Dear Editors,

We would like to express our sincerest gratitude to you and the reviewers for your careful reviews, helpful comments and time spent on our manuscript titled: “Nrf2 participates in progression of osteoarthritis through modulating redox balance”. We are pleased with the Editors’ decision to consider a revised version of our manuscript, addressing all the issues brought up by the reviewers. We had carefully studied the comments point by point and tried to reply with our best answers. We hope that our responses might meet your approval. If you find our replies not satisfactory, we are more than pleased to make further attempts to improve this manuscript.

Below, we will show us how we extensively revised the paper to address each of the comments (in bold) by the reviewers, following the numbering of the comments in the original decision letter. Changes in the revised manuscript are marked in the highlighted font (red).

Best regards,

Dr. Yueqi Chen

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**COMMENTS FOR THE AUTHOR:**

**Reviewer #1: In this review, Deng et al. summarize the dramatic function of oxidative stress in OA pathology, establish a complex regulatory network of Nrf2 in OA progression, and provide new insights into the treatment of OA. It is a well-written manuscript with important implications for the field of OA. Please provide the following comments to improve the manuscript.**

Response: Thank you for your careful review, useful suggestions and spent some time on reviewing our manuscript. We have carefully studied your comments point by point and tried to reply with our best answers. We hope that our answers might meet your approval. If you find our replies not satisfactory, we are more than pleased to make further attempts to improve this manuscript.

**Specific comments****1. In the introduction, please include a more detailed description of the relationship between OA and older people.**

Response: Thank you for your warm suggestion. In order to elucidate a more detailed description of the relationship between OA and older people, we have added some relevant statements in the introduction, which have been shown in the red words in the revised manuscript (Line42-55). The related references are listed as follows and ranked as No. 1, 2, 3, 4, 5 in the revised manuscript. All the changes have been marked in red words in the revised manuscript.

Line42-55: As a common chronic degenerative disease, osteoarthritis (OA) is associated with an increasingly severe obesity and global population aging, which has become a comprehensive public health burden, currently affecting more than 500 million people worldwide. OA is mainly characterized by pain as a primary clinical manifestation, which gradually affects the stability of joint movement and ultimately leads to the disability, thereby diminish the quality of patient’s life. To date, the risk factors that contribute to the development of OA are diverse, including senescence, trauma, obesity, as well as mechanical loading and many other factors. And aging is one of the most evident risk factors for pathogenesis of OA and studies have shown the presence of a large number of senescent chondrocytes in the cartilage of hip and knee joints in OA patients. Notably, with the progression of aging, senescent chondrocytes gradually accumulate in OA joints and secrete a variety of senescence-associated secretory phenotype (SASP), including diverse pro-inflammatory cytokines and matrix metalloproteinases (MMPs), which can activate chronic inflammatory responses and induce oxidative stress, thus contributing to the accumulation of reactive oxygen species (ROS), as well as leading to the disturbance of the antioxidant enzymes and ROS clearing systems.

**2. In the section "Nrf2 and redox balance during OA progression", please include a more detailed description of the role of Nrf2 in aging-related pathways (Zinovkin RA, Kondratenko ND, Zinovkina LA. Does Nrf2 Play a Role of a Master Regulator of Mammalian Aging? Biochemistry (Mosc). 2022 Dec;87(12):1465-1476).**

Response: Thank you for pointing this problem professionally. In order to elucidate a more detailed description of the role of Nrf2 in aging-related pathways, we have carefully read the relevant literature mentioned and added some relevant statements in the section "Nrf2 and redox balance during OA progression", which have been shown in the red words in the revised manuscript (Line201-206). The related references are listed as follows and ranked as No. 50 in the revised manuscript. All the changes have been marked in red words in the revised manuscript.

Line42-55: As is well known, aging is an important pathogenic factor in OA, and Nrf2 can play an indispensable role in inhibiting cellular aging through the antioxidant system. Research has shown that the activity of Nrf2 gradually decreases during the aging process of human fibroblasts. As expected, silencing Nrf2 is able to trigger premature aging, while pharmacologically activating Nrf2 can increase cell lifespan, indicating that in the context of oxidative stress, the inhibition of Nrf2 signaling is capable of facilitating premature cell aging.

**3.** **Are there any drugs in clinical trials that target Nrf2 for the treatment of OA?**

Response: Thank you for your valuable and professional comments. Currently, clinical drugs targeting Nrf2 have been approved and used for the treatment in other diseases, but they have not been found for the treatment in OA. In order to elucidate a more detailed description of the clinical application of Nrf2-related drugs and their limitations, we have added some relevant statements in the section "Nrf2 and redox balance during OA progression", which have been shown in the red words in the revised manuscript (Line249-262). The related references are listed as follows and ranked as No. 58, 59, 60 in the revised manuscript. All the changes have been marked in red words in the revised manuscript.

Line249-262: Additionally, with the in-depth study of Nrf2, clinical medicines targeting OA at present have not been found yet, but a variety of new clinical drugs have been developed for the treatment of other diseases. For example, based on a randomized, double-blind, placebo-controlled phase 3 clinical trial (CARDINAL), the Nrf2 activator Bardoxolone methyl has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic kidney disease (CKD) caused by Alport syndrome. Another Nrf2 activator, Dimethyl fumarate, can induce upregulation of antioxidant genes expression, and is therefore also approved by the FDA and the European Medicines Agency as a first‐line therapy for adult patients with relapsing‐remitting MS (RMSS). However, it has been shown that the activation of Nrf2 plays a double-edged role in cancers. On the one hand, Nrf2 can prevent the progression of cancers caused by oxidative stress, on the other hand, the specific activation of Nrf2 in different cancers can promote the proliferation of cancer cells as well as induce chemoresistance and radioresistance of cancer cells. Therefore, potential therapeutic strategies accurately targeting Nrf2-regulated signaling pathways may have clinical value in ameliorating the progression of OA and much still remains to be done.

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**Reviewer #2: The authors have summarized the dramatic function of oxidative stress in OA pathology, established a complex regulatory network of Nrf2 in OA progression, and aimed to provide novel insight into the treatment of OA. This is a great review that can be accepted for publication. Suggest adding some pictures.**

Response: Thank you for your warm suggestion. We have added the valuable diagram and figure to figure out the complex regulation network for the OA progression in Figure 1.