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Review article

Interactions between silica and titanium nanoparticles and oral and gastrointestinal epithelia: Consequences for inflammatory diseases and cancer

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ABSTRACT

Engineered nanoparticles (NPs) composed of elements such as silica and titanium, smaller than 100 nm in diameter and their aggregates, are found in consumer products such as cosmetics, food, antimicrobials and drug delivery systems, and oral health products such as toothpaste and dental materials. They may also interact accidently with epithelial tissues in the intestines and oral cavity, where they can aggregate into larger particles and induce inflammation through pathways such as inflammasome activation. Persistent inflammation can lead to precancerous lesions. Both the particles and lesions are difficult to detect in biopsies, especially in clinical settings that screen large numbers of patients. As diagnosis of early stages of disease can be lifesaving, there is growing interest in better understanding interactions between NPs and epithelium and developing rapid imaging techniques that could detect foreign particles and markers of inflammation in epithelial tissues. NPs can be labelled with fluorescence or radioactive isotopes, but it is challenging to detect unlabeled NPs with conventional imaging techniques. Different current imaging techniques such as synchrotron radiation X-ray fluorescence spectroscopy are discussed here. Improvements in imaging techniques, coupled with the use of machine learning tools, are needed before diagnosis of particles in biopsies by automated imaging could move usefully into the clinic.

1. Introduction

Engineered nanoparticles (NPs) have been defined as nanomaterials that range in size between 1 and 100 nm (in at least one

Abbreviations: NP, nanoparticle; ROS, reactive oxygen species; FBG, foreign body gingivitis; PAMP, pathogen-assocaited molecular pattern; DAMP, damage-assocaited molecular pattern.

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dimension). NPs are used in the fabrication of numerous consumer goods, including various paints, food, detergents, bactericides, coatings, cosmetics, sunscreens, tires, personal care products, computer construction, and drug and gene delivery [1]. NPs are also present in medical and healthcare goods, sunscreens, toothpaste, and various devices used in dental procedures, such as professional polishing agents and dental restorative materials [1–4]. These NPs can also aggregate into larger particles, which have different effects than the original NPs on biological responses from tissues exposed to the particles.

Given the promising application of NPs, funding for the National Nanotechnology Initiative (NNI) in the United States alone approached $1 billion in 2005. As of 2009, this new technology supported a worldwide market of about a quarter of a trillion dollars, of which about $91 billion was found in U.S. products that include nanomaterials [5]. With the rapid development of nanotechnology and its related commercial products, it was inevitable that NPs would become a common part of our daily lives. The major concern with NPs in terms of their potential health hazards or risks (e.g., the potential for producing reactive oxygen species and associated negative biological consequences) is mainly related to their large surface reactivity due to their unique small dimensions.

Upon interaction with the organism, different NPs have been demonstrated to interact with immune cells and epithelial cells [6–10]. Epithelial cells are particularly important because they are the first cells to encounter foreign particles in the skin and in the oral mucosa and, by secreting cytokines and chemokines, can initiate and orchestrate an immune response. In fact, we and others have described how challenged oral epithelial cells are able to sense and generate immune responses in response to infection [11–13]. Due to the large distribution of NPs in several products used routinely, NPs can be found in human tissue, including oral tissues [6].

Imaging techniques such as light microscopy are the most common imaging methods used by pathologists for detection of tissue anomalies. Even though NPs can be implicated in different pathological conditions, their identification is challenging due to their small size and lack of natural staining. Given that early diagnosis of diseases can improve the quality of life and save people's lives, it is crucial to better understand the relationship between NPs and the epithelium, and to develop efficient and robust imaging techniques that could detect simultaneously inflammatory markers and NPs in epithelial tissues.

The present review will focus on the interactions of silica and titanium nanoparticles with human cells, and their ability to induce immune responses and exacerbate certain pathological conditions. While previous excellent and comprehensive reviews have focused on the factors and cellular mechanisms related to the toxicity of NPs [1,14], and their effects on biological systems [14], the goal of this study is to discuss the interactions of silica and titanium nanoparticles across the continuum of oral and gastrointestinal epithelia. We will also discuss the potential use of innovative imaging techniques and machine learning tools to effectively detect NPs in soft tissue samples for diagnostic purposes.

2. Engineered nanoparticles (NPs)

The following three types of NPs are frequent nanomaterials that the public encounters in daily life.

2.1. Titanium dioxide NPs (TiO_2 NPs)

Titanium dioxide (TiO_2) has traditionally been considered as a biologically inert substance to both animals and humans. As a consequence, TiO_2 NPs are manufactured in large quantities for a wide range of applications as one of most common nanomaterials, such as the nanotechnology and biomedical products, paints, cosmetics, textiles, papers, plastics, sunscreens, and food [2,3]. Among household products, including foods and personal care products, toothpastes and chewing gums have some of the highest content of TiO_2 NPs, up to around 6 mg Ti/g (roughly 10 mg TiO_2/g toothpaste and 3 mg/g chewing gum). Popular brands like Sensodyne, Aquafresh, Colgate, Mentos, Eclipse, and Trident are among the toothpastes/chewing gums with the highest TiO_2 concentrations (for details see (Weir et al., 2012) [2]).

The use of titanium in dental materials and the enormous annual global production and growing commercial popularity of TiO_2 raise the risk of occupational and environmental exposures. Nonetheless, TiO_2 NPs are also known for their potential hazardous effects by triggering harmful responses (e.g., inflammation) in various tissues and animal models [3]. In particular, the introduction of titanium into gingival tissues can result in foreign body gingivitis (FBG), an inflammatory process involving the gingiva [7,15], which will be discussed in the sections below.

2.2. Silicon dioxide NPs (SiO_2 NPs)

SiO_2 NPs possess many unique physical-chemical characteristics; therefore, they are utilized in many aspects of everyday life and many household products. According to the Consumer Products Inventory (CPI), there are over 100 commercial products that contain SiO_2 NPs, including food, toothpastes, cosmetics, paints, electronic devices, and even drugs and dietary supplements. Due to their versatile applications, SiO_2 NPs have become the second most-highly produced nanomaterial [4]. The large-scale production and widespread application of SiO_2 NPs have increased the risk of human exposure. Many published reports confirmed that SiO_2 NPs are capable of inducing proinflammatory responses, NLRP3 inflammasome activation and oxidative stress including reactive oxygen species (ROS) production in various cells and tissues, as reviewed by Dong et al. [4] and Chen et al. [16]. The role of SiO_2 NPs in inducing inflammation in different types of epithelial cells will be discussed in the sections below.

2.3. Cerium oxide NPs (CeO_2 NPs)

Cerium, which is the first element in the lanthanide group (rare earth element family) with 4f electrons, which give cerium oxide

(CeO_2) NPs unique catalytic, magnetic and electronic properties, has attracted attention from researchers in physics, chemistry, biotechnology and materials science [17,18]. Cerium oxide is involved in a wide range of applications, including oil refining (cracking catalysts), polishing agents (for glass mirrors, plate glass, television tubes, ophthalmic lenses, precision optics, electronic wafers), sensors, semiconductors, solar cells, thin-film coatings and solid-oxide fuel cells [17–19]. CeO_2 NPs can also serve as fuel additives, three-way catalysts for automobile exhaust-gas treatments, oxidative coupling of methane and water-gas shift reactions [18,19]. Recently, CeO_2 NPs have been added in many consumer products (cigarette additives, sunscreens, or cosmetics) and as potential pharmacological agents [17,18]. CeO_2 possesses its unique properties due to its varying valence electrons that are either +3 or +4, and its large surface-area-to-volume ratio which creates oxygen defects [20,21]. Earlier studies have suggested that CeO_2 NPs can induce production of ROS [22–25] and can cause immunological responses in rats that included alveolar functional changes, lung tissue inflammation and cytotoxicity [24].

3. Pathogenic effects of NPs on oral and gut epithelia

Because NPs are commonly used as food additives and in dental materials, these particles frequently interact with oral and gut epithelia. To understand the safety of engineered NPs in food, it is important to assess the presence, dissolution, agglomeration state, and release of these materials in the nano-size range from food during human digestion. A study using an *in vitro* digestion model found that SiO_2 NPs (E551) in food additives either disappeared or were only present in low amounts in the gastric stage of digestion; however, SiO_2 NPs became bioavailable under conditions found in the gut lumen. Hence, the human intestinal epithelium is likely exposed daily to SiO_2 NPs [8]. Accordingly, the potential effects of SiO_2 NPs and other NPs on the intestinal mucosa should not be overlooked. The effects of NPs are particularly significant in individuals whose intestinal homeostasis is already disrupted, such as those with inflammatory bowel diseases. Indeed, Ogawa et al. found that the oral administration of small (10 nm) SiO_2 NPs exacerbated intestinal inflammation in a dextran-sulfate sodium (DSS) colitis model through activation of the ASC inflammasome in macrophages [26]. Strikingly, a recent study using a small intestinal epithelial cellular model has found that co-exposure to boscalid, a commonly used pesticide, and TiO_2 (E171) or SiO_2 (E551) downregulated cell junction gene expression, increasing pesticide translocation across the small intestinal epithelium [27].

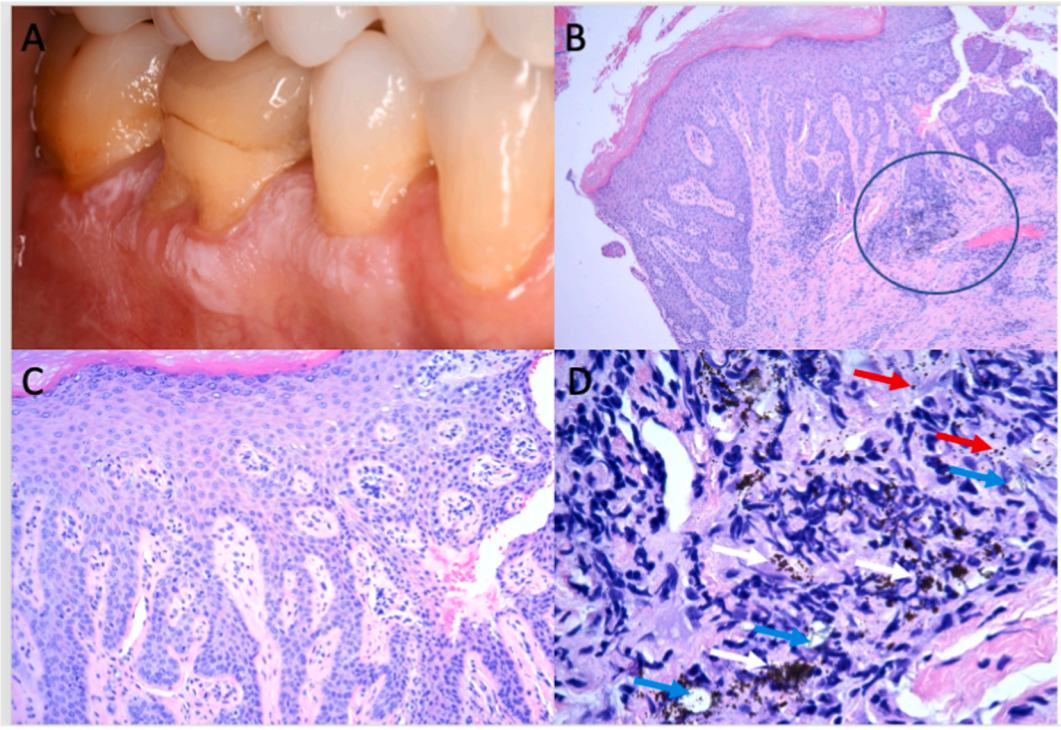

Fig. 1. (A) Foreign body gingivitis may present as a white verrucous plaque in the gingiva. (Clinical photograph is courtesy of Dr. Chainani-Wu, Mountain View, CA) (B) Microscopic image of a biopsy specimen of foreign body gingivitis showing verrucous hyperplasia of the surface squamous epithelium. Area in the circle shows the location of the foreign particles. (C) The epithelial rete ridges show a proliferative appearance and downward growth, and there is a mild increase in the nuclear to cytoplasmic ratio of individual epithelial cells. (D) High power view of the circle area reveals that the foreign material may appear as large clusters of blackish granules (white arrows), larger, colorless, crystalloid particles (blue arrows), or very fine single blackish granules (red arrows) (hematoxylin and eosin, B: 10X, C: 20X, D: 40X). (A) was donated by Dr. Chainani-Wu (Mountain View, CA, USA). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

TiO_2 particles are widely used as a food additive (E171), which is a powder composed of particles with an average grain size larger than 100 nm, but also containing a significant amount of nanosized (<100 nm) particles. TiO_2 in food has been recently declared unsafe, causing several European nations to ban E171 as food additive in early 2022. According to an updated safety assessment from the European Food Safety Authority (EFSA), E171 is no longer considered a safe food additive, particularly due to concerns regarding potential genotoxicity [28]. In addition, a large body of evidence has found that exposure to TiO_2 may cause gut barrier dysfunction and be associated with the etiology and/or exacerbation of inflammatory bowel disease. For instance, a study has reported that orally administered TiO_2 NPs worsen acute colitis in mice and, *in vitro,* TiO_2 particles induced ROS generation and increased epithelial permeability in intestinal epithelial cell monolayers. Most notably, increased levels of titanium were found in the blood of patients with active ulcerative colitis [29]. Exposure to TiO_2 has been shown to affect the morphology of intestinal epithelium as E171 caused disruption of microvilli organization in Caco-2 BBE1 cells *in vitro*. Another *in vitro* study has shown that, in addition to altering tight junctions, acute exposure of Caco-2/HT29-MTX cells to TiO_2 NPs reduces absorptive microvilli. Accordingly, both the protective and absorptive functions of the intestinal epithelium are impaired by TiO_2 exposure [28].

Importantly, TiO_2 is rated by the International Agency for Research on Cancer (IARC) as possibly carcinogenic for humans by inhalation (Group 2B). This fact, when combined with the findings that TiO_2 disturbs the intestinal barrier and induces inflammation, raises concerns about a potential role for titanium in intestinal carcinogenesis. Indeed, TiO_2 has been shown to enhance the formation of intestinal tumors in mice suffering from colitis-associated cancer. This aggravated tumor formation is associated with premalignant changes in the colonic epithelium, but also with a dramatic decrease in goblet cells leading to intestinal barrier disruption. Tumorigenesis could also be attributed to ROS production as well as DNA damage caused by the interaction between E171 and microtubules, or oxidative DNA damage in cells acutely or repeatedly exposed to E171. Finally, TiO_2 NPs have been reported to promote epithelial to mesenchymal transition in colorectal cancer cells. In conclusion, additional studies are needed to better elucidate the potential involvement of TiO_2 particles in the development of colorectal cancer [28].

Foreign body gingivitis (FBG) is a term to describe gingival inflammation associated with the iatrogenic implantation of foreign material [7]. These lesions are thought to occur when damage to the mucosal epithelium during dental or oral hygiene procedures allows the introduction of small foreign particles into the gingival tissues. Unfortunately, quite often the individual foreign particles are less than 1 μm in diameter and very easily overlooked by the pathologist who examines FBG biopsies under light microscopy (Fig. 1D) [6].

When analyzed by energy-dispersive x-ray (EDX) microanalysis, the most common elements detected in FBG lesions were Si, Ca, Al, Zn, and Ti [6,7]. Given that these elements are common constituents of dental materials and the frequency with which dental materials are brushed, rubbed, or cut adjacent to gingival tissues, most authors agree that the foreign particles in FBG are most likely of dental material origin. Abrasive agents from toothpastes, professional polishing agents, and dust of dental restorative materials, such as amalgam, are the most likely culprits [6,7].

Our group has found a significant association between the microscopic presence of foreign particles in gingival biopsies and premalignant (dysplastic) changes in the gingival epithelium (Fig. 1A) such as verrucous hyperplasia (Fig. 1B) (seen in 59% of the FBG cases analyzed) and epithelial dysplasia (Fig. 1C) (seen in 28% of the FBG cases analyzed). In parallel, our *in vitro* results demonstrated that gingival fibroblasts are activated by SiO_2 microparticles and respond with the secretion of increased levels of inflammatory cytokines [6]. These results raise serious concerns regarding the effects of persistent SiO_2-induced inflammation on potential carcinogenesis of the gingival epithelium.

In a more recent study, Sasabe et al. have found that metal NPs such as gold, silver, and palladium, commonly found in dental alloys, are internalized by human oral keratinocytes into cytoplasmic vacuoles and induce autophagic-lysosomal dysfunctions and activate the NLRP3 inflammasome [30]. Thus, there is ample data indicating potential deleterious effects of engineered particles and NPs on intestinal and oral epithelia.

Given our earlier findings of an association between premalignant epithelial changes and the presence of NPs in gingival biopsies, it is imperative to elucidate the molecular effects that these particles exert once incorporated into oral epithelial cells. In this context, it is important to understand better how NPs induce inflammation in oral cells and whether the NLRP3 inflammasome is involved in the process. With regards to diagnosis, it is critical to develop imaging tools that can lead to rapid, automated detection of FBG lesions.

4. Activation of epithelial cell inflammasome by NPs

Host cells promptly activate innate immune responses against viral, bacterial, and fungal infections, and injuries or challenges with foreign particles. One of the first innate immune responses of epithelial cells is the activation of a complex called inflammasomes [11]. We and others have demonstrated that inflammasomes are activated in several cell types including immune cells and epithelial cells [11,31–34].

Inflammasomes are multi-protein cytoplasmic complexes assembled in response to infection or cellular stress, leading to maturation and secretion of pro-inflammatory cytokines, such as IL-1β and IL-18, and/or a type of pro-inflammatory cell death called pyroptosis [35,36]. The NLRP3 inflammasome is the most studied inflammasome to date. The activation of the NLRP3 inflammasome requires two signals: (1) a pathogen-associated molecular pattern (PAMP), such as lipopolysaccharide (LPS) from Gram-negative bacteria, to prime the cells and increase the expression of molecules involved in the inflammasome platform; (2) a damage-associated molecular pattern (DAMP) – for example extracellular ATP or HMGB1 released from stressed, infected or dying cells – which induces assembly of the NLRP3 inflammasome platform for its full activation. Here we will discuss how foreign particles can be involved in the inflammasome activation in different models of study, including oral disease.

Chemically distinct NPs activate the NLRP3 inflammasome in different experimental models, such as NPs containing silica,

titanium, zinc, copper, gold, silver, palladium, and cobalt. SiO_2 NPs can induce NLRP3 inflammasome activation in human primary immune cells in a dose-dependent manner [37,38], in human umbilical vein endothelial cells (HUVEC) [39], and in lung cells [9,10]. It was demonstrated that SiO_2 NPs and TiO_2 NPs activate the NLRP3 inflammasome through a mechanism involving ATP release from the cells, and subsequent ATP, ADP and adenosine receptor signaling [38]. Interestingly, SiO_2 NPs and TiO_2 NPs induced a significant increase in expression of the purinergic receptors P2Y1, P2Y2 and A_{2A} and/or A_{2B}, while decreasing P2X7 receptor expression.

TiO_2 NPs can activate the NLRP3 inflammasome in lung cells and immune cells, exacerbating airway inflammation in mouse models [9,10]. In a separate study, TiO_2 NPs exacerbated DSS-induced colitis in a mouse model via activation of the NLRP3 inflammasome [29]. Other NPs such as zinc oxide NPs, cobalt NPs, and copper oxide NPs can also activate the NLRP3 inflammasome in different experimental models involving cells of the skin [40], hepatocytes [41], and macrophages [42], respectively.

The mechanisms and potential receptors involved in the cellular recognition of NPs are not completely understood. SiO_2 NPs and TiO_2 NPs bind to class A scavenger receptors such as SR-A1 [43,44] and MARCO [43] in human lung epithelial cells and human macrophages. However, because SR-A1 and MARCO-knockout mice and macrophages still show inflammatory responses in response to SiO_2 NPs and TiO_2 NPs, additional receptors may also be involved [43]. On the other hand, alum (aluminum adjuvants) and monosodium urate (MSU) crystals can bind directly to membrane lipid domains, and this lipid ligation can activate Syk and PI3K pathways without the need of protein cell-surface receptors [43,45,46]. More studies on the cellular recognition and intracellular mechanisms induced by NPs are needed to understand better the effects of these molecules in the pathophysiology of several inflammatory diseases.

We and others have reported the presence of NPs in cells of the human oral mucosa [6,7,30]. As stated above, a recent report demonstrated that gold, silver, and palladium NPs (which are frequently used in dental alloys) induced NLRP3 inflammasome activation in human oral cells [30]. Additionally, the epithelium obtained from patients with oral lichenoid lesions (a chronic inflammatory disease that occurs as an allergic response to dental materials) showed a robust increase in NLRP3-, ASC-, caspase-1- and IL-1β-positive keratinocytes, and higher mRNA levels of NLRP3 [30]. However, it is still unclear whether other NPs also activate the inflammasome in oral cells (Fig. 2). The studies described above highlight how NPs can be taken up by a variety of cells to induce inflammasome-dependent responses, which exacerbate several pathological conditions, including airway inflammation and gastrointestinal colitis. Future studies should evaluate the role of silica, titanium, and aluminum NPs in the activation of the inflammasome in oral cells.

Given that SiO_2 NPs and TiO_2 NPs are already known to activate the NLRP3 inflammasome, and that these two types of NPs were found in our previous study in gingival biopsies of patients with foreign body gingivitis [6], it remains to be elucidated whether NP-mediated NLRP3 inflammasome activation contributes to foreign body gingivitis. Clinically, it is important to invest in the development of automated imaging techniques that could detect inflammatory markers (such as inflammasome components and cytokines) and NPs in epithelial tissues efficiently, allowing for early diagnosis and treatment of precancerous lesions such as foreign

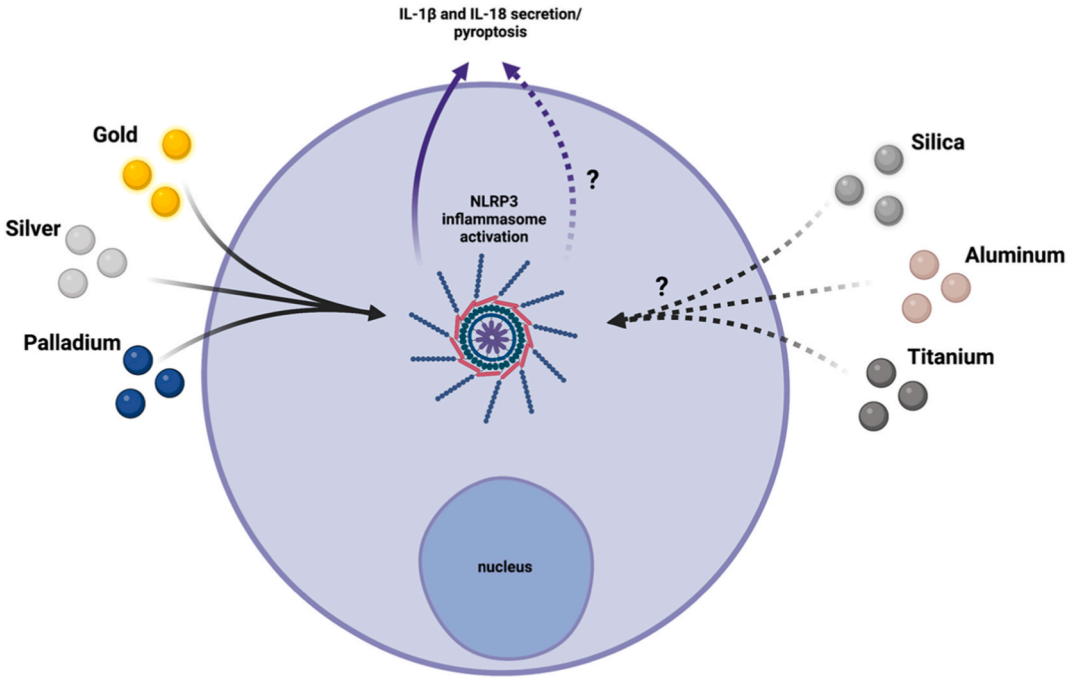

Fig. 2. Effects of different NPs on NLRP3 inflammasome activation in oral epithelial cells. On the left side of the oral cell, gold, silver and palladium NPs are shown to induce inflammasome activation in oral cells. On the right of the oral cell, we postulate that silica, aluminum and titanium NPs may be involved in NLRP3 inflammasome activation in oral cells, although this remains to be shown. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

body gingivitis.

5. Detection of NPs in epithelia

NPs can be labelled with optical fluorescence dyes and radioactive isotopes [47], allowing them to be directly detected with optical fluorescence imaging [48] or nuclear imaging techniques including positron emission tomography (PET) and single photon emission computed tomography scanners [49]. However, it is challenging to quantify and map unlabeled NPs in tissues or epithelia, especially in thick tissues, even if the NPs emit optical fluorescent photons by laser excitation (like quantum dot) [50] or phosphorescent photons by X-ray excitations (like X-ray excitable phosphors) [51,52]. The light microscope is a popular instrument commonly used in a pathology laboratory to examine sections of biopsy specimens. As we have previously shown, it is possible, while not easy, to observe microscale metal particles or clustered NPs [6]. The advantages of light microscopy include low cost, fast scan, and large field of view. The disadvantages of light microscopy are uncertainty of particle types, low contrast ratio between metal particles and soft tissues, and limited penetrating depth. Other imaging technologies, briefly reviewed below, have been used to identify NPs and/or microparticles in biopsy specimens from pathology laboratories, each with its own relative strengths and weaknesses.

In one study, synchrotron radiation X-ray fluorescence spectroscopy (XRXFS) was used to detect metal elements (such as Ca, P, Ti, Fe) in sample sections. The X-ray beam spot size is typically 50 μm in diameter, and detection at each spot takes about 1 min [53]. Fig. 3 depicts schematically this pixel-by-pixel scanning method.

In another study, Olmedo et al. investigated by light microscopy the distribution of metallic particles in the peri-implant soft tissues of failed titanium dental implants, observing macrophages loaded with metal particles. In addition, Energy-Dispersive X-ray (EDX) analysis with Scanning Electronic Microscope (SEM) identified titanium particles in macrophage samples [54]. Flatebo et al. used Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS), as a sensitive and multi-element microanalytical technique, to detect titanium particles in a sample. Specifically, the sample was first imaged by high resolution optical darkfield microscope (HR-ODM) to identify the titanium particle location. This knowledge was then used as a guidance for the LA-ICP-MS, which can only scan the sample by lines or laser beam tracks spacing about 400 μm between tracks [55]. The authors also found that SEM is not a suitable method for detection of titanium in soft tissues [55].

In the future, signal/image processing techniques will be important for particle detection and quantification, especially if imaging data can be combined with machine learning techniques that can allow automated detection of NPs and inflammatory markers in large numbers of biopsies.

Deep learning-based signal/image denoising has so far demonstrated success in a wide range of applications. Earlier deep denoising methods assumed many noisy and clean data pairs, which are referred to as supervised denoising. Since such paired samples are often unavailable in practice, especially in the clinic, supervised denoising was sometimes performed based on simulated data. In addition, weakly-supervised denoising was proposed based on unpaired noise-clean or paired noise-noise data. Furthermore, self-supervised denoising was also recently shown to be feasible based on noisy samples only. Thus, as an example, we designed the first-of-its-kind similarity-based unsupervised deep denoising approach, referred to as Noise2Sim, that works in a nonlocal and nonlinear fashion to suppress not only independent but also correlated noises [56]. Experimentally, Noise2Sim recovers intrinsic features from noisy low-dose and photon-counting computed tomography (CT) images as effectively as or better than supervised learning methods on practical datasets [56]. These improved denoising techniques will become an asset for future studies to detect NPs and markers of

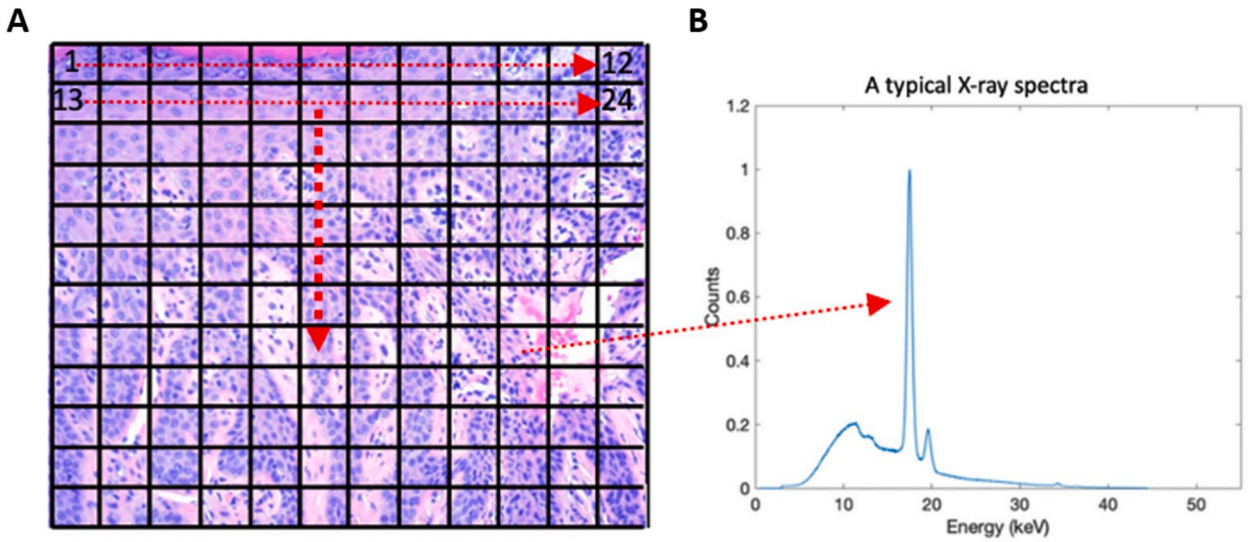

Fig. 3. (A) Pixel-by-pixel based scanning scheme with 60 s for each pixel (figure was donated by Dr. Chainani-Wu); (B) a schematic representation of a typical measured spectra from a typical pixel.

inflammation in epithelial biopsies.

6. Future perspectives

The presence of inorganic NPs or microparticles in epithelial tissues is correlated with inflammation and risk of precancerous lesions in the intestines and gingival mucosa. It is difficult and time-consuming to detect these small particles during routine light microscopic examination of clinical biopsies from patients. Imaging techniques that could detect these particles – and the associated inflammation – rapidly and automatically would aid tremendously in the diagnosis of early stages of particle-induced diseases when they are most amenable to treatment.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare no conflict of interest.

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