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Perspective

Rethinking Osteonecrosis of the Jaw: Could Cellular Senescence Be the Missing Link between ORN and MRONJ?

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Abstract: Osteonecrosis of the jaw (ONJ) is a series bone diseases characteristic with similar diagnostic criteria and clinical manifestations. Phossy jaws, medication-related osteonecrosis of the jaw (MRONJ), and osteoradionecrosis (ORN) are major subtypes of ONJ. Though subtypes of ONJ are considered different diseases in clinical practice, similar diagnostic criteria, clinical presentation, and features prompt the possibility that there is a common pathogenesis mechanism for ONJ subtypes. Current pathogenic theories fail to fully explain the delayed onset, persistent progression, and stimulus-independent nature of ONJ. Here, we propose that cellular senescence could be a common pathogenesis mechanism of ONJ. Radiation, antiresorptive agents, and trauma induce persistent DNA damage and activate the DNA damage response, leading to irreversible senescence in jawbone cells. This model explains key clinical observations and offers a rationale for the failure of stimulus withdrawal to reverse disease progression. We outline future directions to validate this hypothesis. If confirmed, this hypothesis may unify ONJ subtypes under a single pathogenic framework and open avenues for targeted interventions.

Keywords: medication-related osteonecrosis of the jaw; bisphosphonate-related osteonecrosis of the jaw; osteoradionecrosis; cellular senescence

1. Introduction

Osteonecrosis of the jaw (ONJ) is a series of bone diseases characterized by exposed jaw bone that persisted for a specific period after stimulation by irradiants, such as chemicals, radiation, and antiresorptive or antiangiogenic agents. Traditionally, ONJ can be divided into 3 subtypes: phossy jaws, medication-related osteonecrosis of the jaw (MRONJ), and osteoradionecrosis (ORN). However, recent insights into pathomechanisms have led researchers to conclude that phossy jaw and MRONJ are the same entity. This revelation has prompted a reevaluation of the relationship between MRONJ and ORN, which may share a similar historical evolution. Despite being recognized as distinct diseases in clinical practice, the similar clinical

manifestations and symptoms of these two ONJ subtypes suggest a common pathogenesis. Hitherto, pathophysiology of ONJ remains poorly understood. Consequently, this paper aims to explore cellular senescence as a potential unifying pathogenetic mechanism across ONJ subtypes by reviewing the clinical manifestations and pathogenetic hypotheses of MRONJ and ORN.

2. From Etiology to Pathogenesis: Mechanistic Perspectives on ONJ

2.1. Phossy Jaws

The present-day clinical form of ONJ is preceded by "phossy jaws". It was first reported in 1858 that ONJ is developed in a large proportion of friction match workers exposed to toxic fumes containing yellow phosphorous (today called white phosphorus) for 3–5 years [1]. The International Berne (Switzerland) Convention of 1906 proscribed the yellow phosphorous in matchstick paste leading to the sharply decreased incidence of "phossy jaw". Recently, Marx suggested that patients breathed in the P_4O_{10} vapors, which then reacted with the CO_2, H_2O, and amino acids in the tissues to produce a nitrogen-containing bisphosphonate [1]. Thus, "phossy jaw" is actually Bisphosphonate-related osteonecrosis of the jaw (BRONJ).

2.2. Medication-Related Osteonecrosis of the Jaw

Bisphosphonates (BPs) are now widely applied in management of skeletal-related events, such as osteoporosis and bone metastases from solid tumors [2]. Long-term use of BPs can cause BRONJ, which is a severe complication sharing similar clinical features with "phossy jaw" [3]. With the growing number of cases of ONJ associated with other antiresorptive and antiangiogenic medication, the specific committee of the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended changing the term BRONJ with MRONJ [4].

The pathogenesis mechanism of MRONJ is still controversial [5,6]. Several hypotheses have been proposed, including the imbalance between bone resorption and formation, suppression of angiogenesis, inhibition of immunity, and soft tissue toxicity. It is well-known that BPs directly inhibit enzymes of farnesyl pyrophosphate synthase and geranylgeranyl pyrophosphate synthase in the mevalonate pathway to inhibit osteoclast activity [7,8]. BPs also inhibit osteoclast function through the rapid, pH-dependent, selective, and reversible inhibition of V-ATPase, resulting in decreased bone resorption and osteogenesis [9]. A clinical study observed that long-term use of bisphosphonates led to an increase in the number of osteoclasts in the iliac bone; notably, these osteoclasts exhibited specific morphological changes and underwent prolonged apoptosis [10]. In vitro experiments demonstrated an increase in both the number and size of multinucleated osteoclasts following bisphosphonate administration [11]. Cui et al. used a new tetrahedral framework nucleic acid that effectively prevented the formation of BRONJ by counteracting the effects of BPs on osteoclast differentiation and maturation [12]. In addition, epigenetic studies have demonstrated that BPs affect osteoclast function by inhibiting miR-483-5p, which consequently contributes to the onset of BRONJ [13]. BPs can also decrease the differentiation and function of osteoblasts [14]. BPs suppress human osteoblast adhesion and migration by inhibiting integrinavb3 and tenascin C gene expression, which may exacerbate MRONJ [15]. Thus, inhibition of bone remodeling has been recognized as one possible underlying mechanism. Conversely, an alternative perspective suggests that BPs may contribute to the development of MRONJ by inhibiting angiogenesis and the suppression of vascular remodeling. This deleterious effect primarily manifests in BPs' interactions with endothelial cells [16]. Research has demonstrated that BPs adversely affect the activity, proliferation, and migration of both endothelial progenitor and mature endothelial cells, culminating in angiogenesis inhibition [17–20]. Additionally, BPs induce apoptosis in endothelial cells, leading to vascular loss and necrosis, thereby exacerbating the local ischemic conditions within the jaw [19]. Support for this theory comes from the sustained reduction in VEGF serum levels observed in in vivo studies of patients with BRONJ [21]. In vivo experiments further confirm the antiangiogenic properties of BPs, showing significant reductions in microvessel density and area following bisphosphonate treatment [22,23]. The association of other newly developed antiangiogenic agents, such as anti-VEGF antibodies and tyrosine kinase inhibitors, with ONJ underscores the critical role of angiogenesis and hemodialysis in MRONJ development [24,25].

However, a recent study revealed that no diminished vascular network was observed in MRONJ bone samples [26]. In a separate rat model exposed to zoledronic acid (ZOL), investigators likewise observed no statistically significant alterations in the expression of angiogenic factors [27]. These findings suggest that while angiogenesis suppression may contribute to the development of MRONJ, it is unlikely to represent a central pathogenic mechanism. Another view is that necrosis of the jaw is associated with localized inflammation or bacterial infection [28]. Several studies have shown that concurrent periodontal inflammation or infection and bisphosphonate use may precipitate ONJ [29–31]. Furthermore, the prophylactic administration of antibiotics during dental procedures significantly reduces the

incidence of MRONJ [32]. Additionally, research has substantiated the involvement of microbial biofilms in the pathogenesis of MRONJ [32–34]. The fact that patients with immunocompromised states, such as diabetes and rheumatoid arthritis, are at higher risk of MRONJ suggests that immune dysfunction could be a mechanism [35,36]. A case-control study found a significant correlation between several variants of human leukocyte antigen class II (HLA class II) and the development of anti-resorptive agent-induced osteonecrosis of the jaw, supporting the hypothesis that inflammation and infection play a critical role in the pathogenesis of MRONJ [37]. The presence of a reciprocal regulatory relationship between immune cells and bone remodeling cells implies that immune system dysfunction could contribute to MRONJ by disrupting bone remodeling homeostasis [38,39]. BPs can inhibit various cell types including fibroblasts, endothelial cells, and keratinocytes, and promote apoptosis, resulting in delayed wound healing, which is crucial for patients who received tooth extraction [40–43]. However, the common problem for pathogenesis mechanisms mentioned above is that these hypotheses cannot explain why monoclonal antibodies, such as denosumab and romosozumab can also cause MRONJ.

2.3. Osteoradionecrosis

ORN represents a late adverse effect after radiotherapy, first described in 1922. After ORN is developed, complaints range from mild symptoms, such as local swelling, severe pain, and trismus, to severe symptoms, such as suppuration, bone exposure, and pathological fractures of the mandible [44]. ORN remains a huge burden for the healthcare system.

For ORN, the classic sequence in the pathogenesis was radiation, trauma, and infection [45]. A modified model, proposed in 1983, suggested that radiation leads to hypoxic, hypocellular, and hypovascular tissue ("three H" principle), causing chronic nonhealing wounds and the breakdown of bone tissue [46]. In contrast, this model holds that microinfections are confined to surface tissues and do not trigger these conditions. Further histological studies of the mandible have indicated that ischemic necrosis results from radiation-induced vascular disease, rather than from primary radiation-induced osteonecrosis [47]. Subsequent studies have cast doubt on this prevailing theory by suggesting that cellular radiolucency in bone precedes the more familiar vascular changes [48]. Increased subperiosteal bone deposition and jaw thickening in the radiolucent zones of ORN specimens lend support to this theory, indicating that reduced osteoclast viability—often the initial response to radiation—contributes to impaired healing [49]. However, contrasting findings demonstrate that bisphosphonates may facilitate healing in some ORN patients [50]. Recently, radiation-induced fibroatrophic processes were identified and used to interpret ORN [51]. Radiation-induced fibrous atrophy encompasses free radical formation, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis, remodeling, and ultimately bone and tissue necrosis. Consequently, ORN may be characterized as a decline in healing activity at the irradiation site, primarily driven by impaired fibroblast function [52]. According to this model, the progression of ORN unfolds in three distinct phases: an initial pre-fibrotic phase dominated by endothelial cells, a mechanoconstitutive phase characterized by the activation of abnormal fibroblasts, and a subsequent fibro-atrophic phase [53]. Radiation damage to the endothelium is well-documented, and this damage is likely linked to apoptosis induced through the activation of nerve sheath phosphatase by radiation [54,55]. Clinical trials involving anti-radiation fibrosis drugs for treating ORN have yielded improved therapeutic outcomes, further substantiating the theory of radiation-induced fibrosis [56,57]. Similar to MRONJ, the pathogenesis mechanism of ORN is still unclear.

Some hypotheses had been proposed as potential common pathogenesis mechanisms for both MRONJ and ORN. Since the most common clinical manifestation of ONJ is exposure of bone, inflammation and bacterial infection are considered potential mechanisms. A 2005 study underscored the significant role of bacteria in the development of osteonecrosis of the jaw, employing DNA hybridization techniques [58]. However, multiple studies indicate that microorganisms do not play a decisive etiologic role in the development of MRONJ and ORN. He et al. reported that the resident bacteria isolated from ORN and MRONJ lesions lacked specificity relative to those found in osteomyelitis [59]. Culture-based analyses of necrotic bone from ORN showed infection largely restricted to the surface, with no specific pathogen identified [46]. Another clinical study reported that 10%–48% of patients had no documented infection preceding ORN onset [60]. Similarly, although microorganisms are detectable in MRONJ lesions, the microbial communities are highly heterogeneous, which does not implicate a single causative organism [33,61,62]. A study have even reported that antibiotic therapy may exacerbate osteonecrosis, whereas commensal microbiota may play a protective role in early MRONJ progression [63]. In summary, these observations support the interpretation that bacterial infection is secondary—likely a consequence of jawbone exposure rather than a primary driver [64,65].

Taken together, there is no hypothesis can fully explain the pathogenesis mechanism of MRONJ and ORN. The similar clinical manifestation of ONJ indicates that there may be a common pathogenesis mechanism while

existing hypotheses failed to integrate ORN and MRONJ theoretically. The present study aims to propose a hypothesis that can explain ORN and MRONJ simultaneously.

3. Clinical and Pathological Commonalities between MRONJ and ORN

3.1. Similar Diagnostic Criteria

The diagnosis of ONJ is based on clinical manifestations and medical history. The definition of ORN varies significantly, without an international consensus. The diagnostic criteria recommended by Chinese expert groups were as follows: (1) radiation history; (2) bone exposure with or without surrounding mucosal or epidermal damage; (3) radiological evidence of bony destruction; (4) non-existence of tumor recurrence; (5) pathological findings of necrotic or sclerotic bone with empty osteocyte lacunae, blurry or broken bony trabeculae, loss of osteocytes and osteoblasts, and reduced vascularity of connective tissue [66]. The most widely accepted definition of MRONJ was proposed by AAOMS and also recommended by the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and American Society of Clinical Oncology (ASCO) clinical practice guidelines as follows: (1) current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications; (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for >8 weeks; (3) no history of radiation therapy to the jaws or metastatic disease to the jaws [4,67]. Thus, the clinical appearance and diagnostic criteria of ONJ are similar to the necrotic bone after irritation, excluding malignancy.

3.2. Vascular Endothelial Injury

Both ORN and MRONJ showed vascular endothelial injury. Marx et al. reported that ORN is characterized by endothelial cell death and a reduction in blood vessels at the tissue level [46]. Additionally, the adverse effects of BP on vascular endothelial cells have been well documented. Allegra et al. demonstrated increased endothelial cell apoptosis in MRONJ patients through analytical flow cytometry [68]. Immunohistochemical analyses of jawbone specimens from MRONJ patients further confirmed the presence of impaired angiogenesis [69]. Furthermore, in vivo experiments revealed decreased microvessel density in both MRONJ and ORN [22,55]. The shared pathology between ORN and MRONJ suggests a potential common etiologic basis.

3.3. Late-Onset Feature

Another clinical feature of ONJ is late-onset and persistence after a specific period without irritation. ORN always occurs months or decades after the completion of radiotherapy rather than during the treatment [70]. An observational study revealed that the incidence of MRONJ is low within 12 months [71]. Another study analyzed 404 teeth in 92 patients who received antiresorptive agent therapy and found that MRONJ developed from 74 to 1883 days (median 383 days) after the first visit [72]. Meanwhile, long-term antiresorptive therapy increases the risk of MRONJ significantly compared with short-term. Taken together, most cases of ORN and MRONJ exhibit late effects. Similar diagnostic criteria, clinical manifestation, and late-onset feature of ONJ provide the possibility that ORN and MRONJ are the same diseases from a clinical view.

3.4. Persistence after Cessation of Irritation

We noticed that both ORN and MRONJ can still occur even after the cessation of irritation for a while. For head and neck cancer, radiotherapy usually lasts for about one month, while it was reported that the average onset time of ORN is 4.5 years after radiotherapy finishing [70]. A multicenter study conducted by the Japanese Study Group of Cooperative Dentistry with Medicine (JCDM) showed that drug holiday did not reduce the risk of MRONJ [73]. Another study analyzed 173 MRONJ patients and concluded that drug holiday did not promote the separation of sequestra or improve the treatment outcome [74]. This phenomenon is notable since many diseases, such as oral leukoplakia and other mucosal diseases, can be significantly improved after removing the stimulus and/or cessation of risk factors including alcohol, tobacco, and betel nut [75]. When solitary pulmonary nodule is detected, patients are strongly advised to quit smoking to make it stable rather than malignant transformation [76]. This is contradictory to ONJ since cessation of radiotherapy and medication consumption is not associated with a lower incidence rate or better prognosis for MRONJ and ORN. Thus, we hypothesize that there is an intrinsic mechanism driving the occurrence of ONJ even after the cessation of stimulants. The exogenous stressors, such as radiation and medication, act as “trigger” rather than “full participation”.

Taken together, the overlapping clinical presentations, diagnostic criteria, and pathological characteristics of MRONJ and ORN indicate substantial commonalities despite their distinct etiological origins. These parallels provide a rationale for investigating whether shared biological processes underlie both conditions.

4. Cellular Senescence: A Potential Common Ground for ONJ

In addition to their similarities in clinical presentation and histopathological features, MRONJ and ORN share deeper-level commonalities, exemplified by pathophysiological processes such as cellular senescence observed in both conditions.

Cellular senescence is a cellular fate that includes irreversible cell cycle arrest, morphological changes, apoptosis resistance, and active protein synthesis [77]. Cells may enter senescence due to various factors. Ionizing radiation and high doses of drugs or chemicals, as well as their induced production of ROS, can cause damage to DNA and destruction of telomere structure, which can lead to cellular senescence [78]. Also these external stimuli lead to mitochondrial dysfunction, which in turn induces senescence [79].

Cellular stressors further induced DNA damage response signaling, resulting in the activation of key transcription factors and pathways, including signaling pathways such as p53-p21, NF-κB, cGAS/STING, p38, and JAK-STAT. Epigenetic factors such as RNA N^6-adenosine (m^6A)-methyltransferase complex METTL3–METTL14, C/EBPα, high mobility B histone (HMGB), and acetyltransferase 1 (SIRT1) are also involved in the process of the DNA damage response (DDR). This results in an elevated secretion of various senescence-associated factors, collectively termed senescence-associated secretory phenotypes (SASPs) include pro-inflammatory cytokines, chemokines, growth factors, and extracellular matrix proteases, which are responsible for tissue damage in the pathogenesis of chronic diseases [78]. Unprogrammed senescent cells can self-reinforce senescence through autocrine loops and adversely affect healthy neighboring cells through the paracrine effects of SASP products, leading to the accumulation of senescent cells. As a result, the local tissue microenvironment and the whole organism are disturbed and disrupted. This phenomenon explains the delayed onset of ONJ after a period of cessation of stimulation. Among them, IL-6, IL-8, and CXCL/CCL family chemokines not only enhance senescence through autocrine secretion, but also are important mediators of paracrine effects in the tissue microenvironment of senescent cells whereas exosomes are also key mediators mediating the paracrine effects of senescent cells [80–82]. In addition, extracellularly released HMGB1 can induce SASP-mediated paracrine senescence [83].

It is well-known that ionizing radiation (IR) can directly induce DNA double-strand breaks (DSBs) resulting in stress-induced senescence [84]. Radiation-induced cellular senescence is considered a crucial mechanism in the onset and progression of various radiological diseases. Zhong et al. found that IR induced cellular senescence of annulus fibrosus leading to matrix catabolism via MMP-mediated pathways contributing to disc degeneration [85]. A recent study indicated that senescence of vascular smooth muscle cells, induced by IR through the NF-κB/CTCF/p16 pathway, is a key mechanism in the development of radiation-induced atherosclerosis [86]. Radiation-induced pulmonary fibrosis (RIPF), characterized with irreversible destruction of normal lung tissues and hypofunction of lung, is one of the most severe complications for patients who receive thoracic radiotherapy. This condition is associated with senescent-like fibroblasts. Meng et al. used FOXO4-DRI, a cell-penetrating peptide that can induce intrinsic apoptosis of senescent cells, to target radiation-induced senescent fibroblasts to alleviate RIPF [87]. Additionally, persistent cellular senescence was involved in radiation ulcer development, and inhibition of radiation-induced senescence could prevent the occurrence of radiation ulcer [88]. Although the specific contribution of cellular senescence to ORN has not been conclusively established, prior studies have investigated radiation-induced senescence in bone tissue within related disease contexts. Studies have shown that radiation induces cellular senescence of bone marrow-derived mesenchymal stem cells (BMSCs), which play a crucial role in maintaining bone microenvironment homeostasis [89,90]. Radiation also causes significant DNA damage in primary osteoblasts, leading to an imbalance in bone reconstruction by triggering osteoblast senescence and promoting an associated secretory phenotype [91]. Furthermore, Guo et al. discovered that biomass-derived carbon dots from L. barbarum attenuate radiation-induced bone damage in an m6A-dependent manner via the METTL3/Clip3 associated with cellular senescence, and effectively prevented ORN in rats in vivo. This finding suggests that cellular senescence plays a critical role in ORN [92].

The association between BPs and cellular senescence is supported by accumulating experimental evidence. Studies have shown that ZOL induces a DNA damage response in normal human oral keratinocytes (NHOKs), which in turn leads to cell-cycle arrest [93]. In addition, exposure of the human oral keratinocyte line OKF6/TERT-2 and normal human oral fibroblasts (NHOFs) to ZOL resulted in significant release of SASPs, including MMP-3 and IL-8 [94]. Another study reported that pamidronate (PAM), at defined concentrations, induced senescence

in NHOKs, with disruption of protein geranylgeranylation in the mevalonate pathway playing a pivotal role; furthermore, using a 3D organotypic oral mucosal model, the authors showed that PAM-induced senescence impaired re-epithelialization [95]. Collectively, these findings provide a plausible mechanistic basis for the impaired wound healing observed in MRONJ. Additionally, bisphosphonates stimulate IL-6 secretion from osteoblasts and osteoclasts in a dose-dependent manner [96]. Moreover, genetic polymorphism studies have suggested that SNPs in the genes encoding interleukins 1A and 1B may contribute to the development of MRONJ [97]. And IL-1α and IL-1β are considered to be among the most widely studied SASP factors [78]. However, another in vivo study demonstrated that specific interventions significantly reduced circulating SASP factors such as CCL7, IL-1β, TNFRSF1A, and TGFβ1, suggesting that the cellular senescence effects of bisphosphonates may be influenced by other regulatory networks [98]. There is also evidence supporting the close relationship between cellular senescence and MRONJ. SIRT1 has been well studied for its involvement in ageing as a senescence inhibitor [99,100]. During cellular senescence, reduced SIRT1 expression negatively regulates the expression of SASP factors at the transcriptional level [101]. The association of SIRT1 with MRONJ has been extensively studied recently. SIRT1 is involved in regulating mesenchymal stem cell (MSC) senescence via Bmi1 deacetylation and nuclear translocation [102]. One study identified SIRT1-mediated oxidative stress as a contributing factor to the occurrence of MRONJ [103]. Another study demonstrated that BPs aggravate inflammation in human oral keratinocytes (HOK) via SIRT1-mediated oxidative stress and mitochondrial dysfunction, key factors in mucosal nonhealing associated with MRONJ [104]. Gene sequencing studies have confirmed the link between SIRT1 and MRONJ. Yang et al. illustrated that SIRT1 is closely related to MRONJ by whole-exome sequencing [105]. Furthermore, they found that promoter SNP rs932658 regulates the expression of SIRT1 and lowers the risk of MRONJ by increasing SIRT1 expression [106]. Recent studies have further validated the association between the SNP rs932658 and the incidence of MRONJ [107].

Furthermore, studies have demonstrated that HMGB1, regulated by SIRT1, contributes to the pathogenesis of MRONJ. SIRT1 directly interacts with HMGB1 and deacetylates lysine residues within its N-terminal domain, thereby restraining HMGB1 nuclear-to-cytoplasmic translocation and extracellular release [108,109]. Moreover, pharmacological inhibition of HMGB1 nuclear export was associated with a reduced incidence of MRONJ [110]. In parallel, HMGB proteins are essential for establishing the senescent phenotype. And research has shown that nuclear depletion of HMGB1 leads to the upregulation of SASP gene expression [111]. These findings suggest that SNP-mediated dysregulation of the SIRT1–HMGB1 pathway, leading to cellular senescence, may contribute to the pathogenesis of MRONJ. However, no studies have yet clarified whether cellular senescence mediated by SIRT1 is the definitive mechanism by which BPs cause MRONJ, nor is the role of cellular senescence in the development of MRONJ fully understood.

Trauma injury can induce DNA damage and cellular senescence. A mice model study illustrated that unilateral iatrogenic vas deferens trauma can cause an increase in DNA damage [112]. Primary and secondary traumatic brain injury induces persistent DNA damage and leads to enhanced cellular senescence [113]. Dominik et al. found increased DNA damage and accumulation of senescent cells in the bone fracture healing process [114]. Though the exact mechanism of DNA damage caused by traumatic injury is unclear, it may be closely related to the cell apoptosis directly induced by traumatic injury and leading to an inflammatory microenvironment. Based on the evidence above, we believed that DNA damage caused by tooth extraction is also important in the occurrence of ONJ.

5. Exploring a Senescence-Based Theory Unifying MRONJ and ORN

The accumulating evidence outlined above suggests that cellular senescence functions not merely as an associated phenomenon, but as a plausible shared mechanism linking MRONJ and ORN—serving as a central integrative process through which their distinct etiological triggers may converge. Building on this perspective, we propose a mechanistic hypothesis placing cellular senescence at the core of ONJ pathogenesis.

We hypothesize that cellular senescence is the common pathogenesis mechanism of both ORN and MRONJ. Radiation and chemotherapy act as stressors to activate the DDR pathway by causing DSBs. As a checkpoint, DDR prevents the delivery of corrupted genetic information to daughter cells. However, persistent DNA damage, causing prolonged DDR signaling, will induce irreversible cellular senescence of jaw bone cells. Moreover, traumatic injury of tooth extraction, the most frequent trigger of ONJ, also contributes to the rapid accumulation of DNA damage [112–114]. Importantly, a positive feedback loop can amplify the impact of senescent cells. Senescent cells persistently affect other healthy cells via SASP. These newly senescent cells then further enhance the secretion of SASP factors through paracrine effects, accelerating the senescence of additional cells and creating a cascading effect. The consequences of this positive feedback loop mediated by SASP on the bone

microenvironment include an increased proportion of senescent cells, enhanced local inflammation, diminished angiogenic potential, and finally tissue necrosis. This senescence-centered model also parsimoniously explains ONJ persistence and latency: SCAP-mediated apoptosis resistance sustains SASP-driven chronic lesions, while gradual, injury-induced senescent-cell accumulation creates a threshold for delayed onset; by contrast, vascular and infectious models lack a compelling mechanism for long latency and protracted non-healing. The schematic diagram of the proposed hypothesis is shown in Figure 1.

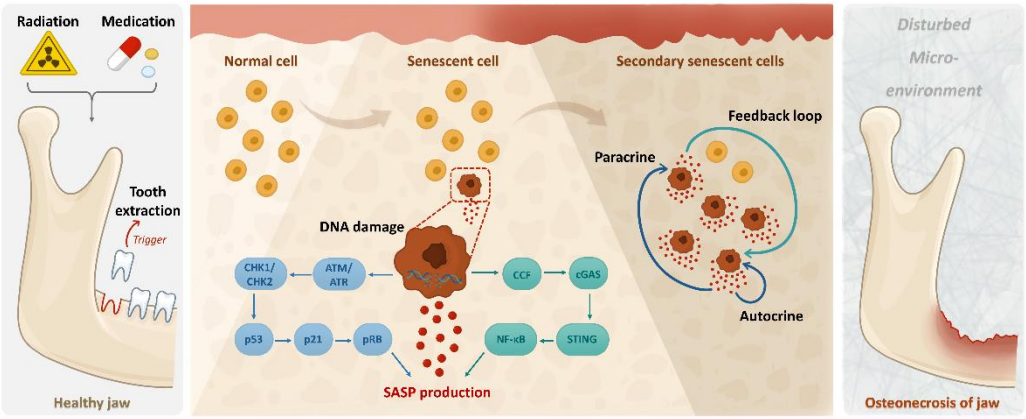

Figure 1. Schematic image of the hypothesis. Cellular senescence is the potential mechanism underlying osteonecrosis of the jaw. Radiation and medication, acting as exogenous stressors, induce DNA damage response and DNA double-strand breaks, resulting in senescence of bone cells. By secreting senescence-associated secretory phenotype related bioactive factors, senescent bone cells can induce self-enforced cellular senescence by autocrine and transform neighboring normal cells into senescent ones. This feedback loop can continuously run after cessation of radiation and medication consumption, leading to the disturbed bone microenvironment. Tooth extraction, which also contribute to DNA double-strand damage and cellular senescence, can cause the occurrence of osteonecrosis of the jaw.

Future directions aiming to provide the evidence of the hypothesis are present as follows: First, the relation between cellular senescence and ONJ should be preliminarily demonstrated. The expression levels of cellular senescence markers and their genes, such as SA-β-gal, p16, p21, IL1a, IL11, CCL20, etc., should be detected in jawbone tissues originating from patients with ORN and MRONJ; and DNA damage-related markers should be detected, to demonstrate the damaging effects of external stimuli on cells. The concentration of SASP factors in peripheral blood should also be analyzed. The expression of senescence biomarkers, as well as SASP factors, are expected to be increased in ORN and MRONJ, compared with a healthy jaw and osteomyelitis of the jaw. This is the basis of the present hypothesis. Second, to further explore the important role of senescent cell paracrine effects in the genesis of ONJ, senescent cells should be prepared in vitro and transplanted into rat/mouse models to testify whether senescent cells promote the occurrence of ORN and MRONJ. In this part, senescent cells should not only be injected into the jaw bone, but also be administered intraperitoneally. In this way, the function of SASP factors secreted by senescent cells can be confirmed if senescent cells, injected intraperitoneally, can promote the occurrence of ONJ. To confirm which SASP factors are involved in the process, in vitro cellular assays are screened using drugs that can target SASP-activated receptors or their key downstream pathways, and verified by RNA interference. Third, after identifying the relevant SASP factors and signaling pathways, therapy targeting senescent cells should be adopted to explore whether clearance of senescent cells will alleviate the symptom and prevent the occurrence of ONJ. Finally, the concentration of SASP factors in peripheral blood and/or saliva, collected from patients who finished radiotherapy or cessation of medication therapy, should be measured. Observing the variation trend of SASP concentration with time and if ONJ occurs to testify that radiotherapy and medication act as “trigger” and cellular senescence is the intrinsic mechanism driving the occurrence of ONJ.

6. Conclusions

MRONJ and ORN show marked overlap in diagnostic criteria, histopathological characteristics, patterns of vascular injury, and their capacity to persist long after the initiating factor has been removed. On the basis of combined clinical, pathological, and mechanistic observations, we suggest that both conditions may reflect a single disease process in which cellular senescence is a central pathogenic driver. Framing them within a shared

classification could help standardize diagnostic criteria, unify staging systems, and incorporate senescence-associated biomarkers to improve prognostic assessment and guide therapeutic decision-making. Progress toward such integration is constrained by an incomplete understanding of disease mechanisms: current treatment is limited to conservative approaches with modest benefit or surgical options that are technically challenging and prone to recurrence. In this context, targeting senescent cells emerges as a plausible and potentially practice-changing strategy. Senolytic agents, which selectively eliminate senescent cells, have shown consistent efficacy across diverse experimental models and—if validated in ONJ—could redefine therapeutic practice [115]. However, human data remain limited, underscoring the need for biomarker-anchored, stratified evaluations [116]. Future research should focus on testing the senescence-based disease model, refining biomarker-driven staging, and developing clinically applicable senescence-targeted interventions, with the ultimate goal of unifying management approaches for MRONJ and ORN and improving long-term outcomes.

Author Contributions

J.Z.: Writing—Original Draft, Writing—review & editing, Methodology, Investigation, Data Curation, Conceptualization. Y.L.: Writing—Original Draft, Writing—review & editing, Visualization, Methodology, Investigation, Data Curation, Conceptualization. J.L.: Supervision, Resources, Methodology, Data Curation, Conceptualization. X.T.: Supervision, Resources, Methodology, Data Curation, Conceptualization. C.L.: Supervision, Resources, Methodology, Data Curation, Conceptualization. Z.G.: Writing—review & editing, Data Curation, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI in Writing

During the preparation of this work the authors used ChatGPT in order to improve the language and polish the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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