama	: Dr. Hari Basuki Notobroto, dr., M.Kes
NIP	: 196506251992031002
Pangkat/Golongan	: Pembina (Gol. IV/a)
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1	Acute Respiratory Infections Associated with Exposure to Biomass Cooking Fuels and Cigarette Smoke among Children Under Five Years of Age in Developing Countries (C6)	2022
2	Challenges and strategy in treatment with exosomes for cell-free-based tissue engineering in dentistry (C7)	2021
3	Extracellular vesicles: a promising cell-free therapy for cartilage repair (C8)	2019
4	Plant-derived exosome-like nanoparticles: A concise review on its extraction methods, content, bioactivities, and potential as functional food ingredient (C10)	2021
5	Prospect of Stem Cells as Promising Therapy for Brachial Plexus Injury: A Systematic Review (C12)	2022
6	The potential of mesenchymal stem-cell secretome for regeneration of intervertebral disc: A review article (C34)	2021
7	Towards Prevention and Eradication of Leprosy : Current Status and Research Needed in Community Health & Immune Dysregulation (C75)	2020
8	Health risks associated with high waist circumference: A systematic review (C82)	2020
9	Associated Risk of Death From Covid-19 Infection in Patients with Hypertension Co-Morbidities (C120)	2021

Adapun penelitian tersebut layak dilakukan dan menghasilkan output yang sangat baik, meskipun belum ada ***Uji Ethical Clearance*** karena merupakan penelitian menggunakan metode **Systematic Review**.

Demikian surat keterangan ini kami buat untuk dapat dipergunakan sebagai persyaratan pengusulan Jabatan Fungsional Guru Besar.

Surabaya, 24 April 2023
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Review

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Extracellular vesicles: a promising cell-free therapy for cartilage repair

Rizka Musdalifah Amsar[1], Christofora Hanny Wijaya[2], Ika Dewi Ana[3], Atik Choirul Hidajah[4], Hari Basuki Notobroto[5], Triati Dewi Kencana Wungu[6,7] & Anggraini Barlian*[,1,7]

[1]School of Life Science & Technology, Institut Teknologi Bandung, Bandung, West Java, 40132, Indonesia
[2]Department of Food Science & Technology, Bogor Agricultural University, West Java, 16680, Indonesia
[3]Department of Dental Biomedical Sciences, Faculty of Dentistry, Gadjah Mada University, Yogyakarta, 55281, Indonesia
[4]Department of Epidemiology Faculty of Public Health, Airlangga University, East Java, 60115, Indonesia
[5]Department of Biostatics & Population Faculty of Public Health, Airlangga University, East Java, 60115, Indonesia
[6]Nuclear Physics & Biophysics Research Group, Department of Physics, Faculty of Mathematics & Natural Sciences, Institut Teknologi Bandung, West Java, 40132, Indonesia
[7]Research Center for Nanoscience & Nanotechnology, Institut Teknologi Bandung, West Java, 40132, Indonesia
*Author for correspondence: aang@sith.itb.ac.id

Few effective therapies for cartilage repair have been found as cartilage has a low regenerative capacity. Extracellular vesicles (EVs), including exosomes, are produced by cells and contain bioactive components such as nucleic acids, proteins, lipids and other metabolites that have potential for treating cartilage injuries. Challenges like the difficulty in standardizing targeted therapy have prevented EVs from being used frequently as a treatment option. In this review we present current studies, mechanisms and delivery strategies of EVs. Additionally, we describe the challenges and future directions of EVs as therapeutic agents for cartilage repair.

Lay abstract: Repairing cartilage damage is challenging due to the tissue's low regenerative capacity. Extracellular vesicles (EVs) contain bioactive components that may be able to treat cartilage injuries. However, EV-based therapy is not widely used. This review summarizes the current state of knowledge regarding the use of EVs for cartilage repair, including the mechanisms, delivery strategies, challenges and future directions.

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Keywords: cartilage repair • chondrocyte • exosomes • extracellular vesicles • stem cell • therapeutic strategies

Cartilage is a type of connective tissue in the body that contains extracellular matrix and chondrocytes. Cartilage damage can be caused by both degenerative disease and trauma. Treatment of cartilage damage remains challenging due to the nature of the tissue, which does not readily regenerate. Cartilage is avascular, alymphatic and aneural. Osteochondral grafts, collected from bone and intact articular cartilage from a non-weight-bearing portion of the knee, can be used to treat cartilage damage in a weight-bearing site. Microfracture, another therapy, is based on cell homing [1]. Microfractures are created at 3- to 4-mm intervals, stimulating production of a blood clot containing bone marrow stem cells. The stem cells will differentiate into chondrocytes and secrete extracellular matrix (ECM) to produce cartilage. Cell-based therapy such as autologous chondrocyte implantation (ACI) is used to treat cartilage defects [2]. ACI includes chondrocyte isolation, *in vitro* culture and implantation into the injury site. ACI can be modified by using chondrocytes seeded in matrix (matrix-associated ACI) to improve cell delivery. The source availability, risk of graft rejection and formation of fibrocartilage rather than hyaline cartilage are all issues with current treatment methods [3].

Stem cells are commonly used as therapeutic cells in tissue regeneration. Stem cells can be implanted directly at injury sites or used as the cell source for tissue engineering [4]. Stem cells are more readily available than chondrocytes. Stem cells needed to treat damaged cartilage can be obtained from induced pluripotent stem cells [5],

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amniotic fluid stem cells (AFSCs) [6], Wharton jelly-derived stem cells [7], adipose-derived stem cells (ADSCs) [8] and bone marrow-derived stem cells (BMSCs) [9]. Stem cells present some advantages in cell-based therapies. For instance, mesenchymal stem cells (MSCs) can proliferate and differentiate into specific cell types and replace the targeted affected tissue [10]. Another advantage of using MSCs in therapy is that the cells participate in immunomodulation [11].

Recent studies have attributed the value of stem cells in therapy to their paracrine secretion [12]. Cells release paracrine factors via extracellular vesicles (EVs) such as exosomes. Exosomes function in cell–cell communication and can be found in all bodily fluids, including milk [13], urine [14], blood [15] and saliva [16]. Their cargo depends on their cell of origin [17]. Exosomes have potential uses in the repair and regeneration of damaged cartilage [18,19]. Exosomes stimulate cell proliferation [20] and stem cell differentiation [21]. They also modulate inflammation in injured cartilage [22]. The use of exosomes in cartilage repair can minimize immune rejection [23] . In addition, exosome treatment may result in the formation of hyaline cartilage. Zhang *et al.* demonstrated that intra-articular injection of exosomes weekly for 12 weeks completely restored cartilage and subchondral bone with hyaline cartilage in an osteochondral defect model [24].

EVs' presence and therapeutic function allow for clinical applications in cartilage repair and regeneration. However, the delivery strategy for their use as a targeted therapeutic agent is challenging. EVs have a variable protein or nucleic acid profile, and in small amounts they can be cleared rapidly by the circulatory system.

Here we provide information about EVs, current studies on the potential use of EVs/exosomes for cartilage regeneration, and therapeutic strategies for using EVs as well as their limitations.

EVs & exosomes

Most cells spontaneously secrete vesicles into the extracellular space. EVs are defined as lipid bilayer particles released by cells that are unable to multiply, according to the Minimal Information for Studies of Extracellular Vesicles 2018 (MISEV2018) [25]. Based on their biogenesis, size and content, EVs can be categorized into three types: apoptotic bodies, microvesicles/shedding particles and exosomes [26,27]. During the apoptotic process, dying cells form vesicles called apoptotic bodies. The origin of apoptotic bodies is the outward blebbing (1–5000 nm) of the apoptotic cell membrane [28], and the vesicles are formed to enhance removal of apoptotic material [27]. Microvesicles or exosomes are heterogeneous vesicles with a size range from 100 to 500 nm [29]. Microvesicles are derived from outward budding from the plasma membrane [30]. Exosomes, derived from endosomal origins, are the smallest type of EVs, with sizes ranging from 30 to 100 nm [31–33]. Due to the distinct biogenesis pathway, the molecular profile varies between each type of EV. For instance, the types of protein and lipid content in microvesicles and exosomes are different [34].

The formation of exosomes begins with inward budding of the cell membrane and the production of early endosomes. In the cytosol, early endosomes develop into late endosomes and make multivesicular bodies (MVBs) [35]. The invagination of the MVB membrane produces intraluminal vesicles. There are two usages of MVB in the cytosol: fusion to lysosomes for degradation, or fusion with the cell membrane to release intraluminal vesicles as exosomes [29]. Tetraspanins such as CD63, CD9 and CD81 are used as exosome markers in many studies; however, tetraspanin is also present on the cell surface, while other types of EVs have the marker in their membrane [36]. Because specific exosome markers have not yet been established, the MISEV2018 suggested operational terms for EV subtypes that refer to physical characteristics, biochemical composition and the cell origin of EVs [25]. This review uses the term EV to indicate general vesicles produced by cells, including exosomes.

The composition of lipids in the EV membrane resembles that of the cell plasma membrane [37]. However, Llorente *et al.* reported that exosomes have the highest content of glycosphingolipids, sphingomyelin, cholesterol and phosphatidylserine compared with the parent cell [38]. Lipids in the EV membrane maintain the EV's stability in the extracellular environment and facilitate uptake into recipient cells [37,39]. Protein from the EV membrane plays a role in tissue repair [40]. Moreover, proteins in the EV membrane contribute to the interaction between EVs and recipient cells. EV cargo also includes nucleic acids such as DNA and miRNA, which is the most studied nucleic acid. In cartilage repair and regeneration, exosomal RNA regulates genes involved in inflammation, cell proliferation, apoptosis and ECM synthesis. Mao *et al.* demonstrated that during 14 days of chondrogenesis, MSCs treated with 100 μg/ml exosomal *circ_0001236* expressed more *SOX9* and *COL2A1* than MSCs treated with 50 μg/ml exosomal *circ_0001236* [41]. *SOX9* and *COL2A1* are markers of chondrogenic differentiation, and this study demonstrated that exosomal *circ_0001236* at higher concentrations enhanced chondrogenesis in MSCs.

EVs may interact with recipient cells via contact, membrane fusion or endocytosis as a mediator of intercellular communication. In contact, the membrane ligand on the EVs' surface interacts with the receptor in the cell membrane of the recipient cell and generates cell signals [42,43]. In this case, EVs will not be internalized by the target cells. Another mechanism of interaction between EVs and cell targets is membrane fusion, in which the EV membrane consists of a lipid bilayer that fuses with the cell membrane and releases the cargo into the cytosol. A study by Parolini *et al.* showed that exosome uptake by melanoma cells happened via fusion and increased at low pH [44]. The most commonly studied mechanism of EV internalization is the endocytosis pathway, in which the EVs enter the recipient cell by phagocytosis [45], macropinocytosis [46,47], clathrin-mediated endocytosis [46], caveolin-mediated endocytosis [48] or lipid raft-mediated endocytosis [49]. It is possible that a particular type of EV has more than one mechanism when interacting with a recipient cell. Because EVs have therapeutic potential, their interactions with cells should be studied to develop targeted therapies.

Stem cell-derived EVs are at least as good as, if not better than, stem cells when applied for therapeutic purposes. Overall, they demonstrate less negative potential. A study by Mohammed *et al.* showed that exosomes from ADSCs are more effective as an adjuvant treatment in dentistry for scaling and root planing [50]. Another study performed by Zavatti *et al.* compared AFSCs and their exosomes in animal models of osteoarthritis and found that AFSC-derived exosomes were more effective in treating cartilage damage than the cells [51]. When compared with cell-based therapy using stem cells, EVs have some distinct advantages. For example, EVs have simpler storage needs, allow allogeneic transplantation due to lack of MHC I and MHC II antigens and are less vulnerable to damage at the injury site; it is also possible they can reach a higher circulating dose than bigger cells [23]. Because EVs are non-self-replicating, the possibility of iatrogenic tumor growth is reduced.

MSC exosomes are effective in supporting cartilage repair and regeneration [52]. The application of EVs in cartilage repair has been investigated *in vivo* in many different animal models with a variety of concentrations (Table 1). Small animal models such as mice, rats and rabbits are used in current research on cartilage regeneration. However, more research with larger test animals is required to be clinically appropriate. To improve treatment efficacy, it will also be necessary to standardize the EVs dose calculation.

Sources of EVs

EVs can be obtained from almost all bodily fluids. Parental cell selection should account for the desired therapeutic function of the resultant EVs. EVs can be a therapeutic drug or they can act as a delivery vehicle for a specific drug. For instance, EVs isolated from bovine milk can be utilized to deliver exogenous hsa-miR148a-3p in RNA-based treatment [76]. Although cells from an injury site can produce EVs, they usually do not produce therapeutic EVs; rather, EVs from the cells in a cartilage injury site tend to aggravate the damage [77,78]. However, EVs from therapeutic cells at the same injury site can maintain chondrocyte homeostasis [78]. These therapeutic cells can be differentiated cells or stem cells. Ma *et al.* found that EVs released by chondrocytes induced proliferation and differentiation of umbilical cord MSCs into chondrocytes, indicating that EVs promote cartilage regeneration [79].

EVs from blood components are advantageous because blood collection is less invasive and safer than adipose tissue or bone marrow collection. Otahal *et al.* studied the use of EVs derived from blood for treatment of osteoarthritis [80]. These investigators demonstrated that EVs isolated from citrate-anticoagulated platelet-rich plasma-enhanced desirable chondrogenic gene expression changes in osteoarthritis and prevented proinflammatory cytokine release [80]. Another study by Liu *et al.* showed that EVs derived from platelet-rich plasma promoted proliferation and inhibited chondrocyte apoptosis via the Wnt/β-catenin signaling pathway [81].

Stem cells such as induced pluripotent stem cells and MSC have potential in tissue repair. As cell-based therapy, stem cells can be applied directly or serve as a cell source for tissue engineering. Various types of stem cells produce functional EVs with advantages for cartilage repair. EVs derived from AFSCs can repair cartilage damage in correlation with their TGF-β content [51]. MSCs, which are non-hematopoietic stem cells, are present in various body tissues and are multipotent. The therapeutic effect of MSCs depends on a paracrine mechanism mediated by their EVs [12]. EVs isolated from ADSCs prevent cartilage degeneration and attenuate the progression of osteoarthritis by modulating immune reactivity [20]. Another study, using EVs from BMSCs, showed that BMSC-derived EVs promote ECM synthesis and protect against cartilage damage [65]. MSC-derived exosomes promote proliferation, migration and ECM synthesis, which helps to attenuate apoptosis and modulates immune reactivity in osteochondral defects [82].

Further research is needed to determine the most efficient therapeutic cell source, propagation and storage methods. An *ex vivo* study performed by Li *et al.* compared EVs from ADSCs, BMSCs and synovium MSCs in

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Table 1. A summary of *in vivo* studies that use extracellular vesicles for cartilage repair.

Animal model	Source of extracellular vesicle	Dose	Delivery	Ref.
OA induce in mice	BMSC	500 μg/ml	Intra-articular injection	[41]
OA induced in rat	BMSC	400 μg/ml	Intra-articular injection	[53]
OA induced in rat	SMSC	10^{11} particles/ml	Intra-articular injection – scaffold PLEL	[54]
Mice defect model	L-cells	7 μL	Intra-articular injection	[55]
Rabbit defect model	IPF-MSC	10^{10} particles	Intra-articular injection	[56]
Rat	CESC	10^{5} particles/ml	Intradiscal injection	[57]
Rabbit osteochondral defect model	WJ-MSC	25 μg/ml	Injection	[58]
Rat defect model	UMSC	1 mg/ml	Injection	[59]
OA induced in rat	BMSC	10^{10} particles/ml	Intra-articular injection	[60]
Rat defect model	UMSC	1 mg/ml	Intra-articular injection	[61]
OA induced in rat	BMSC	1 μg/μl	Injection	[62]
OA induced in rat	Dendritic cell (kartogenin)	100 μl	Intra-articular injection	[63]
Rat defect model	UMSC	10^{8} particles/ml	With scaffold implant directly	[64]
OA induced in rat	BMSC	40 μg/100 μl	Intra-articular injection	[65]
Rabbit osteochondral defect model	Embryonic stem cell-derived MSC	200 μg/mL of 3% HA	Intra-articular injection	[66]
OA induced in mice	Chondrogenic progenitor cell	10^{10} particles/ml	Intra-articular injection	[67]
Rabbit defect model	UMSC	10^{10} particles/ml	Intra-articular injection	[68]
OA induced in rat	AFSC	2 μg/μl	Unilateral injection	[51]
OA induced in mice	BMSC	1 μg/μl	Tail vein injection	[69]
IVD degeneration rabbit model	BMSC	1 μg/μl	Intradiscal injection	[70]
Rabbit defect model	BMSC	200 μg/ml	Implantation of ECM/GelMA/exosome scaffold	[71]
OA induced in mice	IPF-MSC	10^{10} particles/ml	Intra-articular injection	[72]
OA induced in rat	MSC	10^{11} particles/ml	Articular cavity injection	[73]
OA induced in rat	Embryonic stem cell-derived MSC	2 μg/μl	Intra-articular injection	[74]
OA induced in rat	SMSC	10^{11} particles/ml	Articular cavity injection	[75]
Rat osteochondral defect model	Embryonic stem cell-derived MSC	1 μg/μl	Intra-articular injection	[24]

AFSC: Amniotic fluid stem cell; BMSC: Bone marrow mesenchymal stem cell; CESC: Cartilage endplate stem cell; ECM: Extracellular matrix; GelMA: Gelatin methacrylate; HA: Hyaluronic acid; IPF-MSC: Infrapatellar fat pad mesenchymal stem cell; IVD: intervertebral disc; OA: Osteoarthritis; MSC: Mesenchymal stem cell; PLEL: poly(D,L-lactide)-b-poly(ethylene glycol)-b-poly(D,L- lactide; SMSC: Synovial mesenchymal stem cell; UMSC: Umbilical cord mesenchymal stem cell; WJ-MSC: Wharton Jelly mesenchymal stem cell.

cartilage regeneration and demonstrated that ADSC-derived EVs are the best candidate for cartilage and bone regeneration [83]. Even though that study was conducted *ex vivo*, it reveals that EVs derived from different cell types have variable effects. Moreover, a proteomic analysis of exosomes isolated from BMSCs, ADSCs and umbilical cord MSCs demonstrated their potential utility in a variety of fields [84].

Mechanism of EVs in cartilage regeneration

Common causes of cartilage damage are trauma and degenerative disease. In articular cartilage, damage often results from violent injury, chronic inflammatory disease or degenerative joint diseases [85]. According to Schulze-Tanzil [86], traumatic cartilage injury causes chondrocyte and synoviocyte stress that leads to inflammation, degradation of the cartilage's ECM and apoptosis. Inflammation in cartilage is often caused by inflammatory cytokines including IL-1β, TNF-α, IL-6, IL-15, IL-17 and IL-18 [87]. Cartilage damage has an effect on the quantity of chondrocytes by triggering cell death [88] and inducing chondrocyte apoptosis [89]. Additionally, injured ECM degrades faster than it can be synthesized. Understanding the pathogenesis of cartilage injury can help scientists develop specific therapies, including therapy for cartilage damage directed to overcome the results of homeostatic changes.

Inflammation in cartilage tends to increase pain and disease progression. Inflammation is a phenomenon in traumatic cartilage injury [86]. If the damage is caused by degenerative disease, such as in the intervertebral disc (IVD), inflammation is caused by an imbalance of the ECM catabolic and anabolic pathways [90]. Treatment using EVs can inhibit the inflammatory cascade. A study by Zhang *et al.* indicated that MSC-derived exosomes reduced IL-1β [74]. IL-1β, as the most important proinflammatory mediator, is also involved in inflammatory responses

Table 2. Role and mechanism of exosome-derived RNA in cartilage regeneration.

Exosomes component	Donor cell	Target cell	Induced mechanism	Ref.
miR-216-5p	BMSC	Chondrocyte	Enhance chondrocyte proliferation, migration and apoptosis repression	[62]
lncRNA H19	UMSC	Chondrocyte	Promote proliferation and prevent apoptosis in chondrocytes	[61]
miR-8485	Chondrocyte	BMSC	Promote chondrogenic differentiation of BMSCs	[96]
mir-145 and mir-221	ADSC	Chondrocyte	Promote proliferation	[97]
miR-100-5p	IPF-MSC	Chondrocyte	Inhibit mTOR autophagy pathway	[72]
miR-92a-3p	BMSC	Chondrocyte, MSC	Promote chondrocyte proliferation and matrix genes expression	[101]

ADSC: Adipose-derived stem cell; BMSC: Bone marrow mesenchymal stem cell; IPF-MSC: Infrapatellar fat pad mesenchymal stem cell; MSC: Mesenchymal stem cell; UMSC: Umbilical cord mesenchymal stem cell.

during disc degeneration [91]. Another study showed that MSC-derived exosomes slowed the progression of IVD degeneration by suppressing inflammatory mediators and NLRP3 inflammasome activation [70]. Suppressing the NLRP3 pathway can prevent pyroptosis, a programmed cell death triggered by proinflammatory signals. Exosomal miR-410 from MSC inhibits the NLRP3 pathway and regulates pyroptosis [92]. Recently, treatments for osteoarthritis have focused on macrophage polarization. Macrophages are immune cells found in the synovial lining that complete a variety of tasks depending on their subtype; they may be proinflammatory (M1) or anti-inflammatory (M2) [93]. A study by Zhang *et al.* demonstrated that exosomes isolated from BMSCs reduced inflammation by regulating macrophage polarization, inhibiting M1 macrophage production and promoting M2 macrophage generation [60].

The purpose of therapy in cartilage repair is to restore the chondrocyte ECM to its original state. ECM components, like collagen type II and proteoglycan, play a role in regulating chondrocyte functions. Therapy can be aimed at synthesizing those specific ECMs. He *et al.* reported that BMSC-derived exosomes upregulated collagen type II production and downregulated MMP13 protein expression in an animal model of osteoarthritis [65]. Another study found that BMSC-derived exosomes promoted ECM production in degenerated nucleus pulposus cells *in vitro* [94]. Thus it appears that EVs play defined roles in recovering cartilage ECM.

Chondrocytes play a role in cartilage regeneration by synthesizing ECM, despite their low number in normal cartilage. Because cartilage injury further diminishes the number of chondrocytes, a therapeutic method is required to maintain their population. The number of chondrocytes can be maintained by several mechanisms, one of which is to differentiate stem cells into chondrocytes. EVs from nucleus pulposus cells induce differentiation of MSC into nucleus pulposus-like cells by inhibiting the Notch1 pathway [95]. One component of EVs, miRNA, can also target the pathway in chondrogenic differentiation. Li *et al.* showed that miR-8485 from exosomal chondrocytes activated the Wnt/β-catenin pathways to stimulate differentiation of BMSCs into chondrocytes [96]. In addition to chondrogenic differentiation of stem cells, increasing chondrocyte proliferation in the injury site improves cartilage regeneration. Some studies have shown that EV cargo – for instance, miRNA [61,62,97 – can promote chondrocyte proliferation.

Chondrocyte loss that is caused by apoptosis and autophagy can be overcome using EV therapy. Cheng *et al.* reported that miR-21 in MSC-derived exosomes prevented nucleus pulposus cell apoptosis [98]. Similarly, studies have shown the utility of EVs in the inhibition of apoptosis induced by endoplasmic reticulum in IVD degeneration [99,100]. Inhibiting apoptosis and increasing cell proliferation in cartilage repair will maintain the number of chondrocytes.

The role of EVs in cartilage treatment is to restore cartilage homeostasis by maintaining the number of chondrocytes and balancing the metabolism of specific ECMs (Figure 1). EVs deliver functional cargo, such as miRNA, for cartilage regeneration (Table 2). Additionally, EV cargo modulates inflammation at the injury site.

Delivery strategies of EVs in cartilage repair

It is necessary to design suitable EVs that are functional therapeutic agents and deliver them to enhance their effectiveness and efficiency in treating damage. For cartilage repair, EVs can be obtained from bodily fluid, tissue or cell culture and delivered by local or intravenous administration. Woo *et al.* isolated EVs from ADSCs and used them to treat osteoarthritis in rats [20]. They found that ADSC-derived EVs enhanced proliferation and migration of

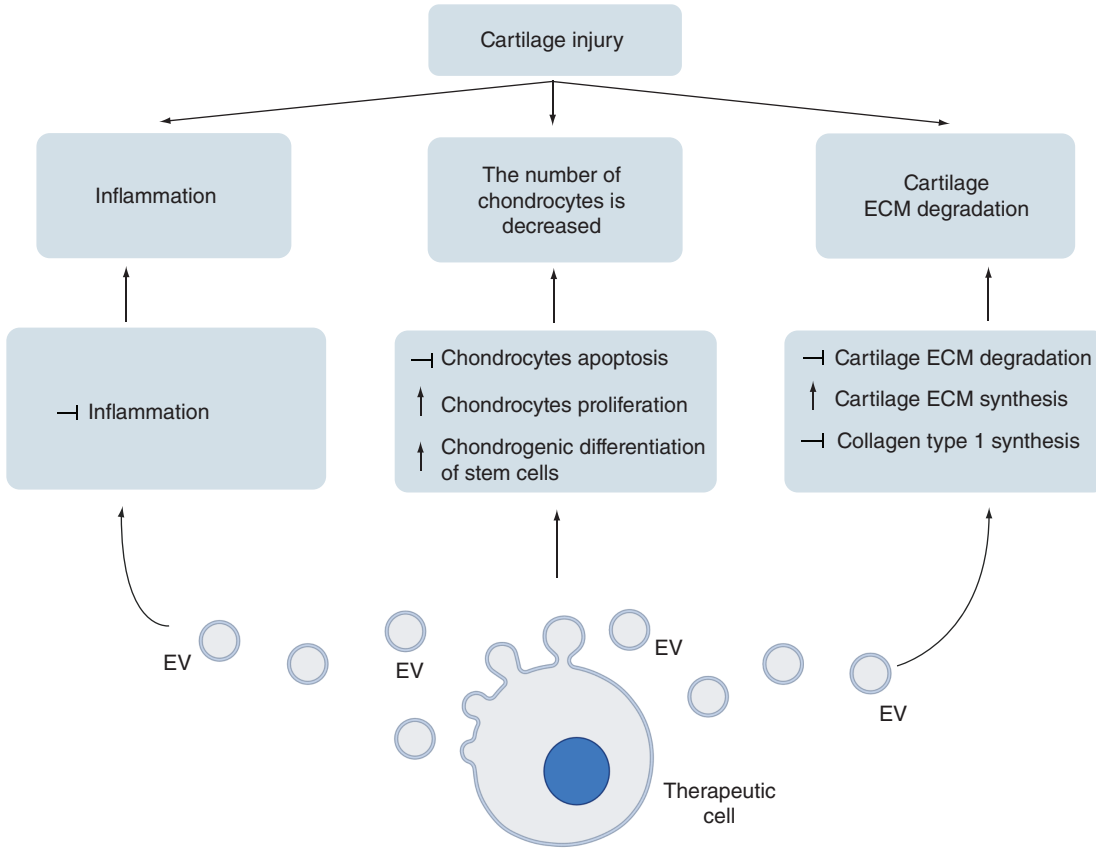

Figure 1. Mechanism of EVs in cartilage repair. Inflammation, chondrocyte reduction, and cartilage extracellular matrix degradation are the three phenomena that occur in cartilage damage. Extracellular vesicles work to overcome this by releasing cargo that can lower inflammation, increase the number of chondrocytes, and restore cartilage extracellular matrix in injury sites. (Created with BioRender.com)
ECM: Extracellular matrix; EV: Extracellular vesicle.

chondrocytes, regulated the expression of catabolic and anticatabolic factors and inhibited macrophage infiltration into synovium, thereby modulating immune reactivity [20]. He *et al.* also demonstrated that EVs derived from BMSCs and injected intra-articularly stimulated cartilage regeneration and ECM synthesis, as well as reducing knee discomfort, in an osteoarthritis model [65].

Engineering cells & their EVs

Engineering parental cells or their EVs can enhance the effectiveness of EVs in therapy. Changes in the cell microenvironment – such as the pretreatment medium, oxygen level and mechanical stimulation – influence cell behavior and affect EV characteristics and functions. For instance, kartogenin has been used to improve stem cell proliferation and chondrogenic differentiation in cartilage regeneration [102]. An examination of EVs from cells pretreated with kartogenin revealed a paracrine change of the cells in chondrogenesis. Liu *et al.* reported that EVs derived from kartogenin-preconditioned BMSCs enhanced chondral matrix synthesis and reduced degradation; thus this approach appears more effective for cartilage repair than the use of EVs from BMSCs without pretreatment with kartogenin [103]. A study using infrapatellar fat pad MSCs showed a similar result: EVs pretreated with kartogenin more effectively promoted articular cartilage defect repair [56]. Thus by altering the cellular environment through the addition of chemical compounds to the cell culture medium, the efficiency of the resultant EVs is improved.

Hypoxic preconditioning of stem cells also affects the efficiency of EVs. Hypoxic pretreatment of BMSCs enhances their release of EVs that increase proliferation, migration and apoptosis inhibition of chondrocytes through the miR-216a-5p/JAK2/STAT3 signaling pathway [62]. The cell microenvironment can also be modified through mechanical stimulation. A study by Yan *et al.* showed that mechanical stimulation using a rotary cell culture system enhanced the yield of EVs from umbilical cord MSC-derived EVs and found that EV function on

cartilage repair was enhanced through upregulation of lncRNA *H19* [61]. Modification of parental cells can also be accomplished by genetic engineering; Thomas *et al*. successfully engineered L-cells with WNT3a and isolated EVs that were able to heal osteochondral defects [55].

Another target of modification for targeted therapy, besides parental cells, is the EV itself, via a method called post-secretion modification. The aim of engineering EVs is to make them a functional drug delivery system. The drug loaded in EVs can be a natural component of therapeutic cell-derived EVs or another chemical agent. Loading a drug into EVs increases its *in vivo* stability, circulation in blood, and cell targeting efficiency [104]. Combining EVs with drugs promoting cartilage regeneration, such as kartogenin, enhances their function. Post-secretion modification of EVs is more efficient than engineering parental cells to deliver drugs. For example, even though kartogenin is beneficial in cartilage regeneration, it has low water solubility. Xu *et al*. isolated EVs from dendritic cells and engineered them to be a delivery agent for kartogenin [63]. They showed that this treatment increased the effectiveness of synovial fluid-derived MSCs to differentiate into chondrocytes [63]. Post-secretion modification can also be performed on the EV surface by adding specific ligands. Engineering the natural surface increased targeting efficiency *in vivo* [105].

For the same dose, delivering EVs through intravenous administration is less effective than local administration in cartilage repair. The half-life of exosomes in blood circulation is about 2 min [106]; healing a cartilage injury requires more time due to the characteristics of cartilage. However, local administration methods such as intra-articular injection require frequent injections that make the patient uncomfortable. Combining EVs with biomaterials or scaffolds could reduce treatment frequency, as the biomaterial will ensure that the EVs remain at the defect site.

EVs embedded in biomaterials

The scaffold acts as a time-controlled delivery system for EVs in cartilage injury, trapping them at the injury site and periodically releasing them. The release of drugs or EVs from a scaffold can be caused by diffusion, polymer dissolution and degradation, or swelling [107]. Scaffolds are defined by their ability to retain EVs at the injury site, gradually release them into the matrix and integrate with the damaged tissue to promote surrounding cell migration [108].

Scaffolds for cartilage regeneration can be made from synthetic or natural materials. Some common synthetic polymer materials are poly(lactic-co-glycolic acid) and polymer of lactic acid [109]. Synthetic materials have the advantages of reproducibility, structure and customizable characteristics. However, synthetic materials are more expensive than natural ones and they have weak cell attachment [109]. Additionally, natural scaffolds such as collagen, fibroin and chitosan tend to be safer because of their biocompatibility and reduced toxicity. The drawbacks of natural scaffolds are their source-dependent mechanical and physical properties [110].

The scaffold form needed to trap EVs and maintain their release can be solid or hydrogel. Hydrogel, a hydrophilic polymer, is widely used in cartilage tissue engineering. Its mechanical behavior permits its use as an articular cartilage substitute [111]. Hydrogel can be fabricated from natural materials or synthetic polymers to mimic the natural ECM and will control the release of EVs embedded in it. Stem cell-derived EVs can be incorporated into a photo-induced crosslinking hydrogel to retain the exosomes inside and enhance cartilage repair [112]. Chen *et al*. showed that EV-impregnated scaffolds from the cartilage ECM and gelatin methacrylate hydrogel promoted cartilage regeneration [71]. Thus studies indicate that biomaterial has a significant role in the delivery of EVs for repairing cartilage damage. Further research should be conducted to explore the various biomaterials that may be used for EV delivery in cartilage repair and regeneration.

Figure 2 summarizes therapeutic strategies utilizing EVs for cartilage repair. There are numerous delivery methods for EVs used to repair cartilage damage, with the primary goal being the restoration of cartilage homeostasis. The simplest method is to use naive EVs isolated from bodily tissue or cell cultures. However, EV parental cell types must be considered, as they affect EV bioactivity. By retaining EVs within the biomaterial and controlling their release, implanting EV-loaded biomaterials may be a way to enhance therapeutic effects. Furthermore, it does not require frequent administration when dosed appropriately.

Limitations

EVs, particularly exosomes, have potential in cell-free therapy for cartilage repair and regeneration. Numerous *in vitro* and *in vivo* studies have delineated the composition of EVs and their role in tissue repair. However, a search of clinicaltrials.gov gave only one result, which involved the use of platelet-rich plasma enriched with exosomes in the treatment of chronic low back pain [113]. It is critical to have appropriate identity and potency parameters when

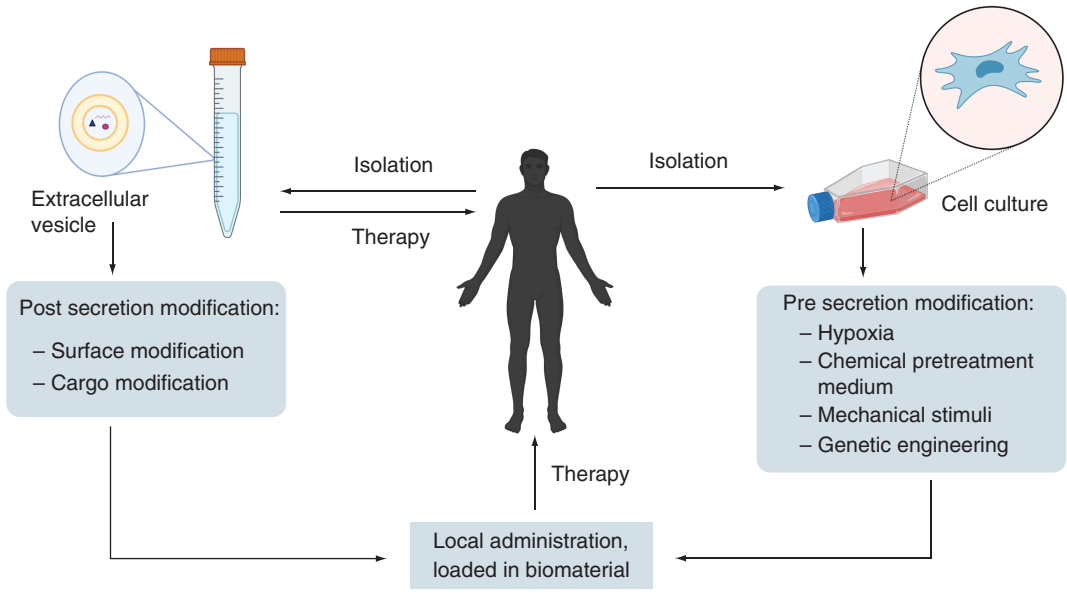

Figure 2. Strategies of extracellular vesicle based therapy in cartilage repair. EVs can be obtained from bodily tissue, fluid, or cell culture. Modification can be performed in cells (pre secretion of EVs) or EVs (post secretion). (Created with BioRender.com)
EV: Extracellular vesicle.

studying EVs to ensure their quality control and reproducibility. Those studying EVs and their effects should refer to the International Society of Extracellular Vesicles' guidelines [25] to promote reproducibility.

While evidence for the use of EVs in cartilage repair is convincing, several factors must be considered prior to initiating clinical trials. Larger animal models should be studied before EVs are used in the clinic. The examination of partial-thickness and full-thickness chondral repair, as well as osteochondral repair, is possible in large animal models with thicker articular cartilage [114]. Further investigation into the choice of EV parental cells and their maintenance is required due to the heterogeneity of EV content. As no single drug fits all diseases, targeted therapy is important. Another consideration is the optimization of large-scale production of EVs, because it is challenging to isolate EVs with high purity in high yields. The most common method for isolating EVs is ultracentrifugation, but this has limitations of low purity and EV aggregation [115]. Tangential flow filtration can be an alternative to achieve reproducible large-scale production [116]. Scale-up methods to produce EVs as a therapeutic agent for cartilage repair need standardization.

The choice of whether or not to engineer EVs for targeted cartilage therapy will depend in part on further research to guarantee their efficacy and safety. Proper EV dose and delivery strategies are also important. EVs wash out easily in the circulatory system, necessitating a higher dose or entrapment in biomaterial. Scaffold in the form of hydrogel is a good candidate as a delivery agent. While live cell transplantation is already widely used, EV-based therapy has a greater potential for repair due to the absence of cells. EV-loaded scaffolds can be adapted to the current surgical techniques applied to repair cartilage defects by implanting the EV-loaded scaffolds in the defect site. It is hoped that this procedure will eliminate the need for repeated operations by optimizing the EV dosage in the scaffold and will increase patient comfort. Additionally, when EVs are used therapeutically, such as in an articular cartilage injury, they can regenerate hyaline cartilage.

EV pharmacokinetics also needs to be considered for therapeutic development. Furthermore, it is necessary to standardize the quality of EVs as a product, such as storage conditions (e.g., temperature and expiration date). Although there are many challenges in the clinical application of EVs for cartilage repair, the evidence on the function of EVs in healing cartilage injury is promising. A better understanding of the potential of EVs in therapy and their greater accessibility may significantly reduce related healthcare costs.

Conclusion & future perspective

EVs, including exosomes, can be obtained from any cell source. Determination of parental cells and therapeutic strategies are important in making EV therapy effective and efficient. EV-based therapy has the potential to

repair cartilage damage by maintaining cartilage homeostasis. To optimize the therapeutic effects of EVs, they can be engineered and loaded with biomaterials to control their release. Proper strategies will lead to an increased accessibility and effectiveness of EV therapy for cartilage repair. To be clinically applicable, the standardization of EV products must be considered to ensure their safety.

Executive summary

- Extracellular vesicles (EVs), including exosomes, have the potential to treat cartilage damage by restoring cartilage homeostasis.
- Due to the heterogeneity of EV content, selection of parental cells and appropriate therapeutic strategies are important in targeted therapy.
- Loading biomaterials into EVs optimizes their effectiveness in cartilage repair.
- Some challenges in large scale production of EVs need to be addressed to facilitate their clinical application.

Author contributions

R Musdalifah Amsar undertook the literature research and drafted the manuscript. A Barlian contributed to supervision and editing of the manuscript. I Dewi Ana, C Hanny Wijaya, A Choirul Hidajah, H Basuki Notobroto and T Dewi Kencana Wungu contributed to revising the manuscript and approving the final version of the article.

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