Update on basic and clinical aspects of osteoarthritis

Dongquan Shi, Jin Dai, Zhihong Xu, Dongyang Chen, Qing Jiang

Sports Medicine & Adult Reconstructive Surgery Service, Drum Tower Hospital, Medicial School of Nanjing University, Nanjing 210008, China

Correspondence to: Qing Jiang. Sports Medicine & Adult Reconstructive Surgery Service, Drum Tower Hospital, Medicial School of Nanjing University, Nanjing 210008, China. Email: qingj@nju.edu.cn.

Submitted Mar 02, 2015. Accepted for publication Jun 01, 2015.

doi: 10.3978/j.issn.2305-5839.2015.06.13

View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.06.13

Osteoarthritis (OA) is one of causes responsible for loss of labor productivity among the mid-aged and the elderly. Its main pathological changes include progressive loss of articular cartilage and formation of osteophytes, with joint pain and deformity and loss of joint function as the manifestations, resulting in decreased activity and quality of life (QoL). According to the latest demographic data, the prevalence of knee OA in China was 1.3-11.1%, while the prevalence of symptomatic knee OA was 19.4% in patients aged 60 years or older.

The research group headed by Professor Jiang Qing from Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School, was committed to identify the pathogenesis of OA, search for appropriate strategy of OA prevention, and improve the outcome of OA treatment. In recent years, they have carried out a series of studies on the susceptibility genes of OA, the susceptibility genes of the developmental dysplasia of the hip (DDH), and the treatment of OA, with quite a few innovative achievements. Up to now they have published 38 scientific articles in SCI-indexed journals, including three articles published in the top journals including *Nature Genetics* and *Nature Medicine*. Most of these articles were published in professional journals such as *Osteoarthritis & Cartilage* and *Arthritis Research & Therapy*. Moreover, 130 articles have been published in Chinese core journals such as the *Chinese Journal of Orthopaedices*. Ten of their representative articles have been cited by other domestic and foreign researchers for 254 times, with extensive and positive evaluations, 38 SCI-indexed articles have been cited by 430 times. Also, they have been granted four patents. The group was granted the 2014 Second-grade National Natural Science Award by the Ministry of Education for their outstanding contributions in the etiological study on OA and in promoting the prevention and treatment of OA.

OA is a common disease with genetic predisposition. The research group disclosed several OA susceptibility genes through genetic researches and excluded several OA susceptibility genes through multi-center studies, which laid the theoretical foundation for the genetic etiology of OA.

(I) ASPN as an OA susceptibility gene in the Chinese population.

A significant correlation between the polymorphism of the aspartic acid (D) repeat in the ASPN gene and knee-OA had been demonstrated by case-control studies. D14 was identified to be the susceptibility allele, while D13 was identified to be the protective allele (1). This study was published in the *Journal of Human Genetic*s and was nominated to be one the most influential international articles from China in 2007. Their further studies disclosed the correlation between the polymorphism of this gene and the onset age for OA (2). This work was also published in the *Journal of Human Genetics*. Moreover, the research group organized and participated in the Meta analysis between this gene and OA, which further confirmed the correlation between ASPN and OA (3). This work was published in *Human Molecular Genetics*.

(II) *GDF5* as an OA susceptibility gene in the Asian population.

The gene *GDF5* was found to be closely associated with OA by case-control studies. *rs143383* was identified to be most significant locus following correlation analysis of multiple tagSNP loci. The association between this locus and OA was further verified through a multi-center study, and different types of *rs143383* allele were associated

with diverse activities of gene promoter (4). This work was published in *Nature Genetics*. Moreover, the research group organized and participated in the Meta analysis between the *GDF5* gene and OA, and this association was validated on a global basis (5,6). These works were published in *Human Molecular Genetics* and *Arthritis & Rheumatism*. Up to date, this gene is the only gene with confirmed association with OA among different ethnic groups.

(III) DVWA as an OA susceptibility gene in the Asian population.

The group performed a genome-wide association study on OA and identified a strong association between the gene polymorphism of chromosome 3p24.3 and OA. Moreover, *rs7639618* was identified to be the most significant locus associated with OA following further validation of single nucleotide polymorphisms. A new gene *DVWA* was identified in the region of this gene (7). This work was published in *Nature Genetics*. The correlation between *DVWA* and OA remains controversial among different ethnic groups. The research group organized and participated in the Meta-analysis between the *DVWA* gene and OA (8). This work was also published in *Human Molecular Genetics*.

(IV) Multi-center validation of OA susceptibility genes.

The correlations of *LRCH1*, *TXNDC3*, *RHOB*, and other genes with OA have been firstly described in European populations, but the conclusions were controversial. In coordination with Asian and European researchers, this research group had conducted multi-center studies and denied the correlation of *LRCH1*, *TXNDC3*, *RHOB*, and other genes with OA (9,10). The findings were published in *Arthritis Research & Therapy* and *Journal of Human Genetics*. The association between the gene polymorphism of HLA region and OA was firstly proposed by Japanese researchers based on a genome-wide association study, with the result verified in the Japanese population and some European populations. The research group conducted genotyping of the target gene loci and case-control analysis in the Chinese Han population and the Australian Caucasian population and demonstrated there was no significant correlation between the gene polymorphism and OA in both of the two populations (11). The research finding was published in *Osteoarthritis and Cartilage*. Japanese researchers proposed the association between *HIF-2a* gene and OA and demonstrated the correlation between the gene polymorphism of *rs17039192* and OA based on case-control studies. The research group conducted genotyping of the target gene locus and case-control analysis in the Japanese population, the Chinese Han population, and the Australian Caucasian population; their findings excluded the association between this locus and OA (12). This work was published in *Nature Medicine*. The research group further organized a multi-center meta-analysis in Asia, Europe, and Australia, with an attempt to investigate the association between this gene and OA (13). The results were published in the *Journal of Orthopaedic Research*.

DDH is a common disease of the skeletal system and is also an important contributor to hip OA (especially the early onset of OA). The research group firstly reported three DDH-related susceptibility genes.

(I) *GDF5* as a DDH-associated susceptibility gene.

GDF5 is a global gene associated with OA. The research group investigated the correlation between *GDF5* and DDH based on the assumption of the intrinsic relations among skeletal system diseases and the known function of *GDF-5* and disclosed the association between this gene and DDH (14). Their findings were published in the *Arthritis Research and Therapy*, and this was also the first report on DDH-related susceptibility genes. The correlation between the *GDF5* gene and DDH has been verified in European populations.

(II) *TBX4* as a DDH-associated susceptibility gene.

TBX4 is known as a gene strongly associated with the development of lower limbs. Developmental defects of lower limbs have been observed in knockout mice. Moreover, the phenotype of patellar dysplasia was also observed in patients carrying heterozygous gene mutations. Considering the association between the *TBX4* gene and the development of lower limbs, the research group investigated the correlation between TBX4 and DDH and disclosed a significant correlation between the polymorphism locus rs3744448 of this gene and DDH (15). The research finding was published in *OA and Cartilage*.

(III) *ASPN* as a DDH-associated susceptibility gene.

As previous report, *ASPN* is associated with OA.

The product of this gene might interfere with the TGF-β signaling pathway and was involved in the pathogenesis of OA. This research group firstly described the correlation between this gene and OA in the Chinese population. Since the TGF-β signaling pathway plays an important role in the development of the skeletal system, the research group investigated the correlation between *ASPN* and DDH and disclosed a correlation between the polymorphism of *ASPN* D-repeat and DDH. The frequency of D14 was significantly higher in case group than in control group, while the frequency of D13 was significantly lower in case group than in control group (16). The findings were published in *Arthritis Research & Therapy*. For the results and GDF5 as a DDH-associated susceptibility gene, Professor John Loughlin from Newcastle University, UK commented that, "the strong correlation between the *ASPN* gene and DDH disclosed by Chinese researchers expanded our understandings of the pathogenesis of common diseases and the complexity of common genetic risk has been highlighted."

For the treatment of OA, the research group has conducted a series of studies on medications against OA, surgical treatment and post-operative complication management, and treatment of injured intraarticular structures.

(I) Role of p38 mitogen-activated protein kinase signaling pathway in the treatment of OA.

A mouse model of OA was established through resection of anterior cruciate ligament and partial meniscal resection to examine the expression profile of P38 mitogen-activated protein kinase. The expression of p38 mitogen-activated protein kinase was found to be elevated in osteoarthritic cartilage. In the mouse model of OA, treatment with the inhibitor of p38 mitogen-activated protein kinase was associated with effective suppression of chondrocyte apoptosis and improvement of joint degeneration compared with the control group.

(II) Femoral prosthesis locator for knee arthroplasty.

In clinical practice, knee replacement is an effective intervention for severe OA. Intraoperative prosthesis placement is particularly important for the postoperative outcomes. Unfortunately, the relative position between prosthesis and bone structure is difficult to be determined due to limited intraoperative exposure. Base on intraoperative experiences, the research group designed and developed a novel femoral prosthesis locator for knee arthroplasty for the intraoperative placement of joint prostheses, which can simplify the operation procedure and improve the outcomes. This design has been patented in China.

(III) Exerciser for ankle-joint flexion and extension.

For patients with OA of the hip or knee joint, lower-extremity deep venous thrombosis (DVT) is one of the main complications after arthroplasty. Postoperative anticoagulation and active ankle-joint flexion and extension can effectively reduce the risk of lower extremity DVT. The research group designed and developed an apparatus for ankle-joint flexion and extension. It is great helpful for rehabilitation post-operation. This apparatus could promote the flexion and extension exercises of ankle-joint, aiming to reduce the incidence of DVT and improve patient prognosis. This design has been patented in China.

(IV) Artificial meniscus and cruciate ligament.

Injuries of meniscal and cruciate ligament knee are common sports injuries of knee and important causes of traumatic knee OA. For fresh meniscal injuries, meniscal suture can be considered only if the injured area was located in areas with rich blood supply. For other types of meniscal injuries, possible interventions may include conservative treatments, meniscus-plasty, and meniscectomy. However, these interventions may induce partial or complete loss of meniscal function, resulting in the occurrence of OA. Both acute and chronic cruciate ligament injury are irreparable, and only conservative treatment or reconstruction can be considered. Conservative treatment is directly associated with the instable knee joint, which is prone to OA of the affected knee. Reconstruction of knee ligament may restore the stability of knee joint, but use of tendon autograft can cause additional damages to the body. Moreover, reconstruction using tendon allograft has many disadvantages such as high cost, limited sources, and risk of infections. Therefore, the use of artificial meniscus and cruciate ligament in the reconstruction of damaged tissue of the joints may restore the integrity and stability of the joints without causing any damage to other tissues. Thus, this approach can effectively prevent or delay the occurrence of post-traumatic OA. With

silk collagen as the raw material, this research group constructed artificial meniscus and cruciate ligament by using a specific weaving method. The biological and mechanical characteristics of these products are similar as natural ones. Both of these two designs have been patented in China.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Shi D, Dai J, Xu Z, Chen D, Jiang Q. Update on basic and clinical aspects of osteoarthritis. Ann Transl Med 2015;3(10):142. doi: 10.3978/j.issn.2305-5839.2015.06.13

