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Electrochemical sensing for real-time monitoring of nanoplastics – Induced toxicity: Dynamic measurements at the exposure-organism interface

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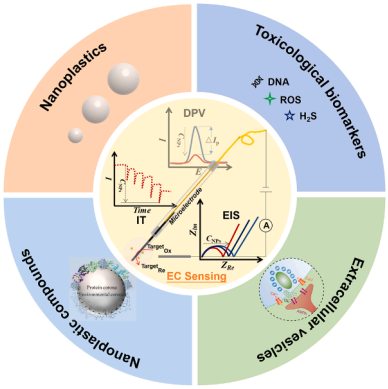
HIGHLIGHTS

- Functionalized electrode toolbox enables multiplex detection of toxicity biomarkers.
- Miniature electrochemical sensors detect nanoplastic-induced toxicity with high sensitivity.
- In situ detection supports rapid response to environmental nanoplastic exposure.
- Real-time sensing overcomes endpoint toxicity profiling limitations.

GRAPHICAL ABSTRACT



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ABSTRACT

There are many biochemical processes and biomarkers that potentially can be picked up by electrochemical sensing. By creating understanding of the techniques of measurement and by linking them to the related biochemical processes, a plethora of opportunities arise to develop real-time measurements on organisms exposed to pollutants. This ultimately can address the difference between "endpoint toxicity profiling" and "whole-process toxicity response monitoring". Application of electrochemical sensing to acquire data in real time is urgently needed because we know that the processes which chemicals and materials undergo at the abiotic-biotic interface are highly dynamic. This perspective focuses on nanoplastics (NPLs) and the interactions that occur within natural waters, in biofilm environments, and biological fluids. It has been proven that detecting NPLs is notoriously difficult, and expanding the toolbox of measuring techniques is needed. Thus, we provide a summary of electrochemical sensing methods and explain our newly developed electrochemical sensing platform

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that focuses on advanced cellular analyses by utilizing universal microelectrode modification strategies, and thereby also providing a comprehensive characterization of a wide range of ecosystem damages caused by plastic contamination (especially NPLs). The in-depth knowledge is valuable in fields like environmental and human toxicology and nanomedicine.

1. Introduction

Nanoplastics (NPLs) are defined as small plastics with sizes ≤ 1 μm and can be formed from larger plastics, which are found ubiquitously in the environment [55]. Once inside biological systems, NPLs can penetrate cellular membranes [40,62], which makes them potentially harmful for living organisms. The internal distribution of NPLs is described within the literature as a cause for cytotoxicity within cells [51] and NPLs have the possibility to cross biological barriers such as the blood-brain [2] and placenta [12] barriers. This leads to the possibility of causing malformations in chicken embryos and birth defects in animals [1,64]. NPLs are so small that specialized techniques are needed to detect and study them [55]. Furthermore, the processes at the exposure – organism interface are highly dynamic and many different conditions, like the presence of binding ligands, pH, ionic strength, and the complexity of the exposure matrix (such as freshwater, seawater, wastewater, biological fluids, and biofilms), can significantly enhance or mitigate the toxic potential of NPLs [33,60,67]. The complexity of these organic and inorganic matrices poses severe analytical challenges, as environmental samples often contain a variety of natural organic matter, dissolved salts, and colloidal particles, which can interfere with the detection and identification of NPLs. This means that NPL detection within the exposure matrix is a real challenge. This is basically the case because the environmental matrix contains a lot of carbon sources interfering with the detection of NPLs. To understand the processes by which NPLs interact with organisms and cause adverse effects, the possibility is needed not only to accurately detect these emerging contaminants, but also to gain insight into biomarker alterations at the cellular and molecular levels [4,58].

The urgency to innovate and refine analytical techniques capable of detecting and monitoring NPLs receives lots of attention. Methods such as microscopic techniques, light scattering techniques and pyrolysis gas chromatography-mass spectrometry (Py-GC/MS) are valuable for accurate and comprehensive analyses of NPLs [21,42,5,57]. Additionally through the efforts of Zhang et al. [72] to advance Raman imaging detection techniques for plastic particles in the micron size range to NPLs in very small sizes (as low as 100 nm), and to combine machine learning algorithms with these detection techniques, the challenges of identifying Raman spectra of small-size NPLs and dealing with samples from complex environments, were successfully solved. Moreover, a significant number of interesting studies have focused on the use of techniques such as fluorescence imaging towards a more comprehensive picture of the distribution and accumulation of NPLs ingested by cells, tissues and organs, zooplankton and plants [11,20,41,61]. Looking back at the series of analytical methods currently available for the investigation of NPLs, we conclude that these techniques focus mostly on the tracking of particles. Next to that, NPL-induced responses are obtained in separate measurements with the help of additional protocols (e.g., MTT assays, flow cytometry, LC-MS, ELISA, as well as a variety of active enzyme kits, etc.) [55,65,75]. It is noteworthy that all these techniques currently seriously lack the *in-situ* quantification of the dynamics of toxic responses. Fortunately, **e**lectrochemical sensing technology has grown considerably in recent years with advances in nanofabrication as well as electronic identification devices. Based on its advantages such as superior real-time responsiveness, low cost, high sensitivity without the need for labeling, and greater compatibility with miniaturized, *in-situ* monitoring, it is expected to enhance the temporal and spatial resolution and reduce the cellular damage of microelectrodes, thus advancing cellular electrochemical analyses.

In this perspective, we explore the transformative potential of electrochemical sensing for the dynamic and real-time assessment of NPLs toxicity (Fig. 1). The perspective consists of the following sections: (1) Current challenges of NPL detection in complex matrices, (2) Opportunities for electrochemical sensing to uncover dynamic toxicological responses, (3) Key strategies of Toolbox for microelectrode modification and sensing, and (4) Future outlook on integrating machine learning and real-time monitoring. Considering all of this, we are initiating the development of analytical platforms with the urgent necessity of satisfying 1) the requirements for in-situ detection of NPLs and 2) the exposure induced release of toxicological biomarker responses from organisms. Within this latter response, the heterogeneity of the NPLs exposure is inherently accounted. Hence, it will be realized that the use of this strategy can go beyond the limitations of endpoint analysis to obtain a more subtle insight into the dynamics or the so-called temporal progression of the toxic effects of NPLs. We believe that these advancements will not only shape the future of environmental and human toxicology but also the advancements made within for instance nanomedicine research in which NPLs have the potential to be used as coatings which effectively enhance or mitigate absorption of pharmaceutically active chemicals to target organs.

2. Ad/absorption and biochemical responses induced by NPLs

In natural environments, individual NPL particles often aggregate to carbon sources like organic materials, biofilms and cell secretions which form complexes [60,9]. With changes in pH, ionic stress, etc. of the exposure medium, the aggregates can reversely de-aggregate into single NPL. Meanwhile, many uncertainties exist regarding the particle nature, shape, size, and surface properties, which significantly affect toxicity [11]. Except for particularly small sizes (between 4 and 10 nm) that directly penetrate cell membranes, NPLs in the size range of 10–100 nm are predominantly taken up via pinocytosis, whereas the entry of aggregates or functionalized NPLs with a size larger than 100 nm is dependent on phagocytosis [22]. And the cellular internalization of all these NPLs begins with adhesion to the cell membrane through hydrophobic interactions and van der Waals forces [23,34,79] In addition, cell membranes possess selective permeability, and the size, shape, and surface functional groups of plastic particles can determine the contribution of the cytosolic pathway [28,34]. On the other hand, when diffusion is based on receptors such as lattice proteins and small hole proteins, receptor aggregation binding sites can mediate particle internalization. These factors also work together to determine the rate and amount of internalization of NPLs [34]. Then, when NPLs migrate into the cytoplasm, the presence of proteins therein may further cover the surface of NPLs to form a biomolecular corona [22,29]. The proteins adsorbed and bound on the surface of NPLs may act as different types of biological ligands, and the mode of transport or storage of the matching receptors in the cytosol and organelles largely determines where NPLs accumulate [60]. Thus, these mechanisms of internalization can significantly influence the bioavailability and subsequent bioconcentration of these plastic particles.

As NPLs are internalized, their bioaccumulation in the cytoplasm, organelles, etc. gradually occurs, and this gradually produces toxic responses of various extents. NPLs' exposure has been linked to the activation of detoxifying enzymes like glutathione S-transferase (GST), which reflects the organism's attempt to mitigate NPL-induced oxidative damage [37]. Thus, investigations of exposure to NPLs inducing an imbalance in the oxidative state (i.e., increase in ROS or modulation of

antioxidant gene expression or activity) have revealed the occurrence of oxidative damage to cellular macromolecules [14,35,38,39,63,73]. On the molecular level, transcriptomics or gene expression analysis has been an important approach for predicting toxicity or understanding the mechanism of action associated with NPLs exposure. As shown in the outcome of research by Parolini et al. [10] the organisms exposed to NPLs also undergo a number of gene expression changes in response to different alterations in physiological functions including oxidative stress response and energy metabolism [10,26,46]. Overall, these biochemical markers, such as cytochrome c release, further highlight the initiation of apoptosis, a programmed cell death pathway, indicating severe cellular stress and potential tissue damage [47,65]. Furthermore, it is also discovered that an organism has a concurrent process of self-protective removal of internalized NPLs. This is mainly that since NPLs, when encapsulated within lysosomes, are transported outside the cell membrane for excretion through a typical exocytosis process [45,8]. The rate of exocytosis is related to the number and size of plastic particles in the cell, mainly because smaller particles have fewer interactions with the receptor, which in turn have lower binding constants between the receptor and the particles, and are more likely to dissociate [8]. When cells excrete NPLs via exocytosis, the vesicles contain a large number of biomarkers of research value, such as proteins, lipids, nucleic acids, and small molecule metabolites [23,28,79]. These biomarkers not only reflect the vesicle origin and function, but also provide an important tool for the study of intercellular communication and biological mechanisms under the stress of NPLs. Therefore, the significance of achieving a perfect match between internal NPL concentrations and toxicological biomarkers cannot be overstated [6].

3. Electrochemical sensing for monitoring the toxic responses to NPLs

3.1. Electrochemical sensing of NPLs

Electrochemical sensing technology used within NPLs research is not explored widely, although we know about the numerous advantages that it could bring. Notably, electrochemical detection of NPLs is primarily based on the electrical properties of their surfaces and does not involve the redox reactions themselves. Therefore, the electrochemical sensors developed for the detection of this novel type of environmental contaminants mainly focus on the unique electronic properties exhibited by NPLs and other microparticles in the presence of an electric field [15]. By performing the analysis of electrochemical responses such as current and impedance presented by mixed nanoparticles in complex matrices, it is possible to perform a qualitative and quantitative assessment. Therefore, this strategy aims to explore the changes in the electrochemical properties of functional electrode surfaces and to investigate the interactions between NPLs and electrode surface recognition units. Currently, several commonly used and classical electrochemical techniques, including electrochemical impedance spectroscopy (EIS), chronoamperometry, and voltammetry, have been successfully applied for the detection of MPLs/NPLs [15,27,31,56]. The reported mechanisms of action for this effective capturing of MPLs/NPLs are mainly π-π interactions, electrostatic interactions, and hydrophobic effects, which will also guide the further development of a wide variety of functional electrodes. For example, exfoliated $Ti_3C_2T_x$ MXene microparticles presenting a multilayered structure were briefly processed by annealing in air, and then a Pt layer was deposited and modified with magnetic γ-Fe_2O_3 nanoparticles on their surfaces, finally the γ-Fe_2O_3/Pt/TiO_2 microrobot was fabricated. The challenge of rapid and excellent NPLs capture was solved, and then this novel highly conductive material was combined with EIS technology to achieve pre-enrichment and continuous low-cost electrochemical detection of NPLs[56]. In addition, a sandwich-based electrochemical recognition strategy was used to determine NPLs from the structural design of the functional electrodes. Positively charged gold nanoparticles were first coated on a gold electrode, which in turn selectively captured negatively charged NPLs with electrostatic interactions in an aqueous environment. The presentation of the electrical signal relied on the signaling molecule ferrocene to recognize the NPLs with hydrophobic interactions. This sandwich-type detection strategy is suitable for the detection of widely commercialized packages made of PS, polypropylene (PP), polyethylene (PE) and polyamide (PA) [27]. Depending on the main theme of electronegativity and hydrophobicity of NPLs, a wide variety of electrochemical sensors are expected to be developed [18,31,32]. It is worth noting that the performance of electrochemical sensors in practical assays is likely to be significantly affected by other factors such as current density and electrolyte composition. Alternatively, some detection platforms based on electrochemical techniques combined with other analytical methods are sprouting up, like electro-sorption coupled with

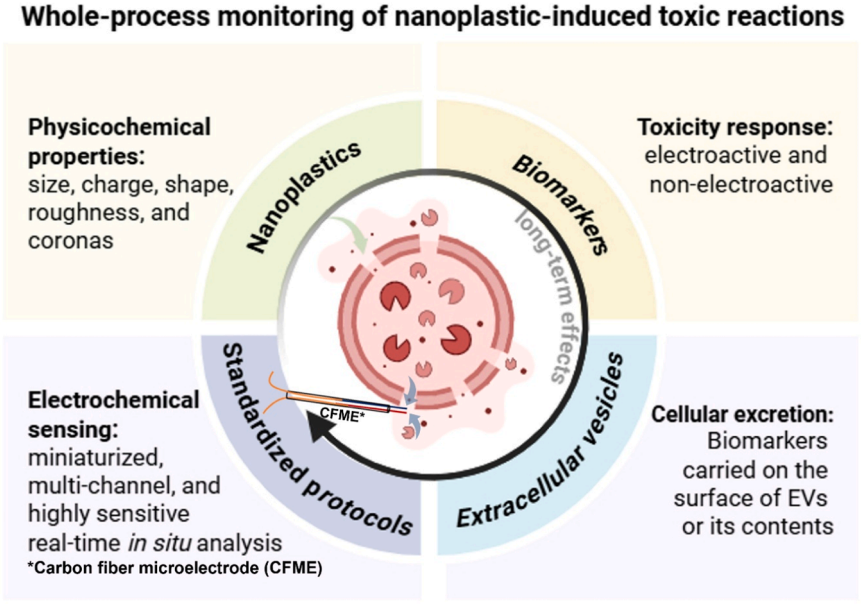

Fig. 1. Electrochemical sensing for *in-situ* monitoring of the various biomarkers and extracellular vesicles (EVs) to uncover the whole toxicity response induced by NPLs due to different physicochemical properties in organisms. Created in BioRender. Zhou, H. (2025) https://BioRender.com/undefined.

surface-enhanced Raman spectroscopy [32,66] and photoelectrochemical-electrochemical dual-mode sensing [70], which can be used to selectively enrich and detect PS NPLs of different sizes based on the differences in the electromigration behavior of PS at different sizes, and thus controlling the time of electro-sorption. Excitingly, there are initial explorations of the development of sensors with NPL identification and size-resolution capabilities based on small-sized microelectrodes, which provided an advantageous tool and practical guidance for the study of NPLs in cellular microenvironments [76]. Through an effective pretreatment process, also with electrostatic and hydrophobic interactions, these methods applied to mixed PS NPLs with different surface properties and different particle sizes can provide accurate average particle sizes, which will ensure their application in ecotoxicological evaluation [15].

3.2. Electroactive and non-electroactive biomarkers

Available evidence suggests that NPLs can induce a range of oxidative stress responses in biological systems, leading to cytotoxicity, DNA damage, and inflammation. Additionally, they may disrupt immune function, damage cell and organelle membranes, induce neurotoxicity and neurodegenerative disorders, impair energy metabolism, and even hamper reproduction [16,44]. This is mainly due to the fact that NPLs induce a biochemical process from exposure, adsorption, absorption to internalization, and have distinctive biological information at different stages (as shown in Fig. 2). Then, the influx of a large number of biomarkers as NPLs cause damage to cell membranes has allowed electrochemical sensing strategies based on a variety of miniaturized electrodes to meet the demand. For example, it is generally accepted that NPLs can trigger oxidative stress in organisms or exacerbate existing oxidative reactions. When oxidative stress occurs, cells produce a series of molecular products of oxidative stress, the most critical chemical indicators of which are ROS and reactive nitrogen species (RNS) [43,80], which cause free radical peroxidation, further exacerbating the overall cellular damage and having significant effects on physiological processes and pathologic pathways [3,75]. Most importantly, the study of this model will demonstrate the advantages and characteristics of electrochemical sensing for monitoring cytotoxic responses. Here again an experimental design in which we measure ROS levels before and after NPLs application allows us to compare ROS levels in living organisms and differentiate between the normal metabolic phase, the acute toxicity phase and the defense phase. The methodological reference and feasibility basis for the implementation of a proposed electrochemical sensing strategy to execute this study, are provided by Huang et al. [49,68,81]. They successfully realized the quantitative distinction of the major intracellular ROS/RNS by utilizing the high electrochemical resolution of SiC@Pt nanoelectrodes, and also revealed the origin of their precursors by observing and conclusively proving that during NPL exposure, the level of NO (RNS precursor) increased significantly, while the O_2^- (ROS precursor) levels remain relatively stable [49,68,81]. Even for non-electroactive substances, electrochemical sensing technology enables continuous, real-time monitoring of toxic reactions by designing specific identifications and introducing electrical signaling molecules. Recently developed electrochemical methods based on nucleotide metabolism are used for cytotoxicity detection of environmental pollutants [54,85,86]. The intensity of these electrical signals can indicate cell viability, which can further be used to assess the toxic response to exposure to NPLs. Among them, aptamer sensors are powerful representatives. Short single-stranded oligonucleotides composed of DNA or RNA are immobilized on the microelectrode surface by self-assembly or hybridization, showing specific affinity and selectivity for particular target molecules, and these customized sequences can be simply amplified by PCR [18,24]. Such aptamer sensors offer many advantages such as high selectivity, rapid synthesis, cost-effectiveness and environmental tolerance [53]. By capitalizing on these strengths, aptamers have the potential to identify environmental pollutants and biomarkers of toxicity response by providing a more efficient, affordable, and trustworthy tool [50]. In addition, this robust customizability is even more conducive to the precise capture of non-electrically active markers of biomolecules (shown in Fig. 2). Besides that, there are many successful precedents available [18]. Although they were not designed to evaluate the hazardous response to exposure to NPLs, they will all offer chances for the suggested electrochemical analysis platform since they include a detailed explanation of the characteristics of biomarkers and the creation of functioning electrodes.

3.2. Real-time monitoring of NPLs ecotoxicity responses

As the threat of NPLs contamination grows, there is an urgent need for monitoring systems that not only track the presence of NPLs, but also provide timely insight into the course of their toxic response, which offers the potential for early toxicity alerts and protective interventions. Electrochemical sensors are particularly notable for their fast response, user-friendly operation, multi-channel integration, portability and

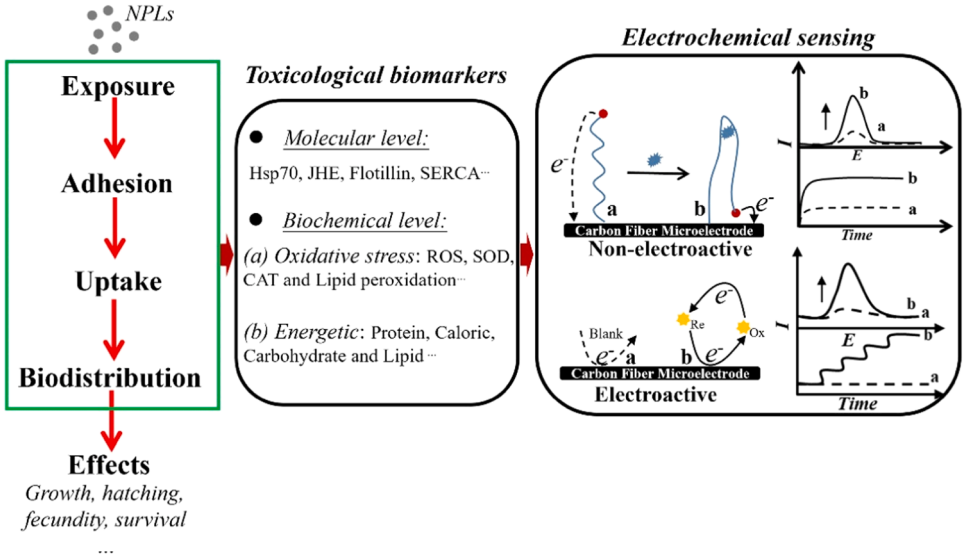

Fig. 2. Schematic illustration of the process of an organism from exposure to toxic effects occurring at NPLs. Respective toxicological biomarkers during this toxic response process are of interest, and categorization of biomarkers on the basis of electroactivity or non-electroactivity allows for the rational design of electrochemical sensors to monitor biomarkers.

affordability. This implies that they are convenient for on-site testing of various samples compared to other conventional methods, mitigating the need for prior separation of MPLs/NPLs. Combining the previous studies on electrochemical strategies for the detection of NPLs and toxicological biomarkers as well as our accumulated knowledge, we propose, as in Fig. 3, a real-time and simultaneous monitoring of the ecotoxicity response of NPLs by designing an electrochemical sensing platform. This is a multi-detection channel assay where one channel monitors the level of encroaching NPLs and the other channels monitor the type and amounts of toxicological biomarkers of the cell at that NPLs level. For instance, by synchronizing measurements of NPL levels with the detection of specific biomarkers, researchers can construct a temporal profile of the organism's response to exposure. Such data are invaluable for understanding how the accumulation of NPLs correlates with shifts in physiological state, allowing for a comprehensive evaluation of the toxicity response trajectory. More importantly, this ideal electrochemical sensing platform for toxicology studies of NPLs is not merely two or more functional microelectrodes in juxtaposition for detection. It cores in accurately and robustly matching fluctuations in NPLs concentration levels to toxicological biomarkers of expression in organisms subjected to NPLs. Additionally, the feasibility of this platform can also be confirmed from the discussion in Section 2, as the increase in various toxicological biomarkers of the extracellular environment is an inevitable trend with the exposure of organisms to NPLs as well as the increase in cell membrane permeability. The detection of NPLs is complicated by the fact that NPLs are usually present at trace levels in environmental samples and are gradually transferred to organisms. Fortunately, the incorporation of machine learning into electrochemical sensing is also gaining traction, which offers promising solutions by enhancing sensitivity, specificity, and real-time monitoring capabilities. Machine learning algorithms such as Random Forests, Support Vector Machines, and Principal Component Analysis can effectively process complex electrochemical signals, distinguish NPL responses from background noise, and enable automated calibration and signal interpretation. Deep learning models like convolutional neural networks further allow for dynamic toxicity response monitoring and predictive analysis. The combination of this analytics platform with an AI-driven analytical model could optimize sensor performance by identifying patterns in complex datasets and automating calibration processes. While challenges remain, including limited high-quality datasets and model interpretability, and the possible effects of various complex interferences on the repeatability, accuracy and signal overlap of the sensing system, AI-driven electrochemical sensing holds great potential for transitioning from traditional endpoint toxicity profiling to continuous, real-time toxicity assessment. Overall, through enabling continuous monitoring, the designed electrochemical sensors can track the progress of biochemical reactions in real time, providing key insights into the short- and long-term effects of an organism after external exposure [82–84].

4. Future technology directions

4.1. Release of toxicological information from extracellular vesicles

There is increasing evidence that bioaccumulation of NPLs in various organisms, including humans, causes health effects. It is well known that endocytosis is the main pathway for nanoparticles to enter cells, and the process can be divided into phagocytosis and pinocytosis.(Liu, L. et al., 2021) However, understanding the cellular internalization and release of M/NPLs is important to predict their cytotoxicity as suggested by [34]. After internalization, the distribution of NPL particles in the organelle is a key factor in exocytosis action, and in a typical cytosolic process, particles encapsulated in lysosomes are more readily transported to the cell membrane for excretion via an energy-dependent and independent pathway than particles in the cytoplasm. More interestingly, extracellular vesicles (EVs), a state of cellular excretion, are membrane-encapsulated nano or microscopic particles whose internal contents are not attacked by external proteases and other enzymes retaining their most pristine nature. Based on this feature, EVs become highly stable in biofluids for long periods of time, which also makes it possible to develop EVs-based assays for characterization of markers [7]. With higher sensitivity and real-time performance than traditional Western blotting, immunoblotting and enzyme-linked immunosorbent assay (ELISA) detection techniques, electrochemical methods have attracted much attention and even become the method of choice for EVs detection, most notably due to their ability to overcome the limitations of commonly used techniques that require a large number of samples to be consumed [36]. Currently, microelectrode-based electrochemical sensing is focused on the pathological evolution of tumors and neurological diseases. In the course of this research, the understanding of EVs

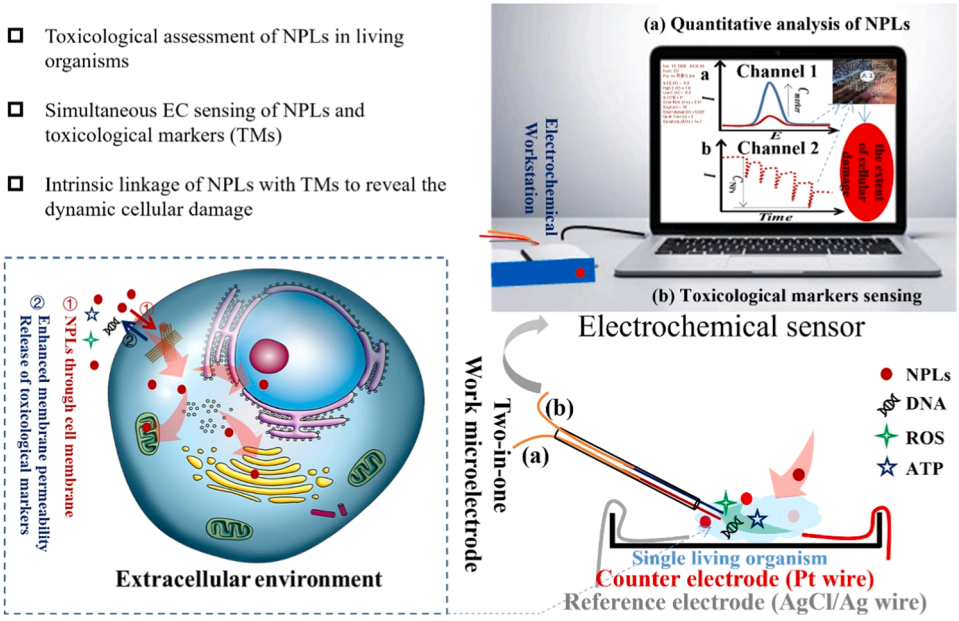

Fig. 3. Platform for dynamic and simultaneous analysis of NPLs ecotoxicity responses by multiple sensing channels.

has evolved from what was initially thought of as "cellular dust" to a rich and stable source of biomolecules (markers) containing proteins, RNA/miRNAs, and DNA, which can be studied in detail as cellular substitutes[71]. For example, tumor-associated vesicles can be used as effective alternative biomarkers to define tumor type, stage and mutation, as well as to monitor treatment response. Also, the *in-situ* quantitative analysis of neuronal vesicles at constant potential is crucial for the study of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (PD) [17,69]. However, the exploration of the contents of EVs seems to disclose more useful information. Therefore, researchers developed intracellular vesicle impact electrochemical cytometry (VIEC) in order to infer vesicle contents during extracellular secretion [30,36]. Namely, vesicles are adhered to the electrode surface at a constant potential and vesicle rupture is induced by electroporation. In turn, the vesicle contents are discharged and subsequently detected at the microelectrode, which is an effective technique capable of quantifying the storage of biomarkers in individual vesicles in living cells [13]. The application of this strategy provides a powerful method for studying the effects of physical or chemical stimuli, ions, proteins and drugs on chemical neurotransmission [77]. Therefore, electrochemical sensing based on the EVs with the ability to track real-time toxicity responses opens up opportunities for studying the long-term effects of NPLs exposure, such as chronic inflammation, genotoxicity, or carcinogenicity. Meanwhile, it is important to identify the EVs released from cells, not only to study the amount, kinetics, pathways, particle size, and number of NPLs released during cytokinesis but also to monitor the types and levels of typical biomarkers. These studies can provide critical data for understanding how NPLs affect organisms over prolonged periods.

4.2. Electrochemical sensing of NPLs in complex systems

Common electrochemical sensing of NPLs is mainly devoted to examining the analytical performance in artificial water samples. This sensing strategy in complex exposure waters with lots of carbon sources and interfering substances is still a huge challenge to tackle [59]. Therefore, further investigation of the electrical information of heterogeneous components and their role on electrochemical detection under more realistic detection conditions would be a crucial step to deal with the measurement noise due to these interfering substances and to consider further enhancement of the electrochemical detection performance of MPLs/NPLs. In addition, it is inevitable that investigations on NPL interfaces must also take into account surface changes (i.e., corona formation) due to spontaneous adsorption formation of biocomplexes, which include both protein corona and ecological molecular corona (eco-corona) formation in NPLs, consisting of proteins, lipids, complement proteins, metabolites, etc [22]. Furthermore, it has been shown that the corona formation can be controlled by a number of parameters, including the physicochemical properties of the NPLs (e.g., size, charge, shape, and roughness) as well as environmental parameters (e.g., exposure time, temperature, and flow conditions) [29]. As corona formation not only contributes to the complex nature of NPLs complexes inducing confusing toxicological responses, it also poses a great difficulty for the characterization and quantification of NPLs. As a result, capture mechanisms based on electrostatic, hydrophobic, and π-π interactions originally designed for the bare surfaces of NPLs are probably failing. In order to effectively address these dilemmas, the most straightforward approach is to polish the surface of the NPLs through strategies such as acid digestion, thereby exposing the original physicochemical properties. The implementation of this strategy actually expands the sample pre-treatment process, which has significant advantages in improving the qualitative and quantitative accuracy of NPLs, but it is not powerful enough to probe the migration of NPLs *in-situ* and to reveal the dose-relative toxicological response of NPLs in a more realistic way.

4.3. Toolbox for microelectrode modification

We see to build analytical platforms that provide simultaneous measurements on response and detection in a single electrochemical technique, which is urgent and can both reveal the levels of NPLs and record the detailed processes underlying toxicologic responses of organisms following exposure to NPLs. Nevertheless, the most critical factor in realizing all of the above-mentioned vision lies in the development of high-performance functional microelectrodes. Confronted with complex and diverse detection objectives, identifying commonalities and characteristics through classification scrutiny of targets is the most effective to realize high selectivity and high sensitivity detection. Further, more emphasis is placed on the design, synthesis, and screening of functional materials with high electrocatalytic activity for electroactive biomarkers, and in order to ensure the long-term stability of the microelectrodes, professional materials, such as hydrogels, which are resistant to biofouling, should be introduced into the system as well. However, more targeted strategies are expected to emerge for biomarkers that require multi-procedure detection. Due to limitations in the purification of EVs and the lack of knowledge of specific biomarkers for different subtypes of EVs, this will inevitably be confounded by other populations of EVs and components of the cellular microenvironment [19]. Analyses of the contents and surfaces of EVs are promising for drawing precise conclusions about the cells from which they originate and the underlying pathological conditions. This is because the nature of the contents of EVs depends more importantly on the type and physiological state of their donor cells. Once EVs such as those from cells that have suffered NPL damage are released into the extracellular space, it delivers its contents to the recipient cell, which in turn triggers a functional continuum of responses. Therefore, for electrochemical detection of intracapsular and extracapsular markers (non-electroactive) of EVs various separation procedures, manipulation methods, signal amplification strategies and biorecognition components will be involved. For complex coated NPLs, Liu et al. [78]. exemplified a general approach to characterize the composition of protein coronas interacting with nanoparticles by means of a photocatalytic protein proximity labelling method. The photosensitive reagent was coupled to amino modifiers on PS nanospheres, and under light irradiation, the neighboring interacting proteome was photo-oxidized and labelled with amino alkynes, which were then used for further click enrichment and LC-MS/MS identification. This strategy revealed the intensive involvement of mitochondria-associated proteins in the formation of protein corona, which in turn revealed the existence of substantial interactions between the plastic nanoparticles and mitochondria [78]. Obviously, this would be a great opportunity for an effective strategy to get to the heart of the matter and understand the types and physicochemical properties of the stable, tightly adsorbed "hard" protein corona on the surface of NPLs, and at the same time the concept can also be derived to EVs and toxicological biomarker detection, and thus to build a corresponding dataset based on a large number of standardized assays (Fig. 4). Additionally, the work of Liu and his colleagues is also extremely inspiring. They have come up with a promising solution, making full use of systematic evolution of ligands by exponential enrichment (SELEX) in their research by screening the most suitable aptamers from DNA libraries through preliminary adsorption experiments, which led to the isolation of a set of pyrimidine-rich sequenced DNA aptamers for two of the most abundant plastic materials that polyvinyl chloride (PVC) and PS [74]. The selected aptamers selectively bind to a variety of plastic materials, showing potential for the detection of M/NPLs. More importantly, once the screened aptamers are experimentally validated, they can be amplified in large quantities and with homogeneity, which will lay the foundation for the subsequent systematic development of the corresponding sensors. Based on this approach, the toxicological study of NPLs has become more enlightened. Whether it concerns the complex corona on the surface of NPLs or the various biomarkers inside and outside the cell, rigorous comparison, screening, and targeted modifications have enabled

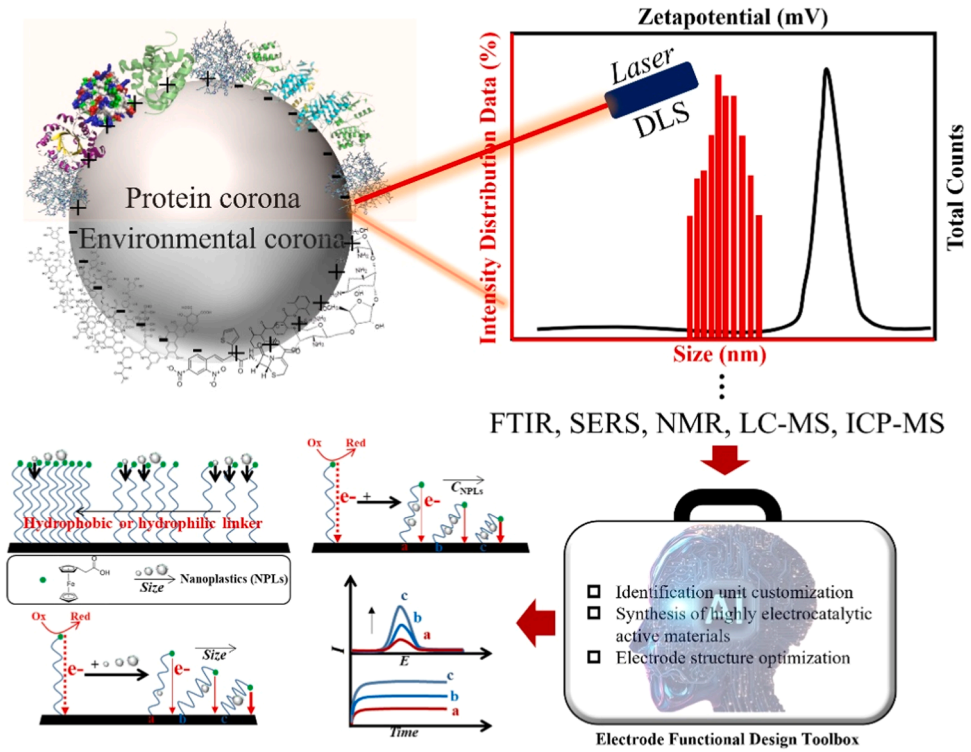

Fig. 4. Protein corona and ecological molecular corona are formed on the surface of NPLs in complex systems. Their physicochemical properties are revealed by multiple characterization tools, based on which a toolbox is built to customize the functional recognition unit for highly selective electrochemical sensing of these NPLs.

researchers to address each factor specifically. Therefore, based on this objective-oriented previous knowledge cumulation, as well as the already known properties of the detection environment, such as the blood circulatory system consisting mainly of serum albumin, immunoglobulin, transferrin, fibrinogen, etc. [25], it will be insightful to modify the microelectrodes for the construction of the proposed electrochemical sensing platform. Depending on the characteristics of the functional groups on NPLs of these organic chemicals, even protein corona, there are various methods for designing and constructing recognition units on the surface of the base electrode for highly selective detection. Initial success in warding off interfering agents has already been shown [48,52]. Consequently, it is now possible to build a data-rich, fully functional toolbox. Together with the advantages of adjustability, customization and versatility of functional electrode preparation in electrochemical sensing, this powerful toolbox can be relied upon to be fully prepared and standardized for rational application to real-world analyses. The reliable detection of the content of NPLs in such a complex and also more realistic system, combined with the accurate monitoring of the types and levels of the corresponding toxicological biomarkers at that concentration scale, will hopefully outline a more complete toxicological timeline that can help predict the acute and chronic effects of NPLs.

5. Perspectives

A range of mostly static *in vivo* and *in vitro* toxicological characterization techniques have been developed to investigate the short- and long-term effects of NPL-induced ecotoxicity. On top of that, we plea to enlarge the toolbox of techniques with real-time monitoring techniques that are able to detect NPLs-induced responses. This ultimately can address the difference between "endpoint toxicity profiling" and "whole-process toxicity response monitoring". This is urgently needed because we know that responses induced by NPLs alter with intrinsic NPL properties (e.g. size, shape, composition) as well as matrix conditions (e.g. pH, ligand presence) and are dynamic. Advances in miniaturized, multi-channel, and highly sensitive real-time in-situ analytical electrochemical sensing technologies contribute to an understanding of the dynamic interactions between NPLs and natural waters, biofilm environments, and biological fluids. It is also our future work focus will collect real-time data within laboratory experiments to address the validity, robustness and reliability of the proposed electrochemical sensing platform. The real-time monitoring based on the proposed multichannel microelectrode sensing platform can assist in deepening our understanding of the dose-response dynamics which aid ecotoxicological and human health studies to NPLs fate and effects as well as aid nanomedicine prospects where NPLs are used as medicine coatings.

CRediT authorship contribution statement

Martina G. Vijver: Writing – review & editing, Supervision. **Haifeng Zhou:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Peijnenburg Willie J. G. M.:** Writing – review & editing, Supervision.

Declaration of Competing 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.

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Data availability

Data will be made available on request.

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