Journal of Orthopaedic Translation 24 (2020) 131–137

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Original Article

Progress of orthopaedic research in China over the last decade

Jun Lin [a], Lin Chen [b], Dou Dou [c,*]

[a] Department of Orthopaedic Surgery, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China
[b] Department of Wound Repair and Rehabilitation Medicine, State Key Laboratory of Trauma, Burns and Combined Injury, Trauma Center, Research Institute of Surgery, Daping Hospital, Army Medical University, Chongqing, China
[c] Department of Health Sciences, National Natural Science Foundation of China, Beijing, China

ARTICLE INFO

Keywords:
Achievement
Challenge
Natural scientific fund
Orthopaedics

SUMMARY

Objective: To summarize the representative scientific achievements in the past decade, and discuss the future challenges and directions for orthopaedic research in China.
Methods: In this review, we used the data provided by National Natural Science Foundation of China (NSFC) for analysis.
Results: Over the last decade, NSFC has initiated various research programs with a total funding of over 1149 million RMB to support orthopaedic exploration. Under the strong support of NSFC, great progresses have been made in basic research, talent training, platform construction and the clinical translation in the field of orthopaedics in China.
Conclusion: In general, since the establishment of the Department of Health Sciences of NSFC 10 years ago, both the amount of funding and the scale of researchers in the field of orthopaedic research have increased substantially. Despite of several shortcomings in orthopaedic research, with continuous support from NSFC both in funding and in policy, we believe that the orthopaedic research in China will surely make steady and significant progress.
The translational potential of this article: This article summarizes the representative scientific achievements in the past decade and puts forward the future challenges and directions for orthopaedic research in China.

Musculoskeletal disorders are a major type of disease that threaten the human health worldwide. Most of the world population will experience different types of musculoskeletal diseases and/or injuries at some point in their life. According to reports from the World Health Organization (WHO), about 25% world population needs medical interventions for their musculoskeletal disorders. In developing countries, about 25% of health care costs are used for the prevention, treatment, care and rehabilitation of musculoskeletal diseases.

The spectrum of the musculoskeletal disease in China has the similar characteristics as that in both developed and developing countries. On the one hand, with the aging of the population, the degeneration related diseases of the osteoarticular and muscular system have become the common health problems for the elderly people. With the increase of the elderly population, the incidence of osteoporosis and related fractures, osteoarthritis, intervertebral disc degeneration and other related skeletal diseases has been increased year by year. These common diseases of the musculoskeletal system are major causes for the loss of labor and disability in China. On the other hand, with the rapid development of industry, various disasters and accidents have also led to a gradual increase of musculoskeletal injuries. According to the report published by the Lancet [1], musculoskeletal disease has become the major cause of disability in China in 2017. It has caused great physical and mental pain to the patients, meanwhile brought a heavy economic burden to patients' family and society. Therefore, musculoskeletal disorders have become a major public health problem that affects the economic and social development of the country.

The improvement of clinical management cannot be separated from the progress and breakthrough of basic biomedical research. National Natural Science Foundation of China (NSFC) is one of the major funding agencies for the basic biomedical research in China. NSFC has funded 205,215 projects with the total funding of over 893 billion RMB in the field of life science and health science ever since 1986 when NSFC was formally established. In response to the need to improve national public health and accelerate translational biomedical research, NSFC established the Department of Health Sciences in September 2009 to support the basic research aiming to address scientific issues in disease

* Corresponding author. Department of Health Sciences, National Natural Science Foundation of China, 83 Shuangqing Road, Beijing, 100085, China.
E-mail address: doudou@nsfc.gov.cn (D. Dou).

https://doi.org/10.1016/j.jot.2020.04.010
Received 19 March 2020; Received in revised form 26 April 2020; Accepted 28 April 2020
Available online 16 May 2020

prevention, control and treatment, with the focus on the structural, functional, developmental, genetic and immune abnormalities of human being, as well as the occurrence, development, outcome, diagnosis, treatment and prevention of diseases. The Department of Health Sciences has been accepting applications since 2010. The application codes include 31 primary application codes (H01 to H31) and many relevant secondary codes. Applications of orthopaedic research are mainly distributed in the primary application code of H06 (Abnormalities and Diseases of Locomotor System) and its 13 secondary codes. Over the past decade, the Department of Health Sciences has initiated a number of research programs with a total funding of over 1149 million RMB to advance orthopaedic research. Under the continuous support of NSFC, significant progresses have been made in basic research, talent training, platform construction and the clinical translation in the field of orthopaedics in China. In this review, we will analyze the data from NSFC and summarize the progress of orthopaedic research in the past decade.

Funding for orthopaedic research from NSFC in the past decade

During the past decade, 14,743 applications of orthopaedic research were received by the Department of Health Sciences, 2455 of them were funded with a total funding of 1149, 552, 200 RMB (funding has been divided into direct and indirect cost since 2015, the funding of the projects funded since 2015 in this paper were all direct cost). As shown in Fig. 1, the number of applications, grants and funding for orthopaedic research increased steadily from 2010 to 2019. The number of applications increased from 848 in 2010–2411 in 2019, with an increase of 184.3%. As the number of applications augmented, the number of grants supported also increased from 149 in 2010 to 291 in 2019. However, the increase of grant was 95.3%, far less than that of applications. The annual funding in 2019 was over 168 million RMB, nearly 4.1 times higher than in 2010 (Fig. 1).

The major types of grants mentioned above are mainly classified into research-related projects and talent-oriented projects. As shown in Table 1 and Fig. 2, the number of grants for different types of program has increased significantly.

Research-related projects mainly include General Program, Key Program, Major Program, Major Research Plan, etc. General Program supports scientists to do basic research on bottom-up based topics within the funding scope of NSFC to conduct innovative research and promote a balanced, coordinated and sustained development of all disciplines. Over the past 10 years, 1234 projects in General Program were funded, which was the most among all types of grants, accounting for more than half of the total projects. The number of projects increased from 90 in 2010 to 143 in 2019, and the average funding augmented from 300,000 RMB in 2010 to 550,000 RMB (direct cost) in 2019. The decline in 2013 and 2014 was due to the implementation of application limit policy, by which the applicants were not allowed to apply for General Program if they were funded for general program as the PI in the previous year or has not been funded for two consecutive years of that program (Table 1 and Fig. 2). Key Program supports researchers to conduct in-depth, systematic and innovative research in directions with sound research basis or where new growth points of scientific disciplines might emerge, so as to promote disciplinary development and breakthroughs in important fields or scientific frontiers. An average of 2.6 projects per year has been funded in Key Program during the past 10 years, and the average funding for direct costs was almost 3 million RMB per project. The number of these projects has been climbing for nearly five years (Table 1 and Fig. 2). Major Program serves the major needs of the scientific frontiers, national economic, social and S&T (Science and Technology) development and national security, deploys in advance, conducts multidisciplinary research, and plays the supporting and guiding role in improving the capability of indigenous innovation of China's basic research. The first project of orthopaedic research in Major Program has been funded with a direct cost of 18 million RMB in 2019, which will focus on the role and regulatory mechanisms of bone-derived factors in maintaining the homeostasis of the body and important organs (Table 1 and Fig. 2).

Talent-oriented projects mainly include Young Scientists Fund, Fund for Less Developed Regions, Excellent Young Scientists Fund, National Science Fund for Distinguished Young Scholars, Science Fund for Creative Research Groups, etc. Young Scientists Fund supports young scientists to freely choose their research topics within the funding scope of NSFC to conduct basic research, fosters the ability of young scientists to independently undertake research projects and conduct creative research, cultivates the innovative thinking of young scientists, and trains backup talents for basic research. In the past decade, 887 projects in Young Scientists Fund were funded with an average funding of 200,000 RMB. The amount of grants has been more than doubled in 10 years from 45 in 2010 to 106 in 2019, indicating that the number of young talents in the field of orthopaedic research is gradually growing (Table 1 and Fig. 2). Fund for Less Developed Regions supports scientists in specified regions of China to conduct creative research within the funding scope of NSFC, so as to foster and support researchers in the regions, to stabilize and gather outstanding talents to facilitate the construction of the regional innovation system as well as the social and economic development of these regions. During the past ten years, although the Fund for Less Developed Regions was greatly increased, the total amount was still low (Table 1 and Fig. 2). National Science Fund for Distinguished Young Scholars supports young scholars who have made outstanding achievements in basic research to choose their own research directions and conduct innovative research, so as to accelerate the growth of young scientific talents, attract overseas talents and foster a group of prominent academic pacemakers at the forefront of international science and technology. Excellent Young Scientists Fund supports young scholars with

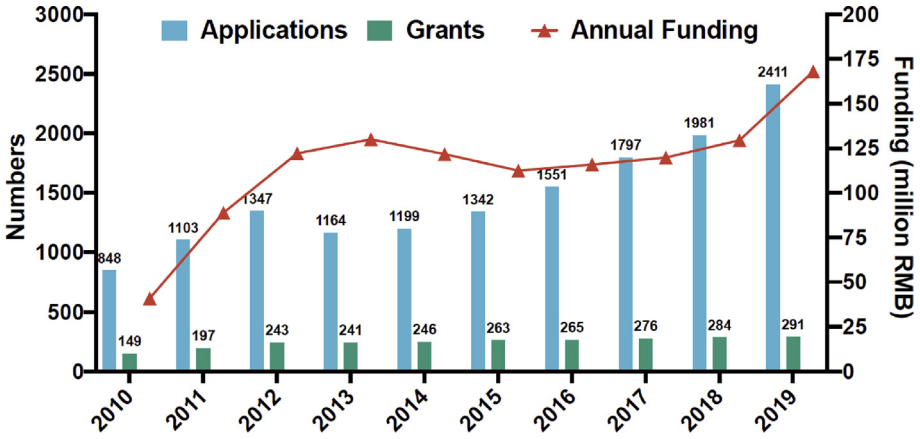

Figure 1. The number of applications received by NSFC (left axis), grants (left axis) and funding (right axis) supported by NSFC for orthopaedic research from 2010 to 2019.

Table 1
The number of projects funded by NSFC for orthopaedic research from 2010 to 2019.

Project Type		Year										Sum
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	
Research-related Projects	General Program	90	110	129	117	119	130	126	137	142	143	1243
	Key Program	0	1	1	5	0	2	3	4	5	5	26
	Major Program	0	0	0	0	0	0	0	0	0	1	1
	International (Regional) Cooperation and Exchange Program	0	0	1	1	1	2	1	0	1	0	7
	Major Research Plan	0	0	0	0	0	0	1	0	3	1	5
Talant-oriented Projects	Young Scientists Fund	45	66	80	86	97	95	98	108	106	106	887
	Fund for Less Developed Regions	9	15	19	17	21	27	22	25	24	25	204
	Excellent Young Scientists Fund	0	0	1	1	0	1	2	1	1	2	9
	National Science Fund for Distinguished Young Scholars	0	2	0	0	0	0	1	1	0	1	5
	Science Fund for Creative Research Groups	0	0	0	0	0	0	0	0	0	0	0
	Joint Research Fund for Overseas Chinese Scholars and Scholars in Hong Kong and Macao	0	0	1	1	0	0	0	0	1	0	3

good achievements in basic research to conduct innovative research in their own research field, so as to promote fast growth of creative young talents and foster a group of outstanding talents on the international science frontiers. Over the past 10 years, the number of funded projects in National Science Fund for Distinguished Young Scholars and Excellent Young Scientists Fund in H06 was significantly lower than that of other disciplines, indicating that there is still a great shortage of outstanding young talents in the field of basic orthopaedic research (Table 1 and Fig. 2).

The primary application codes of Department of Health Sciences are mainly arranged according to the order of organs or systems, and the secondary application codes are arranged in the order from basic to clinical research as well as from structural, functional and developmental abnormalities of diseases, covering both basic and clinical research related to the given organs or systems. According to the research direction, 13 secondary application codes has been set up under the primary application code H06, which are as follows: H0601 (structural, functional and developmental abnormalities of locomotor system), H0602 (hereditary diseases of locomotor system), H0603 (immune related diseases of locomotor system), H0604 (biomedical materials of bone, joint and soft tissue), H0605 (damage and repair of bone, joint and soft tissue), H0606 (transplantation and reconstruction of bone, joint and soft tissue), H0607 (infection of bone, joint and soft tissue), H0608 (fatigue and recuperation of bone, joint and soft tissue), H0609 (degenerative disease of bone, joint and soft tissue), H0610 (sports injury of bone, joint and soft tissue), H0611 (deformity and correction of locomotor system), H0612 (novel technologies for the diagnosis and treatment of diseases in locomotor system), H0613 (other scientific issues of diseases in locomotor system). During the period of 2010–2019, the funded projects have been concentrated in the research fields of the musculoskeletal damage and repair (H0605) and the degenerative diseases of bone, joint and soft tissue (H0609). In contrast, the number of projects funded in field of fatigue and recuperation of bone, joint and soft tissue (H0608) was still very small (Fig. 3), which is consistent with the clinical spectrum of diseases in locomotor system.

Progress of orthopaedic research in the past decade

With the support of government funding, orthopaedic research in China has developed rapidly. Over the past ten years, the number of Science Citation Index (SCI)-cited publications in the field of orthopaedic

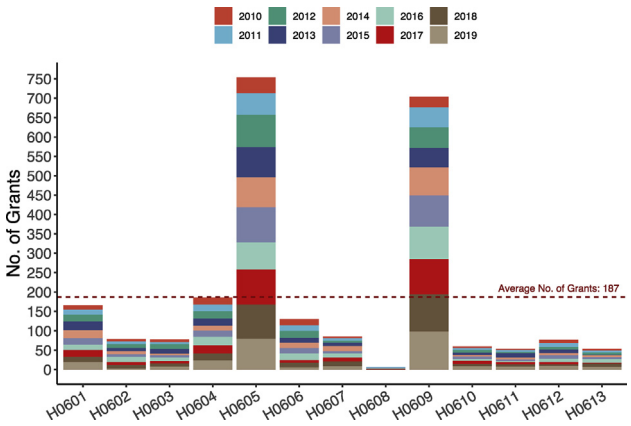

Figure 3. Distribution of projects funded by NSFC for orthopaedic research under different secondary application codes from 2010 to 2019.

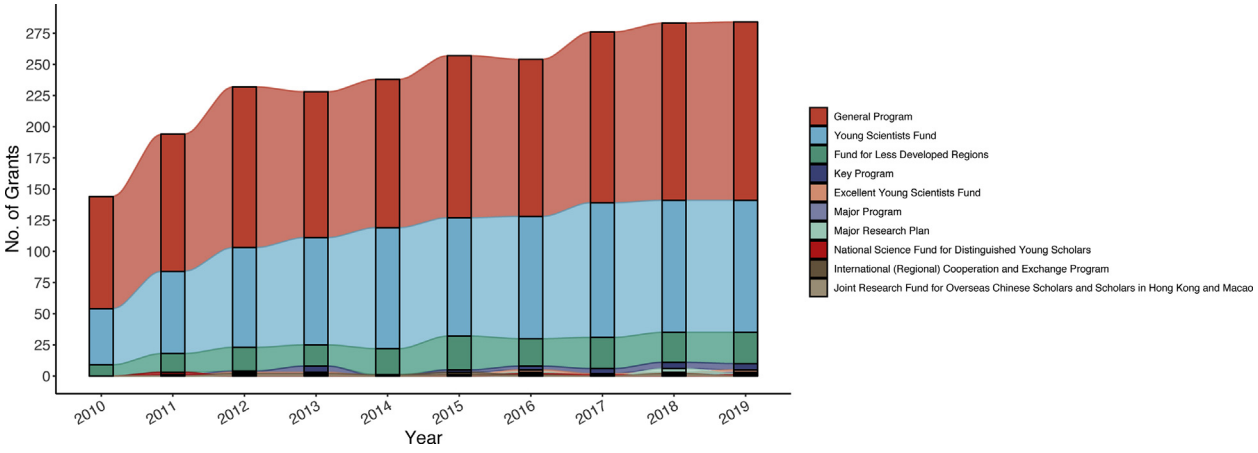

Figure 2. The number of projects funded by NSFC for orthopaedic research from 2010 to 2019.

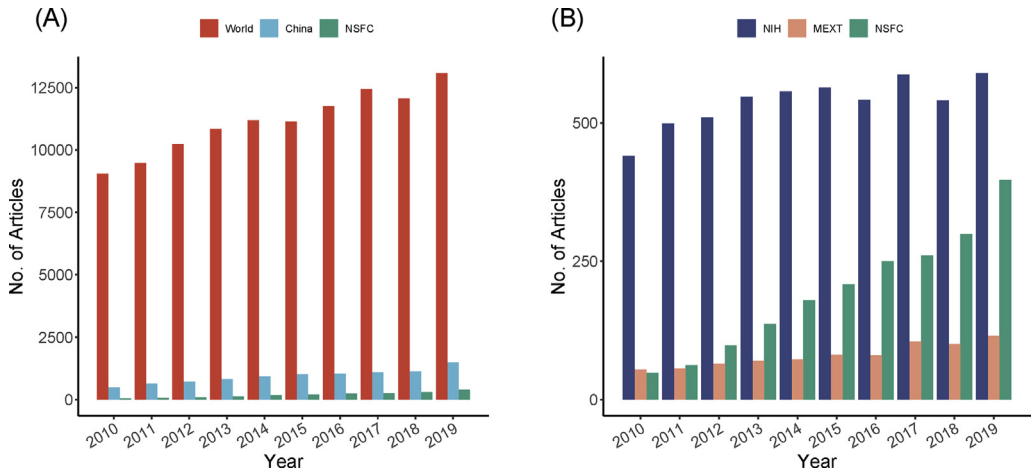

Figure 4. (*A*) The number of publications in orthopaedic research from NSFC, China and the world (*B*) The number of publications in orthopaedic research supported by NIH, MEXT and NSFC.

research from China has gradually increased. In 2010, there were 9049 SCI publications in this field worldwide, among which 480 were published by research institutions from China, accounting for 5.3%. Ten years later, 1487 SCI papers of orthopaedic research from China were published in 2019, accounting for 11.4% of SCI papers of orthopaedic research worldwide (Fig. 4A). As one of the main agencies funding the basic research of China, NSFC plays an important role. From 2010 to 2019, 1938 papers were published with the support of at least one grant from NSFC in the field of orthopaedic research, accounting for 20.8% of that in China. The number of SCI papers supported by NSFC increased by more than 7 times from 48 in 2010 to 397 in 2019. Compared with National Institutes of Health (NIH) in USA and Ministry of Education Culture Sports Science and Technology (MEXT) in Japan, the number of SCI publications in orthopaedic research supported by NSFC is only 10.9% of that supported by NIH and 88.8% of that supported by MEXT in 2010, which was increasingly comparable with that of NIH and was more than 3 times that of MEXT in 2019 (Fig. 4B).

The co-occurrence network and the detailed distribution of the keywords from the publications mentioned above are shown in Fig. 5. In the field of orthopaedic research, osteoarthritis, MRI and cartilage were the

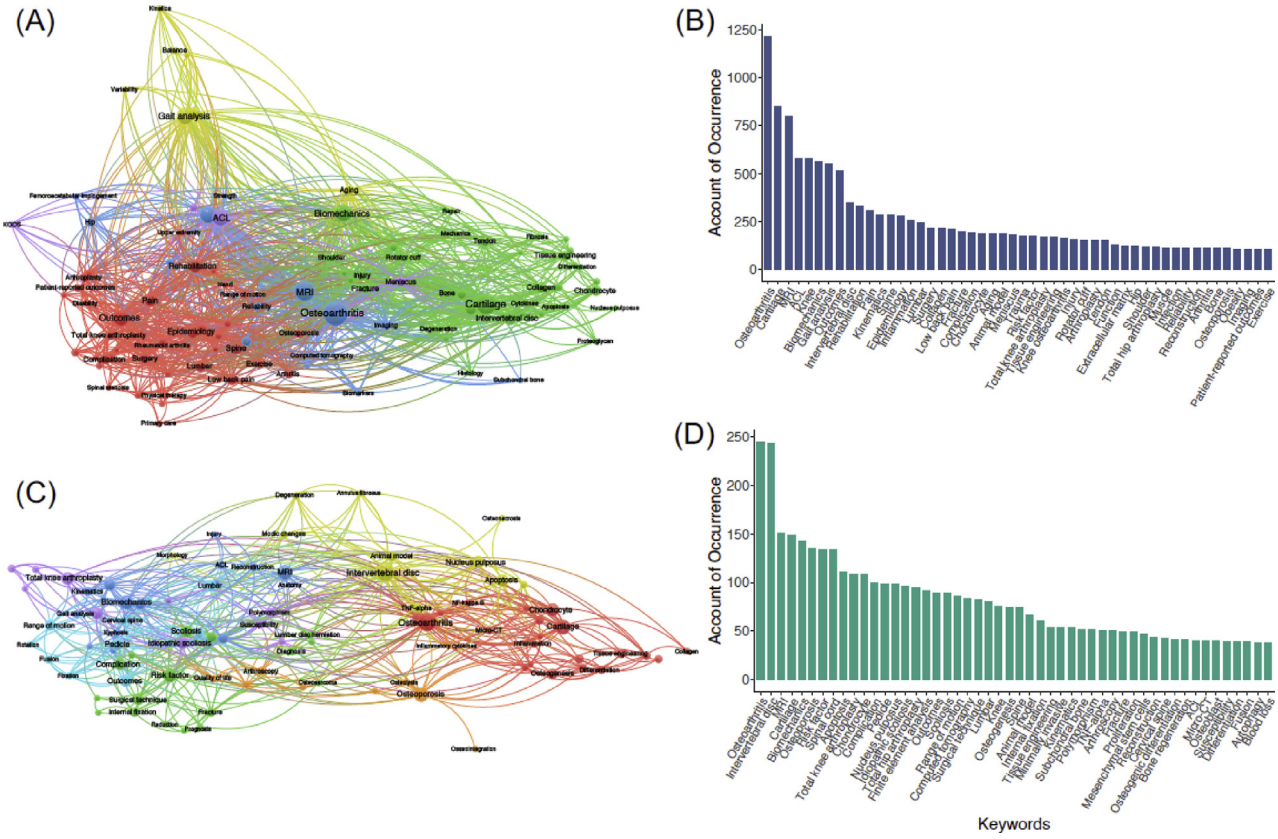

Figure 5. The co-occurrence network of the top-100 keywords and the distribution of top-50 keywords the in the publications supported by NIH (*A, B*) or NSFC (*C, D*). (A) The co-occurrence network of the top-100 keywords supported by NIH. (B) The distribution of top-50 keywords the in the publications supported by NIH. The analysis was performed by VOSviewer [2]. (C) The co-occurrence network of the top-100 keywords supported by NSFC. (D) The distribution of top-50 keywords the in the publications supported by NSFC.

three most commonly used keywords in the publications supported by NSFC or NIH. According to the distribution of keywords, it seemed that NIH-funded studies were more concentrated in the area of epidemiological research, pain management, rehabilitation, and outcomes, while NSFC-funded research were more focused on osteoporosis, intervertebral disc degeneration, and complications related. Keywords among the top 100 of NSFC, which are related to basic research such as apoptosis, autophagy, oxidative stress, etc., accounted for 17.4%, while that was 10.2% of NIH. The result was probably related to the fact that NSFC primarily supports basic research whereas NIH supports not only basic research but also clinical translational research.

Representative achievements of orthopaedic research in China in the last decade

Congenital musculoskeletal anomalies usually cause long-term disability, and also heavy economic burden to the families and society. There are at least 436 types of genetic diseases with musculoskeletal abnormalities, and more than 100 unknown specific pathogenic genes for these diseases. The huge population base and the large number of patients with various developmental abnormalities and genetic diseases in China have laid a good foundation for the research of musculoskeletal development and genetic diseases. The NSFC-funded awardees have identified several genetic mutations responsible for inherited musculoskeletal disorders. Wu N et al. analyzed congenital scoliosis patients in the Han population by using comparative genomic hybridization and related technologies, and found that 11% of patients with congenital scoliosis had rare invalid mutations and a composite inheritance of TBX6 sub-allele [3]. Zhu Z et al. identified four susceptibility loci at 1p36.32 AJAP1, 2q36.1 PAX3, 18q21.33 BCL-2, and 10q24.32 LBX1AS1 for adolescent idiopathic scoliosis in Chinese girls [4]. Cai Z et al. provided the first identification of autosomal dominant SLC26A2 mutations in patients with dysplastic spondylolysis [5]. Zhang Z et al. established a large sample of skeletal genetic disease resource pool for the Han population with a large collection of pedigrees including osteogenesis imperfecta, hypophosphatemic rickets/osteomalacia, osteosclerosis, and spinal abnormalities. They further demonstrated that SLCO2A1 mutations could inactivate PGE2 transport, and are the pathogenic cause of primary hypertrophic osteoarthropathy [6]. Qi H et al. developed a series of point mutation mouse models, mimicking human achondroplasia and acrocephalosyndactyly. They also identified the important role of FGF2/FGFRs in regulating skeletal development, the pathogenesis of achondroplasia and craniosynostosis [7,8]. Wu C et al. uncovered a previously unrecognized function of Kindlin-2, regulating chondrogenesis via controlling TGF-β signaling and Sox 9 expression [9]. Bai M et al. identified IRX5 as a critical gene in skeleton development through AG-haESC-mediated functional mutagenic screening [10].

Musculoskeletal degenerative diseases are one of the most common health problems for elderly people worldwide and are also the focus of current orthopaedic research. Huang B et al. studied the role of mTORC1/mTORC2 signaling pathway in bone metabolism and aging bone loss and its regulatory mechanism [11–15]. Cheng P et al. identified a series of non-coding RNA that play important physiological roles in osteoblast differentiation and contribute to osteoporosis via their effect on osteoblasts [16–18]. Zou W et al. studied the roles and associated mechanisms of Cdh1, LSD1, mTOR/Raptor, Smurf2, and SETD2 in regulation of bone homeostasis and osteogenesis [19–22]. Jiang Q et al. revealed that epigenetic PPARγ suppression plays a key role in osteoarthritis progression and PPARγ preservation possesses promising therapeutic potentials in clinical treatment of osteoarthritis [23]. Ji Q et al. performed high-precision single-cell transcriptome sequencing of cells from different pathological sites in patients with osteoarthritis for the first time, and identified that HPIP was essential for osteoarthritis development [24,25]. NSFC awardees also identified Bmal1 [26, 27], CBX4 [28], and miR-100-5p-abundant infrapatellar fat pad MSCs derived exosomes [29] as novel regulators of chondrocyte homeostasis. Novel signal pathways, like circVMA21/miR-200c/XIAP [30] and miR-141/SIRT1/NF-κB [31], were discovered as important regulatory mechanisms in the development of intervertebral disc degeneration.

Musculoskeletal system is often affected by various acute and chronic injuries, most of which develop into chronic diseases with varying degrees of musculoskeletal damage and dysfunction, leading to disability and even death of patients. In recent years, Chinese orthopaedic researchers have made great progresses, and the level of clinical treatment has been improved. Bai Y et al. found mangiferin could enhance endochondral ossification-based bone repair in massive bone defect [32]. Wu R et al. identified Linc-RAM, miR-431 as important regulators on myogenic differentiation and may be potential therapeutic targets in muscular diseases [33,34]. Yin Z et al. identified subpopulations of nestin^{+} tendon stem cells and suggested that the combined use of autologous tendon stem cells, autologous growth factors and biodegradable biological materials is one of the potential therapeutic strategies to promote tendon repair and regeneration [35]. NSFC awardees also discovered the novel roles of CTGF/BMP12 [36], AKT/mTOR [37] in regulating tandem differentiation. Duan H et al. established gene modules/programs corresponding to various pathological events at different times after spinal cord injury by using weighted gene co-expression network analysis [38]. Zhou H et al. identified differentially expressed proteins in rats with spinal cord injury through iTRAQ-based quantitative analysis [39].

At present, the routine orthopaedic treatment still needs to be improved. Every year, millions of orthopaedic biomaterials are implanted in patients, which are designed to perform certain biological functions or repair the damages of multiple tissue such as bone, cartilage, or ligament and tendon injury [40]. Researches on the development of orthopaedic biomaterials have been highly encouraged by NSFC during the past decade. Liu C et al. reported a two-step electrofabrication method to create a composite Janus film with a dense and a porous layer [41]. They further confirmed the beneficial features of the Janus composite for guided bone regeneration. Zhang Y et al. revealed the underlying CGRP-involved mechanism by which biodegradable magnesium implants improve fracture healing [42]. The biodegradable magnesium was then employed in the treatment of bone defects, fracture healing, ligament reconstruction, and osteonecrosis [43–46]. They further developed an innovative magnesium/titanium hybrid fixation system for long bone fracture with validated fixation efficacy [47]. Chang J et al. developed a novel silicate bioceramic that could enhance vascularization and osteogenesis [48–50]. Chen P et al. fabricated the radially oriented channel collagen scaffold with SDF-1 to facilitate cell homing, which might be a promising strategy for osteochondral injury repair [51]. Zhang Z et al. simultaneously applied biomechanical, biochemical, and structural cues to achieve anisotropic reconstruction of the meniscus, demonstrating the utility of anisotropic engineered meniscus for long-term knee chondroprotection in vivo [52].

Perspectives

In general, since the establishment of the Department of Health Sciences of NSFC 10 years ago, both the amount of funding and the scale of researchers in the field of orthopaedic research has increased substantially. Accordingly, the high-level scientific research output has also been rapidly increased. However, we should be very conscious that there are still many challenges and unsolved problems in orthopaedic research. First, the lack of original study with high impact. Despite the large number of papers published by researchers from China in recent years, most of them were follow-up studies with relatively low citations. Although there are a large clinical resources in our country, high-quality multi-center clinical researches were rarely carried out. Second, the lack of the distinguished world-renowned scientists. On the international academic community, the impact of Chinese scientists is not strong enough. Third, the lack of the high-level research platform. So far, there is no national orthopaedic key laboratory, which will greatly limit the

research on major scientific issues, the interdisciplinary research and the cultivation of talents. Fourth, the lack of translation from basic research to clinical application. For example, the industrialization of orthopaedic biomedical materials in China lags far behind developed countries. Orthopaedic biomedical materials produced domestically are basically imitation products, with relatively few independent intellectual property rights of products.

In view of the above shortcomings, future directions of orthopaedic research in China will focus on the following aspects: 1) improvement and development of new model animals, new animal models of different diseases, new techniques and methods for the orthopaedic research; 2) research on development, genetic and aging related diseases of musculoskeletal system; 3) mechanisms of musculoskeletal injuries and regeneration; 4) biomedical engineering of musculoskeletal system; 5) study on the integration between musculoskeletal system and other systems; 6) non-surgical prevention and treatment of diseases/injuries in musculoskeletal system; 7) translational medical research based on major diseases and injuries in musculoskeletal system. With continuous support both in funding and in policy, we believe that the orthopaedic research in China will surely achieve significant progress stably.

Funding/support statement

The authors have no acknowledgements to disclose and they received no funding for the work described in this article.

Conflict of interest

The authors have no conflicts of interest to disclose in relation to this article.

References

[1] Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Lond Engl 2019;394(10204):1145–58. https://doi.org/10.1016/S0140-6736(19)30427-1.

[2] van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 2010;84(2):523–38. https://doi.org/10.1007/s11192-009-0146-3.

[3] Wu N, Ming X, Xiao J, Wu Z, Chen X, Shinawi M, et al. TBX6 null variants and a common hypomorphic allele in congenital scoliosis. N Engl J Med 2015;372(4):341–50. https://doi.org/10.1056/NEJMoa1406829.

[4] Zhu Z, Tang NL-S, Xu L, Qin X, Mao S, Song Y, et al. Genome-wide association study identifies new susceptibility loci for adolescent idiopathic scoliosis in Chinese girls. Nat Commun 2015;6:8355. https://doi.org/10.1038/ncomms9355.

[5] Cai T, Yang L, Cai W, Guo S, Yu P, Li J, et al. Dysplastic spondylolysis is caused by mutations in the diastrophic dysplasia sulfate transporter gene. Proc Natl Acad Sci U S A 2015;112(26):8064–9. https://doi.org/10.1073/pnas.1502454112.

[6] Zhang Z, Xia W, He J, Zhang Z, Ke Y, Yue H, et al. Exome sequencing identifies SLCO2A1 mutations as a cause of primary hypertrophic osteoarthropathy. Am J Hum Genet 2012;90(1):125–32. https://doi.org/10.1016/j.ajhg.2011.11.019.

[7] Wang X, Qi H, Wang Q, Zhu Y, Wang X, Jin M, et al. FGFR3/fibroblast growth factor receptor 3 inhibits autophagy through decreasing the ATG12-ATG5 conjugate, leading to the delay of cartilage development in achondroplasia. Autophagy 2015;11(11):1998–2013. https://doi.org/10.1080/15548627.2015.1091551.

[8] Qi H, Jin M, Duan Y, Du X, Zhang Y, Ren F, et al. FGFR3 induces degradation of BMP type I receptor to regulate skeletal development. Biochim Biophys Acta 2014;1843(7):1237–47. https://doi.org/10.1016/j.bbamcr.2014.03.011.

[9] Wu C, Jiao H, Lai Y, Zheng W, Chen K, Qu H, et al. Kindlin-2 controls TGF-β signalling and Sox9 expression to regulate chondrogenesis. Nat Commun 2015;6:7531. https://doi.org/10.1038/ncomms8531.

[10] Bai M, Han Y, Wu Y, Liao J, Li L, Wang L, et al. Targeted genetic screening in mice through haploid embryonic stem cells identifies critical genes in bone development. PLoS Biol 2019;17(7):e3000350. https://doi.org/10.1371/journal.pbio.3000350.

[11] Huang B, Wang Y, Wang W, Chen J, Lai P, Liu Z, et al. mTORC1 prevents preosteoblast differentiation through the notch signaling pathway. PLoS Genet 2015;11(8):e1005426. https://doi.org/10.1371/journal.pgen.1005426.

[12] Yan B, Zhang Z, Jin D, Cai C, Jia C, Liu W, et al. mTORC1 regulates PTHrP to coordinate chondrocyte growth, proliferation and differentiation. Nat Commun 2016;7:11151. https://doi.org/10.1038/ncomms11151.

[13] Zhang H, Wang H, Zeng C, Yan B, Ouyang J, Liu X, et al. mTORC1 activation downregulates FGFR3 and PTH/PTHrP receptor in articular chondrocytes to initiate osteoarthritis. Osteoarthritis Cartilage 2017;25(6):952–63. https://doi.org/10.1016/j.joca.2016.12.024.

[14] Zhang Y, Xu S, Li K, Tan K, Liang K, Wang J, et al. mTORC1 inhibits NF-κB/NFATc1 signaling and prevents osteoclast precursor differentiation, in vitro and in mice. J Bone Miner Res Off J Am Soc Bone Miner Res 2017;32(9):1829–40. https://doi.org/10.1002/jbmr.3172.

[15] Lin C, Liu L, Zeng C, Cui Z-K, Chen Y, Lai P, et al. Activation of mTORC1 in subchondral bone preosteoblasts promotes osteoarthritis by stimulating bone sclerosis and secretion of CXCL12. Bone Res 2019;7:5. https://doi.org/10.1038/s41413-018-0041-8.

[16] Cheng P, Chen C, He H-B, Hu R, Zhou H-D, Xie H, et al. miR-148a regulates osteoclastogenesis by targeting V-maf musculoaponeurotic fibrosarcoma oncogene homolog B. J Bone Miner Res Off J Am Soc Bone Miner Res 2013;28(5):1180–90. https://doi.org/10.1002/jbmr.1845.

[17] Chen C, Cheng P, Xie H, Zhou H-D, Wu X-P, Liao E-Y, et al. MiR-503 regulates osteoclastogenesis via targeting RANK. J Bone Miner Res Off J Am Soc Bone Miner Res 2014;29(2):338–47. https://doi.org/10.1002/jbmr.2032.

[18] Li H, Xie H, Liu W, Hu R, Huang B, Tan Y-F, et al. A novel microRNA targeting HDAC5 regulates osteoblast differentiation in mice and contributes to primary osteoporosis in humans. J Clin Invest 2009;119(12):3666–77. https://doi.org/10.1172/JCI39832.

[19] Xu Z, Greenblatt MB, Yan G, Feng H, Sun J, Lotinun S, et al. SMURF2 regulates bone homeostasis by disrupting SMAD3 interaction with vitamin D receptor in osteoblasts. Nat Commun 2017;8:14570. https://doi.org/10.1038/ncomms14570.

[20] Shao R, Liu J, Yan G, Zhang J, Han Y, Guo J, et al. Cdh1 regulates craniofacial development via APC-dependent ubiquitination and activation of Goosecoid. Cell Res 2016;26(6):699–712. https://doi.org/10.1038/cr.2016.51.

[21] Sun J, Ermann J, Niu N, Yan G, Yang Y, Shi Y, et al. Histone demethylase LSD1 regulates bone mass by controlling WNT7B and BMP2 signaling in osteoblasts. Bone Res 2018;6:14. https://doi.org/10.1038/s41413-018-0015-x.

[22] Dai Q, Xu Z, Ma X, Niu N, Zhou S, Xie F, et al. mTOR/Raptor signaling is critical for skeletogenesis in mice through the regulation of Runx2 expression. Cell Death Differ 2017;24(11):1886–99. https://doi.org/10.1038/cdd.2017.110.

[23] Zhu X, Chen F, Lu K, Wei A, Jiang Q, Cao W. PPARγ preservation via promoter demethylation alleviates osteoarthritis in mice. Ann Rheum Dis 2019;78(10):1420–9. https://doi.org/10.1136/annrheumdis-2018-214940.

[24] Ji Q, Xu X, Kang L, Xu Y, Xiao J, Goodman SB, et al. Hematopoietic PBX-interacting protein mediates cartilage degeneration during the pathogenesis of osteoarthritis. Nat Commun 2019;10(1):313. https://doi.org/10.1038/s41467-018-08277-5.

[25] Ji Q, Zheng Y, Zhang G, Hu Y, Fan X, Hou Y, et al. Single-cell RNA-seq analysis reveals the progression of human osteoarthritis. Ann Rheum Dis 2019;78(1):100–10. https://doi.org/10.1136/annrheumdis-2017-212863.

[26] Yang W, Kang X, Liu J, Li H, Ma Z, Jin X, et al. Clock gene Bmal1 modulates human cartilage gene expression by crosstalk with Sirt1. Endocrinology 2016;157(8):3096–107. https://doi.org/10.1210/en.2015-2042.

[27] Ma Z, Jin X, Qian Z, Li F, Xu M, Zhang Y, et al. Deletion of clock gene Bmal1 impaired the chondrocyte function due to disruption of the HIF1α-VEGF signaling pathway. Cell Cycle Georget Tex 2019;18(13):1473–89. https://doi.org/10.1080/15384101.2019.1620572.

[28] Ren X, Hu B, Song M, Ding Z, Dang Y, Liu Z, et al. Maintenance of nucleolar homeostasis by CBX4 alleviates senescence and osteoarthritis. Cell Rep 2019;26(13):3643–56. https://doi.org/10.1016/j.celrep.2019.02.088. e7.

[29] Wu J, Kuang L, Chen C, Yang J, Zeng W-N, Li T, et al. miR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR in osteoarthritis. Biomaterials 2019;206:87–100. https://doi.org/10.1016/j.biomaterials.2019.03.022.

[30] Cheng X, Zhang L, Zhang K, Zhang G, Hu Y, Sun X, et al. Circular RNA VMA21 protects against intervertebral disc degeneration through targeting miR-200c and X linked inhibitor-of-apoptosis protein. Ann Rheum Dis 2018;77(5):770–9. https://doi.org/10.1136/annrheumdis-2017-212056.

[31] Ji M-L, Jiang H, Zhang X-J, Shi P-L, Li C, Wu H, et al. Preclinical development of a microRNA-based therapy for intervertebral disc degeneration. Nat Commun 2018;9(1):5051. https://doi.org/10.1038/s41467-018-07360-1.

[32] Bai Y, Liu C, Fu L, Gong X, Dou C, Cao Z, et al. Mangiferin enhances endochondral ossification-based bone repair in massive bone defect by inducing autophagy through activating AMP-activated protein kinase signaling pathway. FASEB J Off Publ Fed Am Soc Exp Biol 2018;32(8):4573–84. https://doi.org/10.1096/fj.201701411R.

[33] Wu R, Li H, Zhai L, Zou X, Meng J, Zhong R, et al. MicroRNA-431 accelerates muscle regeneration and ameliorates muscular dystrophy by targeting Pax7 in mice. Nat Commun 2015;6:7713. https://doi.org/10.1038/ncomms8713.

[34] Yu X, Zhang Y, Li T, Ma Z, Jia H, Chen Q, et al. Long non-coding RNA Linc-RAM enhances myogenic differentiation by interacting with MyoD. Nat Commun 2017;8:14016. https://doi.org/10.1038/ncomms14016.

[35] Yin Z, Hu J-J, Yang L, Zheng Z-F, An C-R, Wu B-B, et al. Single-cell analysis reveals a nestin+ tendon stem/progenitor cell population with strong tenogenic potentiality. Sci Adv 2016;2(11):e1600874. https://doi.org/10.1126/sciadv.1600874.

[36] Liu J, Tao X, Chen L, Han W, Zhou Y, Tang K. CTGF positively regulates BMP12 induced tenogenic differentiation of tendon stem cells and signaling. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol 2015;35(5):1831–45. https://doi.org/10.1159/000373994.

[37] Cong XX, Rao XS, Lin JX, Liu XC, Zhang GA, Gao XK, et al. Activation of AKT-mTOR signaling directs tenogenesis of mesenchymal stem cells. Stem Cells Dayt Ohio 2018;36(4):527–39. https://doi.org/10.1002/stem.2765.

[38] Duan H, Ge W, Zhang A, Xi Y, Chen Z, Luo D, et al. Transcriptome analyses reveal molecular mechanisms underlying functional recovery after spinal cord injury. Proc Natl Acad Sci U S A 2015;112(43):13360–5. https://doi.org/10.1073/pnas.1510176112.

[39] Zhou H, Kang Y, Shi Z, Lu L, Li X, Chu T, et al. Identification of differentially expressed proteins in rats with spinal cord injury during the transitional phase using an iTRAQ-based quantitative analysis. Gene 2018;677:66–76. https://doi.org/10.1016/j.gene.2018.07.050.
[40] Navarro M, Michiardi A, Castaño O, Planell JA. Biomaterials in orthopaedics. J R Soc Interface 2008;5(27):1137–58. https://doi.org/10.1098/rsif.2008.0151.
[41] Lei M, Qu X, Liu H, Liu Y, Wang S, Wu S, et al. Programmable electrofabrication of porous Janus films with tunable Janus balance for anisotropic cell guidance and tissue regeneration. Adv Funct Mater 2019;29(18):1900065. https://doi.org/10.1002/adfm.201900065.
[42] Zhang Y, Xu J, Ruan YC, Yu MK, O'Laughlin M, Wise H, et al. Implant-derived magnesium induces local neuronal production of CGRP to improve bone-fracture healing in rats. Nat Med 2016;22(10):1160–9. https://doi.org/10.1038/nm.4162.
[43] Zhao D, Huang S, Lu F, Wang B, Yang L, Qin L, et al. Vascularized bone grafting fixed by biodegradable magnesium screw for treating osteonecrosis of the femoral head. Biomaterials 2016;81:84–92. https://doi.org/10.1016/j.biomaterials.2015.11.038.
[44] Lai Y, Li Y, Cao H, Long J, Wang X, Li L, et al. Osteogenic magnesium incorporated into PLGA/TCP porous scaffold by 3D printing for repairing challenging bone defect. Biomaterials 2019;197:207–19. https://doi.org/10.1016/j.biomaterials.2019.01.013.
[45] Wang J, Wu Y, Li H, Liu Y, Bai X, Chau W, et al. Magnesium alloy based interference screw developed for ACL reconstruction attenuates peri-tunnel bone loss in rabbits. Biomaterials 2018;157:86–97. https://doi.org/10.1016/j.biomaterials.2017.12.007.
[46] Zheng L-Z, Wang J-L, Xu J-K, Zhang X-T, Liu B-Y, Huang L, et al. Magnesium and vitamin C supplementation attenuates steroid-associated osteonecrosis in a rat model. Biomaterials 2020;238:119828. https://doi.org/10.1016/j.biomaterials.2020.119828.
[47] Tian L, Sheng Y, Huang L, Chow DH-K, Chau WH, Tang N, et al. An innovative Mg/Ti hybrid fixation system developed for fracture fixation and healing enhancement at load-bearing skeletal site. Biomaterials 2018;180:173–83. https://doi.org/10.1016/j.biomaterials.2018.07.018.
[48] Guan J, Zhang J, Guo S, Zhu H, Zhu Z, Li H, et al. Human urine-derived stem cells can be induced into osteogenic lineage by silicate bioceramics via activation of the Wnt/β-catenin signaling pathway. Biomaterials 2015;55:1–11. https://doi.org/10.1016/j.biomaterials.2015.03.029.
[49] Li H, Xue K, Kong N, Liu K, Chang J. Silicate bioceramics enhanced vascularization and osteogenesis through stimulating interactions between endothelia cells and bone marrow stromal cells. Biomaterials 2014;35(12):3803–18. https://doi.org/10.1016/j.biomaterials.2014.01.039.
[50] Lin K, Xia L, Li H, Jiang X, Pan H, Xu Y, et al. Enhanced osteoporotic bone regeneration by strontium-substituted calcium silicate bioactive ceramics. Biomaterials 2013;34(38):10028–42. https://doi.org/10.1016/j.biomaterials.2013.09.056.
[51] Chen P, Tao J, Zhu S, Cai Y, Mao Q, Yu D, et al. Radially oriented collagen scaffold with SDF-1 promotes osteochondral repair by facilitating cell homing. Biomaterials 2015;39:114–23. https://doi.org/10.1016/j.biomaterials.2014.10.049.
[52] Zhang Z-Z, Chen Y-R, Wang S-J, Zhao F, Wang X-G, Yang F, et al. Orchestrated biomechanical, structural, and biochemical stimuli for engineering anisotropic meniscus. Sci Transl Med 2019;11(487). https://doi.org/10.1126/scitranslmed.aao0750.