1 Evolving Paradigms in the Pathogenesis and Management of Periodontitis

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Contents

1.1 Introduction

Periodontal diseases are complex diseases of multifactorial origin which are initiated by a diverse group of dysbiotic oral microbial species, yet the disease progression, clinical presentation, and response to therapy are driven by the deregulated and non-resolving inflammatory responses due to host genetic and epigenetic factors, environmental, and systemic perturbations (e.g., improperly designed restorations, obesity, stress, aging, uncontrolled diabetes, immune disorders, and use of certain medications) and lifestyle preferences (e.g., smoking, eating habits) [1–7]. If not treated or properly managed, periodontal disease results in loss of periodontal tissue architecture, creates esthetic and functional complications and eventually tooth loss. Persistent and severe forms of the disease are also associated with numerous systemic complications [8].

Despite many advances in the field, periodontitis continues to be a substantial medical, psychological, and financial burden worldwide affecting more than 50% of the adult population [9]. The prevalence of periodontitis increases with age and considering the increased lifespan, it is imperative to understand the biology of aging periodontal tissues and incorporate the needs of these patients in clinical management [10, 11]. Similarly, with the growing number of implant-supported restorations in clinical practice, the clinicians and researchers are now faced with the challenge of increased prevalence of peri-implantitis, which is a disease affecting the tissues surrounding implants [12, 13].

The ultimate goal of periodontal research is the development of effective preventive and

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therapeutic strategies to improve clinical outcomes and achieve pristine oral and systemic health. As we enter the era of precision medicine which aims to personalize therapies, research efforts are directed to fully characterize the key cellular and molecular factors that regulate periodontal tissue homeostasis, understand the interactions between host and the microbiome, and identify disease susceptibility markers and risk modifiers for more targeted approaches. Integration of biological sciences, engineering, and omics data with the rapidly emerging technologies in clinical, basic, and regenerative medicine will be at the center of personalized periodontics. Future periodontal practice will be shaped by genetic, molecular, cellular and physiological analyses and assessment of environmental exposures and lifestyle preferences and incorporation of biological data and technical advances to plan individualized preventive and treatment strategies [14–18].

Many reports are already available in the literature, which discuss various non-surgical and surgical therapies with and without adjunct antimicrobial and/or anti-inflammatory agents to manage periodontitis and peri-implantitis [15, 19–21]. Most of these therapeutic modalities are considered as the standard mode of clinical practice and effective in the majority of the cases exhibiting mild to moderate forms of the diseases. Yet, the research also indicates that anti-infective therapy using non-specific mechanical approaches and antimicrobials alone does not provide long-term stability and fails to effectively manage almost 25% of periodontitis patients. There are also growing concerns about the development of antibiotic resistance. Moreover, the currently available host modulation therapies exhibit various side effects. Hence, successful management of periodontitis requires alternative modes of preventive and therapeutic strategies assessing individual risk and causation and targeting multiple disease predisposing factors [22].

In this book, we aimed to take our thinking further and provide a glimpse of emerging strategies and concepts which are currently being tested in preclinical and/or clinical settings and show promise as future novel therapies in the era of precision oral care. An up-to-date information is provided in each chapter about novel concepts and new studies toward better management of periodontitis and peri-implantitis. We focus on therapeutics targeting immune response and microbiome as well as recent advances and technologies in laser therapy and regenerative medicine including protein and cell-based approaches and 3D printing. The key biological processes in health and disease in aging periodontal tissues and implications for patient management are also discussed.

Following paragraphs provide a brief overview of the evolving paradigm in the pathogenesis of periodontal diseases and patient management and share perspectives for precision oral health care. More detailed discussions about the critical host immune and inflammatory pathways, oral cavity microbiome in health and disease, and novel periodontal regenerative strategies are highlighted in each subsequent chapter.

1.2 The Pathophysiological Stages of Periodontal Lesion

The periodontium consists of various cells of myeloid and non-myeloid origin distributed within four components including gingiva, periodontal ligament, cementum, and alveolar bone. Even though each periodontal division is distinct in its location and composition, they all function as one unit and the cellular activities occurring in one site can affect the others. The periodontal tissues are constantly exposed to a diverse group of microbiome including commensal and external bacteria, viruses, and fungi as well as stress originating from chemical and mechanical trauma, which trigger activation of immune and inflammatory pathways in an attempt to protect the host and maintain health. The periodontal tissue homeostasis and architecture are preserved by the balance between host destructive and repair processes to this constant stress. Thus, multiple cells with different functions are involved in various stages of periodontal pathology and the interplay between microbial components, the cells of

the periodontal tissues, and the constant influx of inflammatory mediators and tissue-derived enzymes determine the transition from health to disease [23].

The initial inflammatory response in the periodontium is triggered by the sensing of microbial-associated molecular patterns (MAMPs) (e.g., lipopolysaccharide [LPS], lipoproteins) and/or damage/danger-associated molecular patterns (DAMPs) (e.g., nucleic acids, fibrinogen, heat-shock proteins) through specialized pattern-recognition receptors (PRRs) (e.g., Toll-like receptors [TLRs], complement receptors, and NOD-like receptors [NLRs]). These interactions mainly activate nuclear factor kappaB (NF-kB) and mitogen-activated protein kinase (MAPK) signaling pathways, leading to the production of proinflammatory cytokines and chemokines that aid in the development of an efficient innate immune response to eliminate the insult and coordinate development of an adaptive immune response. Although activation of the immune system is crucial to combat infections, it is equally important to have properly functioning regulatory pathways to facilitate timely termination of inflammation, allow resolution and tissue healing thereby prevent collateral tissue damage [8, 24–26].

The periodontal disease progression follows four classical histological stages: *initial*, *early*, *established*, and *advanced* lesions [27, 28] (Fig. 1.1). These definitions are based on the distinctive histological features of the developing lesion with regard to the presence of specific cells and the extent of tissue destruction, yet the disease progression is a highly interactive and dynamic process where there is commonality between each stage, with similar cells and inflammatory mediators, histological characteristics, and clinical symptoms. Further expanding onto these classical definitions of periodontal lesion, the transition from health to disease state was categorized in four schemes as follows: (1) *"acute bacterial challenge phase*" which refers to the initial response to the commensal microbiome (*initial lesion*), (2) "*acute inflammatory phase"* which defines the initial inflammatory reaction (*initial* and *early lesions*); (3) "*immune response phase"* which defines the progression of immune and inflammatory responses involving activation of numerous types of mononuclear cells (*early and established lesions* or gingivitis), and (4) "*regulation and resolution phase*" which defines the stage where a normal protective host response may either terminate (health) or deviate toward a more prolong and destructive chronic immunoinflammatory state in susceptible individuals (*advanced lesion* or periodontitis) [29] (Fig. 1.1). While these histological/clinical phases provide an overview of the events occurring between host and microbiome within the oral cavity leading to health or disease states, the biological processes are not linear and independent from each other and there is significant interplay between phases.

The *initial* sequelae in gingival inflammation is a subclinical acute inflammatory lesion which is characterized with increased vascular dilation and blood flow accompanied by the migration of neutrophils toward the lesion due to chemotactic stimuli originating both from microbial cells and host-derived inflammatory mediators such as IL-8 (CXCL8), complement components C5a and C3, and leukotrienes. There is also activation of complement and kinin systems and arachidonic acid pathways and possible collagen loss. The *initial* lesion is typically response to continuing presence of acute microbial challenge and if the acute inflammation fails to resolve rapidly, it may evolve into a chronic inflammatory lesion [30, 31].

Early lesions display accentuation of the features of the *initial* lesion with increased vascularization, accumulation of more PMNs and lymphocytes (mainly T-cells) as well as continuous activation of complement and arachidonic acid pathways. Macrophages, plasma cells, and mast cells start to appear at the site of acute inflammation. These cells produce pro-inflammatory mediators including TNF-α, IL-1β, IL-6, IL-8, and IL-17, which may exacerbate the inflammatory response and promote progression to more advanced stages of the disease. There is further loss of the collagen fiber network around the inflammatory infiltrate due to the activation of the local immune system. Clinical features may include bleeding, edema,

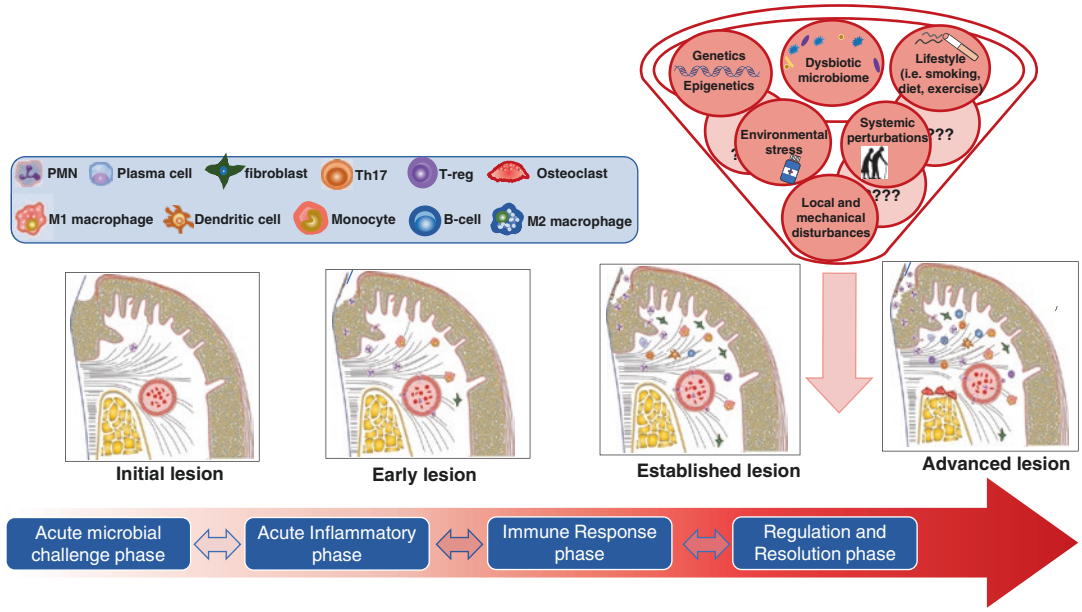

Fig. 1.1 The schematic model of periodontal disease progression. During the initial response, *acute microbial challenge phase,* microbial components (e.g., lipoproteins, LPS, nucleic and fatty acids, and FMLP) trigger the release of inflammatory mediators (e.g., IL-1, IL-8, TNF, prostaglandins, and matrix metalloproteinases) from the epithelial cells. Further release of histamine from mast cells and activation of endothelial cells drive the migration of neutrophils to the site. *The acute inflammatory phase* (early lesion) is characterized by the augmentation of the local inflammatory responses, activation of serum protein systems (e.g., complement), additional leukocyte recruitment, activation of macrophages, and release of more inflammatory and immune mediators and chemotactic substances. *Immune and inflammatory phase* (established lesion) depicts a further increase in inflammatory and cellular activity and transition from an acute lesion to a chronic state. In addition to the continuous activation of macrophages and serum proteins, T cells, B cells, and plasma cells appear in the tissue. During the *regulation and resolution phase*, there is orchestrated activity of all systems to control microbial insult and balance the tissue destructive and healing phases of the immune response. If tissue homeostasis is sustained, the established lesion does not further progress and remains stable with periods of activity and resolution for years. Failure of timely termination of inflammation alters microbial community, and generates a non-resolving inflammatory state which is further perpetuated by microbial dysbiosis eventually leading to the destruction of extracellular matrix and loss of alveolar bone. The advanced lesion of periodontitis is characterized by the initial loss of attachment and alveolar bone. There is increased cellular activity and production of more inflammatory mediators and tissue-derived enzymes by activated PMNs, macrophages, monocytes, lymphocytes, fibroblasts, osteoblasts, and osteoclasts. It is imperative to fully understand the factors which increase susceptibility and molecular and cellular events occurring in each phase to manage the disease

and erythema. Both initial and early lesions constitute the acute inflammatory reactions to oral commensals [30, 31].

As the disease progresses into the *established* or the *immune response phase*, there is a transition from an acute lesion to a chronic state. The manifestations of *early* and *initial* changes still persist, along with the appearance of B-lymphocytes and continuingly increased numbers of PMNs, macrophages, monocytes, and T-cells. There is also the presence of extravascular immunoglobulins in the connective tissue and in the junctional epithelium. In the *established* lesion, which is clinically diagnosed as *gingivitis*, there is a substantial loss of gingival extracellular matrix due to increased collagenase activity and activation of the local immune system, but without bone loss. It is now well recognized that gingivitis is reversible and can remain stable with periods of exacerbation and remission indefinitely and only progresses to periodontitis (*advanced lesion*) in susceptible individuals [30, 31].

The *regulation and resolution phase* determines the final stage of the transition to periodontitis or *advanced lesion*. At this stage, the symptoms of *established lesion* and *immune response phase* persist with the progression of inflammation to involve the alveolar bone. Production of more inflammatory mediators such as cytokines, chemokines, arachidonic acid metabolites (prostaglandins), and complement proteins by activated PMNs, macrophages, monocytes, lymphocytes, fibroblasts, and other host cells can cause oxidative damage by promoting the release of tissue-derived enzymes such as matrix metalloproteinases (MMPs). Furthermore, cytokines can act on stromal and non-stromal cells causing increased expression of receptor activator of nuclear factor kappa-B ligand (RANKL) while decreasing osteoprotegerin (OPG) production. If the inflammation is not resolved, destruction of extracellular matrix and irreversible alveolar bone loss occur (*advanced lesion* or periodontitis) [31] (Fig. 1.1).

Substantial progress has been made in defining the cellular and molecular mechanisms which participate in the pathophysiology of periodontal inflammation. It is revealed that periodontal disease progression does not follow a linear pattern and involves a highly coordinated and interconnected array of biological and cellular events that are shaped by multiple host and environment-specific factors contributing to the susceptibility of the disease (Fig. 1.2). We now know that innate immunity does not simply represent different forms of physical and chemical barriers to

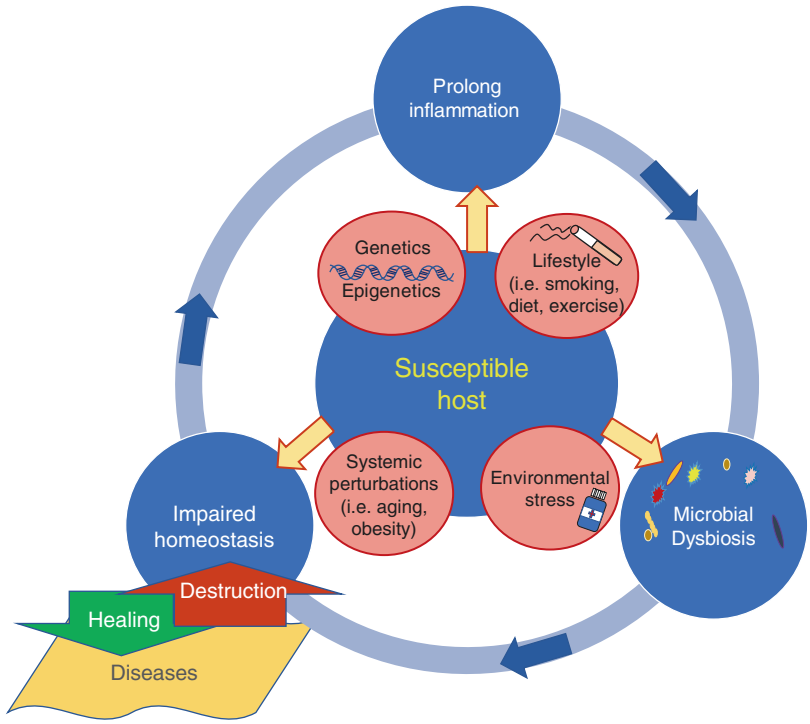

Fig. 1.2 The schematic model of non-resolving and self-perpetuating periodontal inflammation and predisposing factors. Periodontitis is not solely a bacterial infection or a linear host response to a dysbiotic microbiome but rather characterized by a self-perpetuating state of prolonged inflammatory response and impaired tissue homeostasis involving highly coordinated and interconnected array of biological and cellular events which are driven by multiple host and environment-specific factors. Factors which increase susceptibility for periodontitis are still under extensive investigation and include host genetic and epigenetic alterations, systemic perturbations (e.g., obesity, stress, aging, uncontrolled diabetes, immune disorders, and use of certain medications), environmental and local disturbances (e.g., microbial dysbiosis, improperly designed restorations, imbalanced masticatory forces), and lifestyle preferences (e.g., hygiene, smoking, eating/drinking habits, exercise)

microbial insult, but constitutes a highly specialized and organized network of cellular and molecular pathways which interact closely with each other as well as the adaptive arms of the immune response to balance the tissue homeostasis within the oral cavity [31–33]. It has been revealed that local tissues can play a critical role in sustaining homeostasis through local production of homeostatic molecules or endogenous regulators and that cells are trained or programmed based on their specialized niches in the body [34]. The discovery of the dynamic reciprocal interactions between the host immune and inflammatory responses and bone tissue started an emerging field of study named osteoimmunology [35]. While the research over the last decade uncovered the biological pathways and host-pathogen interactions during the course of the initial inflammatory response, we still do not know much about the regulatory pathways that drive the timely termination of inflammation and promote resolution and healing. Defining key regulators of inflammation at the cellular and molecular levels in each stage of the progressing periodontal lesion and understanding the individual factors (e.g., genetic, systemic, and local) that modulate these processes will allow us to predict the disease susceptibility and develop personalized strategies to improve clinical outcomes. In addition, understanding the downstream regulatory factors which play role in maintaining tissue homeostasis will be critical to develop therapeutics without off-target effects.

1.3 Evolving Paradigms in the Pathogenesis of Periodontitis

There has been a significant amount of research over the last 60 years in clinical and basic sciences combined with technological advances which led to distinct "eras" in our understanding of periodontal disease pathogenesis and patient management (Fig. 1.3). The concepts defining the periodontal microbiology have evolved from the "*nonspecific plaque hypothesis*" in the 1960s which associated the amount of the entire plaque microbiota with the disease status [36] to the "*specific plaque hypothesis*" in the 1980s which proposed a direct role of specific bacteria in the etiology of periodontitis [37]. In the 1990s, these two models were modified as the "*ecological plaque hypothesis*" which suggested that molecular and physiological changes within the tissues, such as variations in pH and amount of certain host proteins, could promote the growth of Gram-negative species and trigger more inflammation

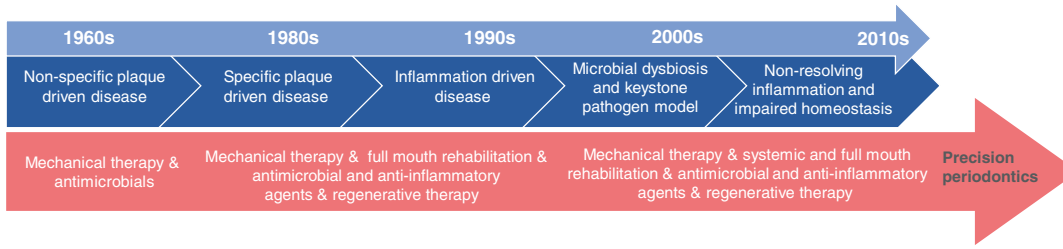

Fig. 1.3 Evolving paradigms in the pathogenesis and management of periodontitis. In the mid-twentieth century, periodontitis was recognized as an infectious disease of multibacterial origin and managed either through extraction or non-specific mechanical therapy with and without antimicrobials and oral hygiene instructions. Over the years, rigorous research in microbiology, immunology and regenerative medicine and the realization that the oral cavity is tightly connected to the rest of the body led to the reappraisal of the pathogenesis and clinical management of the disease. Today, periodontitis is characterized as a non-resolving inflammatory disease to a dysbiotic microbiome and incorporation of host modulation therapy in clinical practice is revealed to improve clinical outcomes. Future periodontal practice will adapt tools of precision medicine to prevent and treat the disease on a personalized level and address the multifactorial nature of the disease and create tailored strategies for each individual's unique biological profile and habits with the premise of achieving better oral and systemic health, decreased financial burden, and improved quality of life

and tissue loss [38]. Around same years, research efforts extended beyond microbiology in an attempt to define the host immune and inflammatory responses during the course of periodontal disease. Several reports highlighted the significance of host-derived factors in the disease pathophysiology and noted that individual variations in host immune response to oral microbiome are the main drivers of the susceptibility of periodontitis [39, 40] (Fig. 1.3).

The awareness of the significance of the inflammatory component of the disease led to the reappraisal of the definition of periodontitis from a classical infectious disease, one being solely of bacterial origin, to an "*inflammatory disease*" [39, 41]. In this new era, periodontitis was characterized by a non-resolving inflammation not fully capable of eliminating the initiating pathogens. Most recently, "*polymicrobial synergy and dysbiosis*" and "*keystone bacteria*" models have been proposed which are consistent with the notion that periodontal bacterial composition is much more diverse than previously predicted and that host response to these distinctive communities vary greatly between individuals which eventually determine the susceptibility for diseases [42, 43]. In the *"dysbiosis theory"*, it is hypothesized that the influence of individual species in a polymicrobial community could alter host-microbial interactions leading to destructive inflammation. It is argued that gingival inflammation, in response to early colonizing bacteria, changes the subgingival environment and promotes the growth of certain endogenous accessory bacteria which then assist in the colonization and metabolic activities of other pathogens until they are outgrown by the more potent pathobionts. This synergistic and symbiotic polymicrobial environment initiated and fueled by the deregulated inflammation further enhances inflammation and tissue destruction [43] (Fig. 1.3).

Today, it is revealed that periodontitis is not solely a bacterial infection or a linear host response to a dysbiotic microbiome but rather characterized by a self-perpetuating state of prolonged inflammation due to various factors involving host and environment subsequently leading to microbial dysbiosis, unsustainable inflammation, and tissue destruction (Fig. 1.2) [44]. Consistently, the research also indicates that anti-infective therapy using mechanical approaches and antimicrobials often fails to effectively manage the disease in the long term [22]. As we continue to investigate the oral cavity microbial communities and characterize their pathogenicity within the changing microenvironments, current paradigm indicates that therapeutics targeting inflammation should be integrated to the periodontal practice to restore tissue homeostasis and microbial dysbiosis. Therefore, continuous research is needed to identify the key biological pathways and downstream regulatory molecules at the interface of host and pathogen interactions to develop more targeted therapies. Subsequent chapters will discuss some of these novel studies.

1.4 Evolving Paradigms in Periodontitis Patient Management

Not many years ago, the goals of traditional periodontal therapy have been to remove deep pockets, control gingival bleeding, and achieve proper oral hygiene in all patients through mechanical therapy with and without antibiotics and continuous supportive periodontal care (Fig. 1.3). In clinical practice, this goal is seldom accomplished and tissue breakdown continues in the majority of cases. In addition, growing concerns about the global antibiotic resistance fueled research efforts toward the identification of more selective modes to manage the disease. Remarkable progress has been made in the understanding of the molecular basis and susceptibility factors of periodontal disease and in the development of new biomaterials and advanced surgical techniques and diagnostic tools [15, 17, 18, 32, 45]. Current periodontal practice has become more focused to individual needs and incorporated full mouth and systemic rehabilitation and addressing predisposing factors such as smoking cessation and diabetes control in patient management. Yet, even this mode of therapy fails to

achieve desired clinical outcomes in certain groups of patients, and periodontitis continues to be the primary cause of tooth loss in industrialized countries predominantly affecting people older than 40 years of age. Thus, the development of better approaches to prevent and successfully treat periodontitis is vital to general and oral health. It became also clear that the host response to the microbiome is under the influence of many factors including genetics, systemic and local factors, and lifestyle choices (Fig. 1.2). Hence, the development of predictable preventive and therapeutic strategies to diminish destructive inflammation and regenerate tissues will depend on taking into consideration individual differences and predisposing factors in clinical decision making.

Strategies that are currently being tested to treat the disease include targeting key inflammatory pathways or microbial components. Periodontal microbial dysbiosis can be targeted by anti-bacterial drugs, probiotic intake, and mechanical debridement [46, 47]. As a non-invasive therapeutic approach for periodontitis, host modulation therapy has been investigated targeting cytokine/chemokine network, MMPs, arachidonic acid metabolites, and more recently endogenous regulators of inflammation and modifying nutrition and lifestyle choices [32, 48–52]. Yet, side effects are of concern for some of the clinically available host modulation therapies including GI complications and impaired wound healing [53]. While the use of low-dose doxycycline has been considered to be safe, concerns with antibiotic resistance limit the use of antibiotics in general [47]. Therefore, recent investigations focus on targeting downstream molecules and regulatory pathways and/or unique microbial components as therapeutics with the premise of eliminating side effects.

Genetics can explain a considerable amount of variation in the clinical presentation of periodontitis and effect of specific genotypes on the key biological events and disease phenotypes are under investigation [54, 55]. Another emerging field in periodontology is epigenetics which investigates the dynamic interactions between genes, environment and human behavior and how they lead to genome modifications, influence gene expression, and subsequently modify susceptibility for periodontitis [56]. With increased lifespan, the influence of aging on disease phenotype should also not be overlooked [10, 57].

The "*precision periodontics*" un-doubtfully is the next phase for our profession which will consider individual inflammatory response, microbial composition and predisposing factors and adapt 4Ps of precision medicine (denoting predictive, preventive, personalized, and participatory) in clinical practice [16, 22] (Fig. 1.3). In this new era, patient management will include personalized strategies for the prevention of periodontal and peri-implant diseases and tailored therapies toward individuals' unique biology and risk profiles, which will take into consideration many elements in clinical decision making including cellular and molecular analyses, genetic and epigenetic factors, environmental and systemic perturbations (e.g., improperly designed restorations, obesity, stress, aging, uncontrolled diabetes, immune disorders, and use of certain medications), and life style preferences (e.g., smoking, diet) [14, 16].

In the following chapters, novel concepts and strategies targeted to complement, cytokines and endogenous regulators of inflammation, lipid mediators, and genetic and epigenetic approaches are discussed in the management of periodontitis and peri-implantitis. Insights are provided about the microbiome in health and disease and new-generation antimicrobials and probiotics. Emerging paradigm in regenerative medicine using cell and protein-based approaches, 3D printing, and laser technology is highlighted. As the population is progressively getting older, the biology of aging and its effect on the periodontium and patient management are reviewed.

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