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REVIEW ARTICLE

Etiologic factors of early-onset periodontal disease in Down syndrome

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Summary Individuals with Down syndrome often develop extensive gingivitis, and exhibit rapid and generalized periodontal breakdown in early adulthood. Earlier studies reported a significant prevalence of periodontal disease in patients with Down syndrome younger than 30 years old, whereas recent studies have indicated that periodontal disease associated with the syndrome is less severe than formerly thought, likely due to improved dental care at home and the dental office. Although the etiology of the condition is not yet fully elucidated, a number of studies have shown that Down syndrome related periodontitis is caused by such factors as immunological deficiency, poor oral hygiene, fragile periodontal tissue, early senescence, salivary deficiency, and poor masticatory function. In addition, those individuals experience very early colonization by various periodontal pathogens, and exhibit an exaggerated innate immune response to produce inflammatory mediators such as prostaglandin E_2 and matrix metalloproteinases. Recent studies regarding Down syndrome cell adhesion molecule (Dscam) provide further evidence for increased susceptibility to bacterial and viral diseases in Down syndrome. In this review, an overview of contemporary findings on the etiology of periodontal disease associated with Down syndrome is presented.

Contents

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1. Introduction

Down syndrome (Down's Syndrome in British English and the WHO International Classification of Diseases) is a genetic disorder caused by the presence of all or part of an extra 21st chromosome [1]. It is named after John Langdon Down, the English physician who initially characterized the appearance and behavior of these patients in 1866, and one of the most common causes of mental retardation in children. The disorder was later identified as a chromosome 21 trisomy in 1959. The incidence of Down syndrome is estimated at 1 in 600—1000 live births, though those statistics are influenced by several factors, in particular, the age of the mother [2,3]. The condition is characterized by a combination of generalized growth and mental deficiencies, and is associated with several other pathological conditions, including congenital cardiac defects and Alzheimer's disease. In addition, hematologic malignancies and autoimmune diseases such as hypothyroidism, and type I diabetes mellitus, occur with increased frequency in Down syndrome [3].

Nine major dental characteristics in Down syndrome children have been reported, including macroglossia (enlarged tongue), fissured tongue, underdeveloped maxilla, tongue thrusting, congenitally missing teeth, malocclusion, high arch palate, salivation, and microdontia [2,4]. One of the most characteristic facial features of Down syndrome is a relative underdevelopment of the middle third of the face. There are also characteristic features in the craniofacial anthropometric pattern profile in those afflicted, i.e., subnormal scores for head length and circumference, as well as external canthal distance.

In 1960, Cohen et al. first reported the marked prevalence of periodontitis in young individuals with Down syndrome [5]. They examined the oral conditions of 100 young Down syndrome patients, and found that all had some form of periodontal disease, ranging from severe gingivitis in the youngest to periodontitis with pocket formation and alveolar bone loss in the older patients [5,6]. Subsequently, many investigations revealed that children and adolescents with Down syndrome often develop extensive gingivitis, and exhibit rapid and generalized periodontal breakdown in early adulthood [7]. The precocious nature of the condition is thought to be due to such factors as immunological deficiency, poor oral hygiene, fragile periodontal tissue, early senescence, and poor masticatory function [2,7], while it is also likely that short tooth roots lead to tooth mobility and subsequent loss. Furthermore, several recent reports have proposed a number of novel etiological factors, which are described below. However, the etiology of the disorder has not been fully elucidated. In this review, we present the latest information on etiologic factors of early-onset periodontal disease in Down syndrome based on abundant findings reported by experts in the field.

2. Prevalence of periodontitis in Down syndrome

Individuals with Down syndrome have an increased prevalence of periodontal disease as compared with normal and

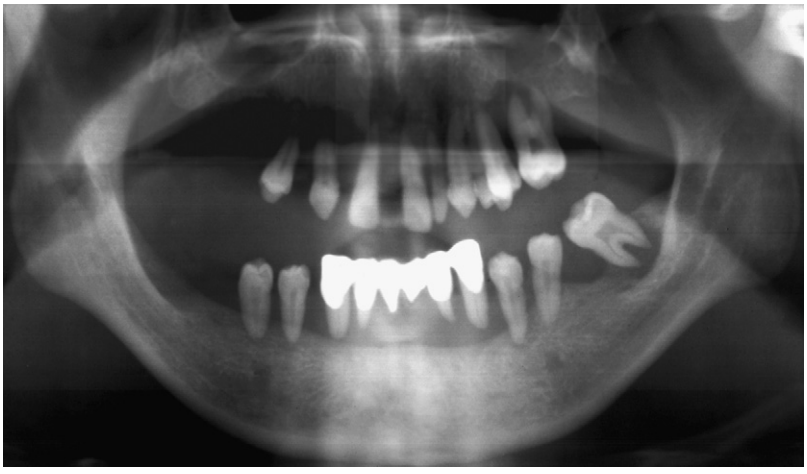

Figure 1 Clinical outcome of early-onset periodontitis in Down syndrome. Panoramic radiograph image of a 29-year-old male with Down syndrome. Early-onset periodontitis generally occurs between the ages of 15 (early adolescence) and 25. In this case, periodontitis appeared to be developed at early 20s, and deteriorated at an accelerating pace. Finally, periodontal status exhibited typical symptoms of rapidly progressive periodontitis with significant alveolar bone resorption.

other mentally compromised patients of similar age distribution [7,8—11]. The disorder develops at an early age and shows conditions similar to those of early-onset periodontitis, including juvenile and prepubertal periodontitis (Fig. 1) [8,9]. Early epidemiological cross-sectional studies revealed that more than 90% of Down syndrome patients under the age of 30 years had periodontal diseases [6,8]. Furthermore, the incidence of alveolar bone loss was found to be twice that of mentally handicapped patients without Down syndrome, with the prevalence of bone loss of 5 mm or more shown in about 70% of the Down syndrome patients, who had a mean age of 24 years [10]. Also, advanced bone loss (crest of the interproximal bone located within the apical 1/3 of the root) was noted in 65% of Down syndrome subjects with a mean age of 35 years in another study [11]. Signs of alveolar bone loss, mainly localized in the mandibular anterior region, have also been reported in Down syndrome subjects as early as 11 years of age [12]. A recent investigation showed that age was significantly and positively correlated with probing depth and alveolar bone loss in Down syndrome subjects (mean $\pm$ S.D.: 20.8 $\pm$ 5.6 years) [13], and another report confirmed a significant correlation between age and prevalence of bone loss in Down syndrome subjects with a mean age of 17.7 $\pm$ 7.1 years [14]. These findings suggest an age-dependent prevalence for periodontal disease in young adults with Down syndrome.

It is likely that some progression of periodontal disease with age is unavoidable in individuals with Down syndrome, however, all are not equally susceptible. Longitudinal studies of these patients have shown that the disease progresses rapidly, though the rate of progression varies among individuals [15—18]. Systemic impairment of the host defense mechanism has been proposed to contribute to the etiology of such rapidly progressive disease in Down syndrome [19], while the subgingival microbial profile was also noted as a cause.

It is noteworthy that more recent studies [13,14,20,21] have found that the severity of periodontal disease in individuals with Down syndrome is now milder as compared with that described in older studies [2,22—24]. This fact is likely attributable to better dental care for these individuals, both at home and the dental office, as compared with the past.

3. Factors related to early-onset periodontal disease in Down syndrome

3.1. Local factors

3.1.1. Oral hygiene and calculus

Mental disability associated with Down syndrome is a major factor in determining oral hygiene and likely has a large effect on periodontal health, as well as oral bacterial ecology. Early reports found that a majority of Down syndrome subjects demonstrated poor oral hygiene as compared to healthy individuals [2,5—10]. Recently, it was also reported that the mean plaque score was 100% in Down syndrome subjects [25], in agreement with other recent studies [20,21]. Though following oral hygiene instructions, Down syndrome adults had a reduced ability to maintain adequate plaque control [25]. Even in Down syndrome children, such a poor oral hygiene reportedly gave rise to earlier, more rapid, and more extensive gingival inflammation in deciduous dentition, as compared to normal control children [7,26]. However, this situation seems to be steadily improved by better dental care for these individuals, both at home and the dental office, as compared with the past. Indeed, some recent reports showed that better oral hygiene existed in Down syndrome children [27], or there was no significant difference as compared to healthy children [28,29]. Furthermore, the effectiveness of a school-based, supervised toothbrushing program was demonstrated in a group of 112 Down syndrome individuals aged 11—22 years old [30]. In consequence, the mean plaque score was significantly decreased from 1.93 to 0.95, and mean gingival score was reduced from 2.00 to 0.83 following supervised toothbrushing and dental health education sessions conducted twice a week for 3 months. Though it might be a hard task to educate adequate plaque control to Down syndrome individuals, an intensive education and care for oral hygiene have been shown to be worthwhile.

Calculus deposits were formerly considered to be abundant in Down syndrome children [5—7]. However, it was recently reported that 90.6% (29 of 32) of Down syndrome individuals aged 15—39 were calculus free, with a significant difference as compared to the greater amount of calculus accumulation in age/gender matched healthy controls [31]. Furthermore, other studies found no significant difference or less prevalence of calculus accumulation in Down syndrome subjects, as compared to healthy controls [32—34]. Despite poor oral hygiene, calculus deposits are likely to be reduced in Down syndrome individuals.

3.1.2. Oral function

Trisomy 21 induces poor neuromotor control, muscle weakness, and dysmorphology [35]. Down syndrome children often show an impairment in such oral functions as tongue protrusion, sucking, mastication, and swallowing due to a hypotonic tongue and perioral muscles [36,37], and a large majority (82.9%) reportedly held their lips apart in a habitual manner [38]. Such impaired functions prevent the optimum tooth intercuspation needed to stabilize the mandible and hyoid bone during mastication and swallowing, thus feeding is particularly affected in infants and children with Down syndrome [37,39], as well as in adults [40]. Abnormal chewing cycles and lowered chewing efficiency were also suggested to lead to a reduction in occlusal contact area [39]. In addition, mature swallowing and chewing skills are impaired in Down syndrome children [41,42]. A recent study also demonstrated that Down syndrome adults also have a variety of feeding problems, such as marked irregularities in masticatory time and cycle, and significantly lower frequency of chewing [40]. These impaired oral functions trigger traumatic occlusion and oral dryness, which cause periodontal destruction in Down syndrome.Habitual bruxism is also a cause of tooth mobility that accelerates periodontal destruction, however, no significant difference in bruxism frequency was found in Down syndrome children, as compared to normal children [43]. Furthermore, no statistically significant associations between bruxism and age, sex, or intellectual disability level were revealed.

3.1.3. Abnormalities in teeth and gingival tissues

3.1.3.1. Tooth morphology. Down syndrome was shown to be associated with irregular crown and root shapes. In these individuals, tooth crowns are usually shorter and smaller than normal [2], and root length is also significantly reduced [2,44].

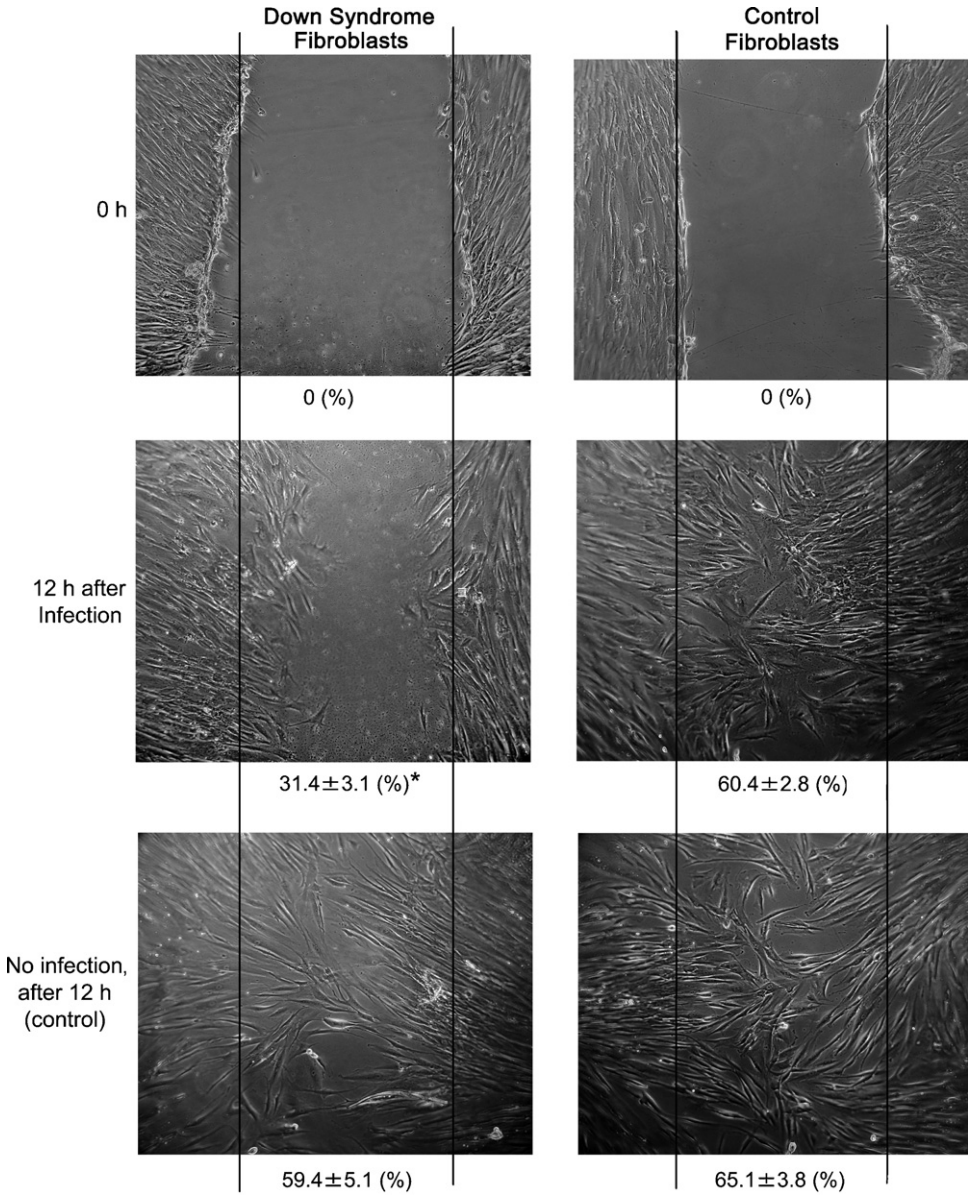

Figure 2 Inhibition of migration of gingival fibroblasts by *P. gingivalis* in Down syndrome. The effects of *P. gingivalis* on cellular motility of gingival fibroblasts from Down syndrome and normal control subjects were examined using an *in vitro* wounding assay (reproduced from Ref. [47], with permission). Confluent fibroblast layers were scratched with a plastic tip and the cells were infected with *P. gingivalis*, after which subsequent cellular motility to fill the wounded scratched areas was assayed at 37 °C for 12 h. Bars show the scratch wound regions at 0 h. Without infection, fibroblasts from both groups migrated to and filled about 60—65% of the scratched area, with no significant difference in closure efficiency. In contrast, *P. gingivalis* infection diminished wound closure, with Down syndrome fibroblasts found to be affected to a significantly greater degree than the control cells. These results suggest that gingival fibroblasts in Down syndrome individuals are more susceptible to the inhibitory effects of *P. gingivalis* on cellular motility. Rates (%) of wound closure for the scratched regions are shown under the images. $^{*}P < 0.05$.

Such an irregular morphology, especially short roots, is suggested to be a cause of periodontitis in Down syndrome [8].

3.1.3.2. Histological abnormalities in gingival tissue. Histological examinations revealed profound gingival inflammation in Down syndrome patients concomitant with hyperinnervation of the gingival sensory component [45]. This hyperinnervation was considered to be due to a sprouting of afferent nerves induced by inflammatory reaction and also suggested to contribute to gingival inflammation in these patients. Alternatively, chemical transmitters released from these nerves might be responsible for the inflammatory reaction. In addition, capillary fragility of gingival tissues was suggested to be related to the initiation and progression of Down syndrome periodontitis [46].

3.1.3.3. Impaired migration of gingival fibroblasts. Cellular motility of gingival fibroblasts is a critical function for wound healing and regeneration of periodontal tissues that are destroyed in an inflammatory process [47]. Cellular

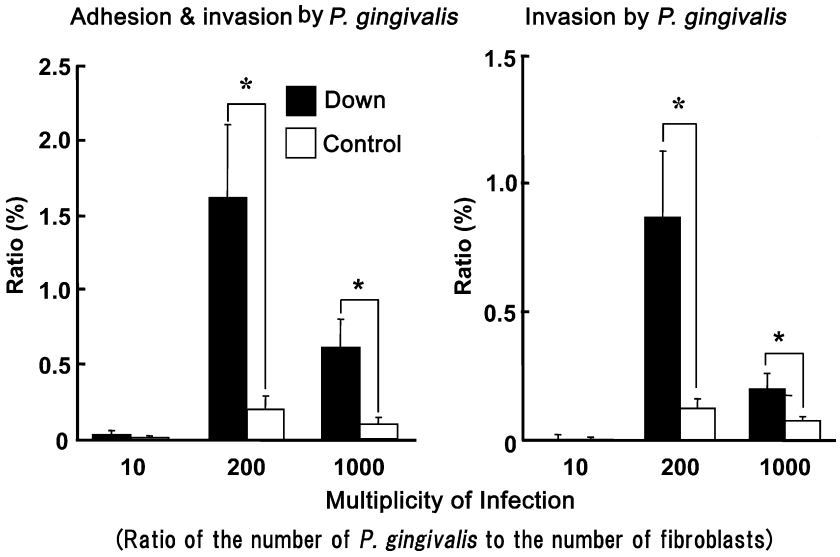

Figure 3 Adhesion to and invasion of fibroblasts by *P. gingivalis*. Gingival fibroblasts from Down syndrome and normal healthy subjects were infected with various numbers of *P. gingivalis* (reproduced from Ref. [47], with permission). The adhesion and invasion efficiencies of *P. gingivalis* were each significantly greater with the cells from the Down syndrome subjects. These results suggest that Down syndrome fibroblasts allow the pathogen to invade more readily, thus preventing cellular motility due to the degradation of cellular focal adhesion. Such characteristics likely have an effect on wound healing and regeneration of periodontal tissues in Down syndrome individuals. Values for the efficiencies of bacterial adherence and invasion are shown as ratios (%). $^{*}P < 0.05$.

migration of cultured gingival fibroblasts in individuals with Down syndrome was significantly impaired by a periodontal pathogen, *Porphyromonas gingivalis*, as compared to normal gingival fibroblasts (Fig. 2), because the former were readily invaded by *P. gingivalis* (Fig. 3) and intracellular pathogens further impaired cellular focal adhesion, which is essential for the migration of fibroblasts [48]. Thus, it is suggested that *P. gingivalis* readily invades gingival tissue and subsequently impairs cellular motility, resulting in prevention of wound healing and regeneration of periodontal tissues, which are characteristics likely involved in the etiology of periodontitis in Down syndrome.

3.1.4. Salivary factors

Human saliva plays an important role in oral health, especially in protecting against noxious compounds produced by microorganisms. Several salivary factors including salivary flow rate, pH buffering capacity, calcium/phosphate concentration, and secretory IgA (sIgA) have been shown to reduce caries risk [48], though there is no agreement as to the actual roles of these salivary factors in the pathogenesis of periodontal disease.

3.1.4.1. Salivary flow. With regard to salivary factors, no significant differences were observed in the concentrations of sialic acid, calcium, phosphorus, and magnesium between 20 Down syndrome and 18 control children aged 1—5 years old [49]. In contrast, protein and sodium concentrations were higher in the Down syndrome group, whereas flow rate, pH level, amylase and peroxidase activities, and potassium concentration were lower. Other studies also indicated a lower flow rate in Down syndrome group aged 6—10 years [50,51]. Although salivary flow in Down syndrome children seems to be lower than in healthy individuals, it is noted that salivary pH, buffering capacity, and flow rate were quite similar between 73 institutionalized Down syndrome children and 70 normal children aged 7—12 years [29]. In adults, salivary secretion is known to be decreased in an age-dependent manner in healthy subjects, and a more drastic decrease was found in Down syndrome older subjects [48]. Another study also showed that resting whole saliva flow rate in 70 Down syndrome adults was 0.05 ml/min (range, 0—0.41 ml/min), compared to 0.55 ml/min (range, 0.05—1.64 ml/min) in healthy control adults, indicating a 90% reduction, with a significant reduction in stimulated parotid saliva secretion also found [52]. Many other reports support an age-dependent deficiency of salivary secretion in Down syndrome individuals [51,53—56].

3.1.4.2. sIgA. There is no consensus concerning the role of the secretory immune system in the development of periodontal disease. However, bacterial colonization was shown to be inhibited by salivary sIgA [57], and adults with low levels of sIgA as well as the specific sIgA antibodies had an increased risk of periodontitis and tooth loss [58,59]. In Down syndrome children, significantly higher levels of salivary sIgA and a marked lower prevalence of tooth caries were reported [29,60]. Salivary sIgA seems to function to prevent tooth decay. In contrast, older Down syndrome patients showed an extreme reduction (>92%) in specific salivary sIgA against *P. gingivalis*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, and *Streptococcus mutans* as compared to age-matched controls [52]. Furthermore, an increased vulnerability to recurrent upper respiratory infections was attributed to this reduction in salivary sIgA secretion [56]. Such a severe salivary immunodeficiency related to age was suggested to intensify the risk of periodontal destruction in Down syndrome adults.

3.1.4.3. Antimicrobial peptides. Antimicrobial peptides are considered to play a major role in the first line of oral defense [61]. These molecules have a direct bactericidal activity and indirectly stimulate the immune system through chemotactic activity as well as induction of cytokines. A deficiency in salivary antimicrobial peptides has not been reported in Down syndrome subjects, while salivary LL-37, a cationic antimicrobial peptide, was found to be normally secreted in those subjects [62]. However, salivary LL-37 at a normal secretory level may be insufficient to prevent periodontitis when accompanied with deficiencies in the oral mucosal acquired immunity (IgA) and systemic immunity encountered in Down syndrome patients.

3.1.5. Subgingival microbial profile

Earlier studies suggested that *A. actinomycetemcomitans* was a causative agent for periodontal disease in Down syndrome [2,7,32]. However, previously, periodontal pathogens were detected by culture techniques that were not generally sensitive and required special skills, especially for the isolation of anaerobic bacteria such as *P. gingivalis*. Following the introduction of a polymerase chain reaction (PCR) method to detect bacterial DNA in 1996 [63], subgingival microbial profiles have become detectable with high specificity and sensitivity. Recent studies [20,64—67] have shown that Down syndrome-specific periodontal pathogens do not exist, but rather those found in those patients are similar to pathogens related to ordinary periodontal diseases. Nevertheless, *P. gingivalis*, *Treponema denticola*, and *Tannerella forsythensis* were found to be significantly prevalent in Down syndrome children as compared to age-matched controls [64], suggesting that periodontal pathogens colonize in the very early childhood of Down syndrome individuals, with early maturation of noxious microflora. A significantly greater prevalence of *P. gingivalis*, *A. actinomycetemcomitans*, and *T. forsythensis* was also shown in 70 Down syndrome subjects aged 8—28 years old, as compared with age-matched healthy individuals and patients with cerebral palsy [21]. These results suggest that virulent periodontal pathogens can colonize in early ages and subsequently survive in the oral cavities of Down syndrome individuals.

In particular, *P. gingivalis* was reported to occur more frequently with aging in Down syndrome individuals [21]. *P. gingivalis* has been classified into six genotypes (types I—V and Ib) based on the diversity of the *fimA* genes encoding its fimbria subunits [68]. Accumulated evidence suggests that *P. gingivalis* strains with type II fimbriae are the most periodontopathic clones in normal subjects. Interestingly *P. gingivalis* clones with types II or Ib fimbriae were also found to be significantly related to initiation and progression of periodontitis in Down syndrome [20,66]. Further, periodontal herpesvirus—bacteria coinfection was suggested to play an important role in the pathogenesis of periodontal destruction in these individuals [67]. Herpesviruses may reduce periodontal defense and promote growth of subgingival bacteria capable of causing periodontal breakdown.

3.2. Systemic factors

3.2.1. Systemic immunodeficiency

The initiation and progression of periodontal disease is largely dependent upon the host immune response, such as humoral and cellular immunity [69]. It is well known that Down syndrome individuals suffer from multiple impairments in their systemic immune system, rendering them susceptible to hematologic malignancies, autoimmune diseases, and infectious diseases including periodontal disease [1,2,69]. Surprisingly, the etiologies of the proposed abnormal humoral and cell-mediated immunological functions in Down syndrome have not been well clarified, with inconsistent results reported [70]. However, apparent defects have been demonstrated in B, T, and natural killer cell functions, as well as in cytokine production, phagocytic and chemotactic responses, and immunoglobulin function [71,72].

3.2.1.1. Phagocytic and chemotactic responses. Impaired chemotaxis of neutrophils and monocytes, and reduced numbers and immature forms of T cells has been well documented in Down syndrome individuals. The initial finding of a neutrophil anomaly in Down syndrome showed less segmented nuclei with normal numbers of neutrophils and leukocytes, indicating the preponderance of younger cell forms [69]. This phenomenon was considered to be due to a tendency for the shortening of the half-life of circulating neutrophils in Down syndrome. In addition, a significant reduction in neutrophil chemotaxis was reported in Down syndrome children [73,74], with defective chemotaxis also found to be significantly correlated with the progression of periodontitis including bone loss in Down syndrome patients [14]. The phagocytic ability of Down syndrome neutrophils has also been shown to be diminished, with significantly inefficient *in vitro* phagocytosis of *Candida albicans* reported [75]. Furthermore, intracellular killing capacity was shown to be decreased for a number of organisms, including *Streptococus aureus*, *Escherichia coli*, and *Candida albicans* [75,76]. In addition, peripheral T cells (lymphocytes) in Down syndrome subjects were reported to be diminished both quantitatively and qualitatively in regard to their ability to recognize and respond to specific antigens [15].

3.2.1.2. Altered oxidative metabolism related to gene on chromosome 21. Earlier studies suggested a great variation in the oxidative metabolic potential of immune cells in Down syndrome individuals, and a more recent and notable observation provides a new clue to the relationship between Down syndrome and the immune system. The gene expression profile analysis in T-lymphocytes from two patients with Down syndrome showed over-expression of the superoxide dismutase (SOD) gene which is located on trisomic chromosome 21q.16 [77]. SOD is a key enzyme in the metabolism of oxygen-derived superoxide (O_2^-) to hydrogen peroxide (H_2O_2) and SOD activity is increased in various tissues in Down syndrome [78—80]. Although the relationship of SOD with the immunopathology of Down syndrome is not well elucidated, increased H_2O_2 produced by abundant SOD may react with transition metals like iron to form the hydroxyl radical, which can initiate lipid peroxidation resulting in damage to cell membranes [81]. Thus, an increase in SOD activity theoretically reduces immunity in Down syndrome individuals. First, such an increase would also increase H_2O_2, which may damage immune cells and impair cellular signal transduction events involved in phagocytosis. Second, it would decrease the concentration of O_2^-, resulting in a decrease in the bactericidal activity of phagocytes. These

possibilities are supported by other reports, in which neutrophils from individuals with Down syndrome were shown to produce less O_2^- than those without Down syndrome. Also, a two-fold overproduction of SOD in intraperitoneal macrophages from transgenic mice resulted in inhibition of extracellular release of O_2^-, increased intracellular production of H_2O_2, and reduced microbicidal and fungicidal activities [82,83].

3.2.1.3. Dscam (Down syndrome cell adhesion molecule) gene on chromosome 21. Another recent finding is Dscam (Down syndrome cell adhesion molecule), which was isolated from chromosome 21q22.2-22.3, and shown to be a novel member of the immunoglobulin superfamily and in a unique class of neural cell adhesion molecules that are relevant to neural wiring [84]. Watson et al. [85] detected protein isoforms of Dscam in *Drosophila* hemocytes and found that loss of Dscam impaired the phagocytic uptake of bacteria, possibly due to reduced bacterial binding such as a diminished expression of surface glycoproteins needed for adhesion to bacteria. The Dscam gene contains 116 coding regions encoding about 20,000 different proteins. The potential ability of Dscam to generate a large protein isoform-repertoire and recognize diverse ligands may be a major link between the nervous and immune systems. It has also been hypothesized that there is increased deletion of thymocytes in the Down syndrome thymus and a diminished proportion of mature T cells.

3.2.1.4. Early senescence of immune system in Down syndrome. An interesting question has arisen regarding whether immune dysfunction in Down syndrome is a congenital immune deficiency or early senescence of the immune system [86], because a majority of individuals with Down syndrome do not show severe features of immunological disease. Many of the above-mentioned immunological alterations may be age-related changes and can be included in the spectrum of multiple signs of early senescence characteristic of the syndrome. Although recent studies regarding SOD and Dscam provide further support for the increased susceptibility to bacterial and viral diseases in Down syndrome, further investigations are necessary to fully address the above question.

3.2.2. Inflammatory mediators and proteolytic enzymes

Periodontal pathogens such as *P. gingivalis* stimulate periodontal cells to produce inflammatory mediators such as prostaglandin E_2 (PGE_2), matrix metalloproteinases (MMPs), and proinflammatory cytokines including interleukin (IL)-1, IL-6, and IL-8 [87]. These mediators further activate host cells to mount excessive host inflammatory responses. Down syndrome individuals are likely to exhibit exaggerated inflammatory responses upon periodontal infection [87—91]. *A. actinomycetemcomitans* lipopolysaccharide significantly enhanced PGE_2 production through the induction of mRNA expression of COX-2 (PGE_2-producing enzyme) by gingival fibroblasts from Down syndrome subjects [88]. We also found that *P. gingivalis* infection significantly induced mRNA expressions of COX-2 as well as IL-6 by gingival fibroblasts in these individuals (Fig. 4) [92]. Excessive expressions of MMPs are responsible for periodontal breakdown [93], while collagenase activities comprised mainly of MMP-8, MMP-9, and MMP-2 in saliva and gingival crevicular fluid were reported to be higher in Down syndrome children as compared to the age-matched healthy subjects [88]. Also, the expressions of membrane-type MMP-1 and MMP-2 by gingival fibroblasts of Down syndrome individuals were found to be augmented, as compared with those of healthy controls [89]. Furthermore, the inhibitory capacity of TIMP-2 against activated MMP-2 was repressed in Down syndrome patients [90]. These features are likely involved in the periodontal destruction seen in individuals afflicted with the syndrome.

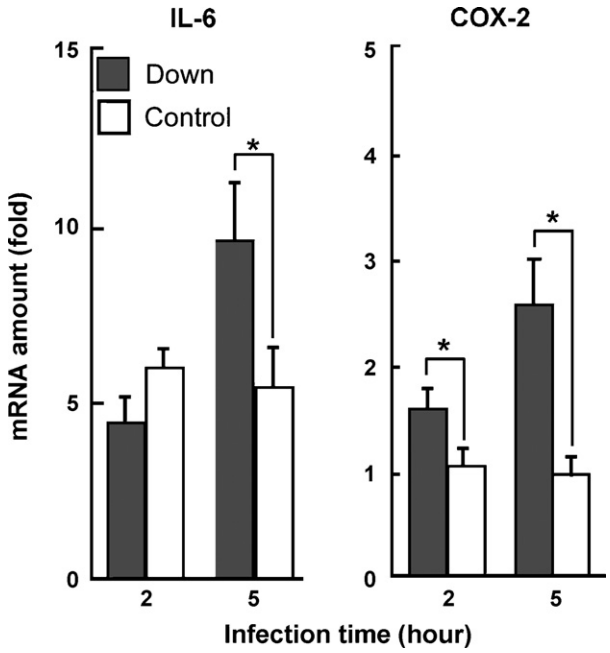

Figure 4 Exaggerated expression of inflammatory mediators by Down syndrome gingival fibroblasts after infection with *P. gingivalis*. Cultured gingival fibroblasts from Down syndrome (Down) and normal control (Control) subjects were infected with *P. gingivalis*. IL-6 and COX-2 were significantly induced in the Down specimens as compared to the control specimens (Ref. [92]). These results suggest that Down syndrome gingival fibroblasts have an exaggerated inflammatory response upon infection of *P. gingivalis*, resulting in severe periodontal destruction.

4. Conclusion

Collectively, individuals with Down syndrome likely respond to common bacterial challenges in an exaggerated manner, due to multiple factors, and develop more severe forms of periodontal disease. There is a higher incidence of oral health problems among individuals with Down syndrome, particularly after 10 years of age [13,14,20], indicating the need for better teaching of tooth brushing and more regular visits to the dentist. Conventional standard procedures of oral hygiene instruction, scaling, and root planing, as well as surgical therapy lead to significant improvements in Down syndrome patients [25,91]. In addition, some products such as the Castillo-Morales palatal plate have been developed to improve impairments in such oral functions as tongue protrusion, sucking, mastication, and swallowing [94,95]. Although there is little doubt that a patient with Down

syndrome is at increased risk for periodontitis, periodic preventive care including rigorous bacterial plaque control is necessary for suppressing the progression of periodontal disease in these individuals. Down syndrome is the second most frequent congenital disorder encountered in the oral—dental field, next to cleft palate/lip [7], thus further investigations are important to elucidate the etiologic factors involved in periodontal disease related to the condition.

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