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Review

Electrochemical Sensors and Biosensors for Redox Analytes Implicated in Oxidative Stress: Review

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Oxidative stress, induced by the imbalance between excessive formation oxidants formation and minimal antioxidant defenses is involved in many pathologies including age-related illnesses, cardiovascular, cancer, inflammatory, neurodegenerative and neuropsychiatric diseases. Reactive oxygen species (ROS), reactive nitrogen species (RNS), reductants, and gasotransmitters are the major biochemical species involved in oxidative stress. ROS and RNS are second messengers in signaling pathways, necessary for biochemical process; however, they are highly toxic to cells at higher levels. Reductants are part of complex antioxidants defenses system scavenge oxidants. Gasotransmitters are gaseous signaling molecules plays significant roles in many physio-pathological processes; but their excess levels are contributing to oxidative stress. The development of *in-situ* electrochemical sensors to detect the productions of these chemicals in live cells is important for the early discovery and treatment of oxidative stress. Nanomaterials incorporated electrochemical sensors are making significant process in the determination of oxidative stress related biomarkers. Particularly, two-dimensional layered materials such as graphene and metal dichalcogenides are some of the capable sensing materials developed in recent years. The oxidative stress analytes focused in this review are, ROS, RNS, reductants and gasotransmitters.

Keywords: Oxidative stress, biomarkers, second messengers, nanotechnology, nanocomposites, modified electrodes, electrochemistry, nanozymes

1. INTRODUCTION

1.1. Oxidative stress

Oxidative stress caused by the imbalance between excessive production of *oxidants* and limited *antioxidant defenses* in living organisms is linked to variety of important diseases including age-related disorders, inflammatory, cancer, cardiovascular, neurodegenerative diseases such as Parkinson's and Alzheimer's diseases, and neuropsychiatric diseases [1]. The oxidants (reactive oxygen and reactive nitrogen species, ROS and RNS) are highly reactive species, while their overproduction and accumulation in body is toxic to cellular components such as proteins, membrane lipids, and DNA leading to severe cell damage [2, 3]. In response to overproduction of oxidants to scavenge them, the production of various enzymatic and nonenzymatic antioxidant protection systems is triggered immediately in cells. Nevertheless, oxidants at certain levels are actually necessary for cellular signaling as second messengers [2, 4]. In a healthy living organism, an equilibrium status of oxidants/antioxidants reactions is maintained. When endogenous or exogenous factors able to shift the equilibrium status in favor of oxidants, it leads to oxidative stress. The concentrations of endogenous chemicals such as, oxidants, reductants and gasotransmitters at given time is directly related to the oxidative stress state of a body. Hence, real-time *in-vivo* quantification of these endogenous chemicals in living cells is of high medicinal significance. Recently, a global redox probing method is described to extract redox chemical information from oxidative stress based markers [1]. The authors used a discovery-based research method to probe serum samples for chemical information relevant to oxidative stress. Their sensor generates electrochemical as well as optical signals.

1.2 Oxidants

During cellular respiration, molecular O_2 majorly undergoes reductive conversion to water via four electrons transfer. However, if O_2 undergoes one, two and three electrons transfer reactions that will lead to the formation of superoxide anion radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\bullet}$) respectively. These derivatives are highly toxic to cells and termed as reactive oxygen species (ROS). Other examples of ROS are singlet oxygen, ozone, hypochlorous acid, and hypobromous acid. RNS are nitrogen containing reactive species such as nitric oxide (NO), nitrogen dioxide radical ($NO_2^{\bullet}$), nitrite (NO_2^-), and peroxynitrite ($ONOO^-$) [5]. Oxidants are generated by both the endogenous and extrinsic sources. Their endogenous development occurs in the mitochondria and peroxisomes as well as from a variety of cytosolic enzyme systems via normal intracellular metabolism [6]. The extrinsic sources are ultraviolet light, ionizing radiation, inflammatory cytokines, environmental toxins, chemotherapeutics and shear stress [7]. ROS such as $OH^{\bullet}$ has short lifetimes, highly reactive, and attack non-selective biological targets, while H_2O_2 and $O_2^{\bullet-}$ are relatively stable. The instability of these reactive species is a major hindrance to their detection; nevertheless, considerable progress is made in recent times in the development of *in-vivo* analytical tools, particularly, for H_2O_2 and $O_2^{\bullet-}$ [8].

1.3 Antioxidant defenses

Glutathione (GSH), vitamins, and enzymes such as catalase, superoxide dismutase and peroxidases are endogenously produced antioxidant defenses to scavenge oxidants. In chemical terms, the antioxidants donate electrons to oxidants in order to neutralize them, which diminish the toxicity of oxidants. Each antioxidant can neutralize thousands of oxidants. The biological system's ability to detoxify the oxidants is largely based on its ability to produce antioxidant defenses. Studies indicates quasi-steady state is maintained by a complex pattern of antioxidant defenses, as they are capable of adapting to challenging needs [3].

1.4 Gasotransmitters

Gasotransmitters are gaseous chemical signals such as nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) released by cells to mediate essential biological functions [9]. Their production is enzymatically regulated and they play substantial roles in regulating cardiovascular, neuronal and immune systems. Gasotransmitters involve in the regulation of ion channels either directly or indirectly (through second messengers) [10]. The interaction of NO, CO and H_2S with ion channel proteins can be correlated to the biological processes such as, S-nitrosylation, carboxylation, and sulfuration, respectively. Due to their small size, these gas molecules are freely permeable to membranes. Nevertheless, their presence at alleviated levels is related to a variety of pathological conditions and their role in oxidative stress, neurodegenerative disease and carcinogenesis are discovered [11]. Moya and group recently reported an important electrochemical method for the measurement of oxidative stress by simultaneous electrochemical determination of oxidized (GSSG) and reduced glutathione (GSH) in biological fluids using a nanocomposite modified electrode [12].

1.5 Live cell electrochemical sensing

Biological living cells perform variety of jobs via complex and controlled signaling pathways. They typically communicate each other using endogenously produced chemicals. For instance, ROS, RNS, and gasotransmitters are small molecules; cells use these molecules as second messengers for their communication. Thus, the *in-vivo* detection and quantification of these endogenous signaling chemicals hold huge biochemical applications. A wide variety of analytical methods including chromatography, mass spectroscopy, electron spin resonance, and chemiluminescence, are available for their detections. However, these methods are laborious, bulky, expensive, and time-consuming; in fact, many of these methods are not viable for *in-vivo* detections. Taking advantage of exceptional traits, such as being easy-to-operate, low-cost, portable, sensitive, and simple-to-fabricate, in recent decades, significant attention has been devoted to develop electrochemical sensors and biosensors for biological oxidants, reductants, and gasotransmitters [13]. Many of these signaling chemicals undergo redox reactions at electrode surface via electrocatalysis; hence, their electroanalytical sensing is feasible. In electroanalytical chemistry, unmodified electrodes encounter poor selectivity, large overpotential, less sensitivity, and lack of reproducibility. To circumvent these issues, chemically modified electrodes are introduced. Due

to their large surface-to-volume ratio, high adsorption, specific surface properties and electrocatalytic properties, nanomaterials modified electrodes emerge as promising probes in electrochemical sensors [14]. The high complexity of living systems typically demands that the sensors show high selectivity, sensitivity, precision, biocompatibility and long-term stability. With the burst in nanomaterials development over the last decade, nanomaterials incorporated analytical devices are making considerable progress in *in vivo* detections [15].

The following are the major challenges in sensing chemical targets released from live cells

- The amounts of endogenous chemicals released in cells are normally in low micromolar range, thus a sensor should exhibit high level of sensitivity relevant to the levels of biological concentration of specific target.
- The biological matrixes comprised of several electroactive compounds. How the electrode is going to capture its target of interest among the mixture of other biological species in living cells is a big challenge.
- Besides, the sensor should be stable enough to conduct the whole experiments and the results should be reproducible.

1.6 Non-enzymatic vs. Enzymatic

Enzymatic biosensors and non-enzymatic sensors are the commonly available electrocatalytic sensors for endogenous chemicals. Enzymatic biosensors can give better selectivity, but they are difficult to be control for construction of sensor, as they are vulnerable to external conditions such as temperature, pH, and humidity. The improper immobilization of enzymes cause enzyme denaturation, loss in shelf life, and poor stability. In addition, many enzymes used in such biosensors are expensive. In contrast, enzyme-free sensing methods based on nanomaterials offer robust alternatives to enzymatic biosensors and low-cost ones [16]. Several metal oxides and nanoparticles, which mimic the utilities of natural enzymes, have been developed as artificial receptors [16]. For e.g., Fe_2O_3, V_2O_5 and Prussian blue are established as peroxidase mimics. Nanoceria and nanogold are recognized as superoxide dismutase and oxidase mimics, respectively. The recent advances in the design and synthesis of nanomaterials have made considerable progress with the non-enzymatic electrochemical sensing technology and make it possible to realize electrochemical sensors with sensitivity and selectivity equal to enzymatic equivalents. The use of nanostructured materials in electrochemical sensors has many advantages including enhanced mass transport, high surface area, high sensitivity and improved signal to noise ratio. Over the past decade, graphene based nanocomposites have been extensively employed as non-enzymatic electrode materials.

2. MATERIALS

2.1 Two-dimensional layered materials

Over the past decade, graphene, two-dimensional (2D) layered nanomaterials have enjoyed widespread fame and applicability in electrochemical sensors because of its outstanding

physicochemical properties [17, 18]. The huge success of graphene has stimulated great interest in the discovery and synthesis of graphene-like layered inorganic materials such as transition metal dichalcogenides (TMDs), transition metal oxides (e.g WO_3), boron nitride (BN), graphitic carbon nitrite (g-C_3N_4), MXenes, etc [19-22]. These materials along with graphene grouped as a family of 2D layered materials, and now they become rising stars in materials science [23]. The outstanding physicochemical properties of these materials include large surface area, high electrical conductivity, high charge carrier mobility, and mechanical flexibility. Their properties of can be tuned via functionalization with other materials as well. These materials are now being actively used in electrocatalysis, electronics, optoelectronics, sensing, energy conversion and storage, and biomedicine [24]. The major preparation routes for 2D materials are micromechanical exfoliation, chemical vapour deposition, nanotubes unzipping, hydrothermal, chemical exfoliation, and electrodeposition methods [23].

2.2 Transition metal dichalcogenides

TMDs are made up of transition metals linked with chalcogens with a formula of MX_2. Here, M denotes transition metals, such as molybdenum, tungsten, and titanium, while X denotes chalcogens such as sulfur or selenium [25]. TMDs comprise a layer of metal atoms sandwiched in transition between two layers of chalcogen atoms. The atoms in these three layers are bound together by strong covalent bonds, while each sheet of three layers is linked by van der Waals interactions to its adjacent sheet. TMDs have been extensively applied in hydrogen evolution reactions (HER) [26], lithium-ion batteries [27], and Supercapacitors [28], electronic/optoelectronic devices [29] and biomedical applications [30].

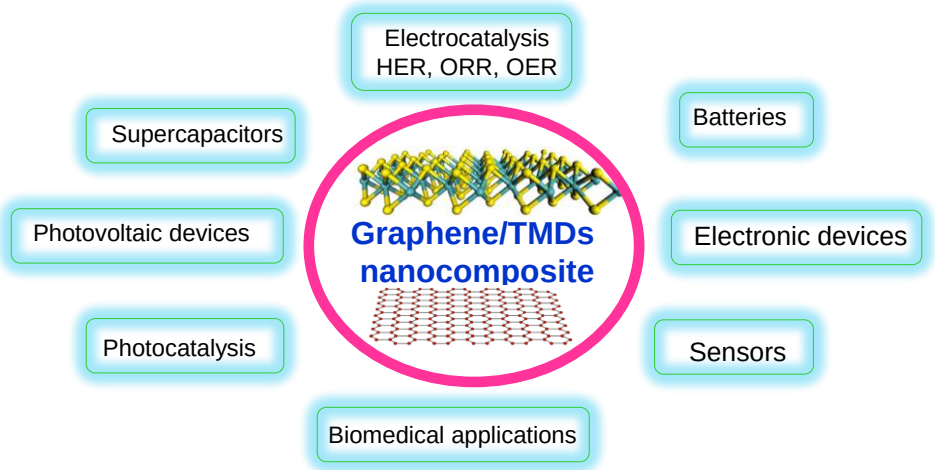

Figure 1. Applications of graphene/TMDs nanocomposites

Similar to graphene, TMDs offer large surface areas and their use as electrode materials in electrochemical sensing applications is emerging area of research [31]. The integration of TMDs with other materials such as, metal nanoparticles, metal oxide, conducting polymers, and quantum dots provide nanocomposites having enhanced sensing properties. MoS_2 is the most investigated material among other TMDs. Some of the TMDs based electrochemical sensors are MoS_2 for dopamine [32],

and H_2O_2 [33], Au nanoparticles/MoS_2 for glucose [34], WS_2/Au nanoparticles aptasensor for estradiol [35], $MoSe_2$ nanoflowers for ochratoxin A [36], and WSe_2 for microRNA [37]. Although both graphene and TMDs individually own individual authorities for various applications, their combinations as hybrid had created a new paradigm in emerging applications [38].

2.3 Nanocomposites of graphene and transition metal dichalcogenides

Nanocomposite materials will have a huge potential in future technologies but the production of optimized nanocomposites with controlled engineering of interfaces has been a challenge. When TMDs alone used as electrode material, they encounter limitations such as, poor intrinsic conductivity, and restacking. Many of the attractive properties of TMDs originate from their large specific surface area, but restacking led significant loss in their effective surface area. Functionalizing or hybridizing TMDs with carbonaceous nanomaterials is the effective way to eliminate these drawbacks and to improve their catalytic properties. Graphene is considered as the most promising carbonaceous matrix for TMDs due to its pronounced advantages, such as electronic conductivity, flexibility and chemical stability. Hybridization controls the physicochemical properties of graphene and TMDs and also creates diverse functionality between each of the components [38]. The unique 3D nanostructured graphene-TMDs composites comprising tunable density, structure, morphology and properties find broad range of applications (Figure 1) [23].

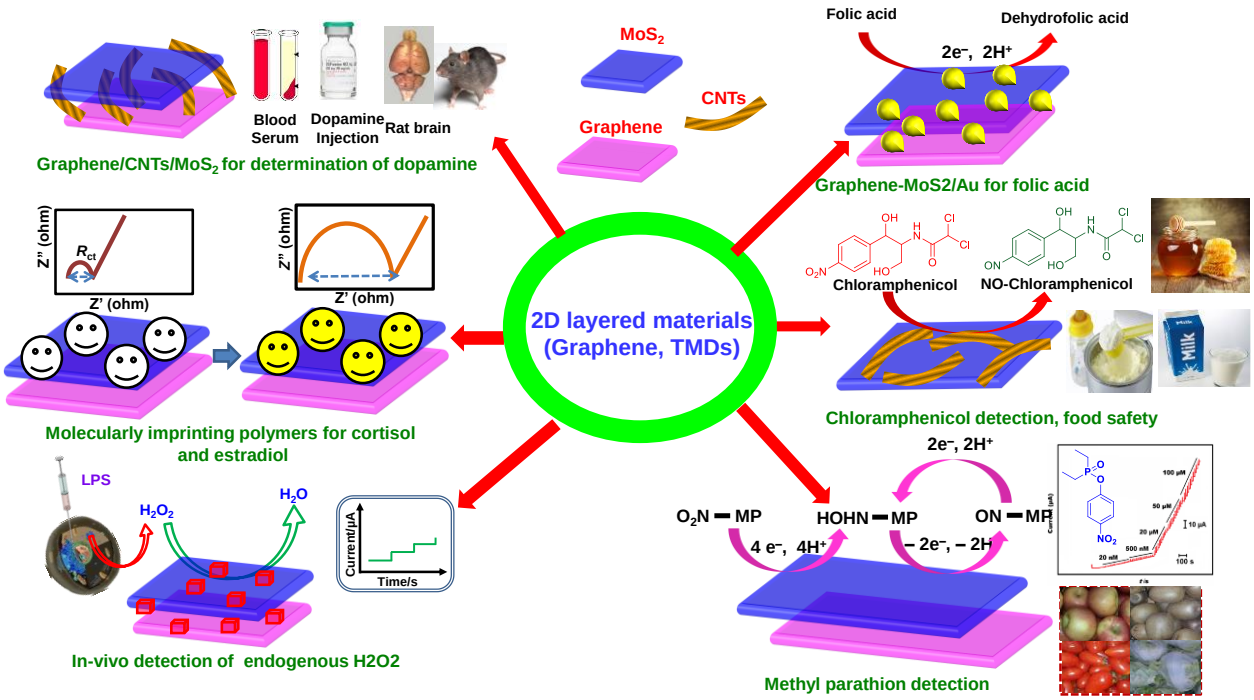

Figure 2. Nanocomposites of graphene-TMDs developed in our lab for redox analytes

Although, several preparation routes ranging from chemical vapour deposition have been reported to prepare graphene-TMDs, i*n situ* solution-phase method is the most profitable method for their bulk production. Remarkably, this method creates plethora of structural defects (vacancies, holes)

and surface functionalities (carboxyl, hydroxyl, epoxy, carboxyl, etc.) [39]. Indeed, creating defects and functionalities on materials surfaces will actually beneficial for electrocatalysis [31]. Graphene/MoS_2 nanocomposites have been extensively employed in electrochemical sensing of acetaminophen, DNA hybridization, methyl parathion, folic acid, dopamine, H_2O_2 etc. [38]. In fact, our research group had developed several graphene-TMDs nanocomposites such as, MoS_2 flowers decorated graphene-CNTs, graphene-MoS_2/molecular imprinted polydopamine, graphene-CNTs-Prussian blue cubes, MoS_2/CNTs, graphene/MoS_2 and graphene-MoS_2/Au for sensing dopamine [40], and H_2O_2 [41], estradiol and cortisol, *in-vivo* H_2O_2 profiling [8], chloramphenicol [42], methyl parathion [43], and folic acid [44] (Figure 2).

3. ELECTROCHEMICAL SENSORS FOR TARGET ANALYTES

Hhydrogen peroxide (H_2O_2), superoxide radical anion ($O_2^{\bullet-}$), peroxynitrite ($ONOO^-$), nitrite (NO_2^-), glutathione (GSH), uric acid (UA), cysteine (CySH), nitric oxide (NO) and hydrogen disulfide (H_2S) are the targeted oxidative stress related analytes in this review (Table 1).

Table 1. Current electrochemical approaches their advantages and disadvantages for endogenous oxidants, reductants and gasotransmitters

Analytes	Methods	Advantageous	Drawbacks	Ref.
H_2O_2	Enzymatic methods using enzymes peroxidase, catalase, cytochrome c, hemoglobin, myoglobin	Highly selective	vulnerable to external conditions (pH & temperature), poor stability, reproducibility and durability, enzyme denaturation, and loss in shelf life	[45]
	Enzymeless sensors	sensitive and stable	Many of the electrode designs are not focused for the real-time *in-vivo* applications	[46]
$O_2^{\bullet-}$	Cu, Zn superoxide dismutase, Mn SOD, and extracellular SOD, Cytochrome c	Highly selective	SOD is highly expensive, vulnerable to external conditions, poor stability and durability, enzyme denaturation, loss in shelf life	[47]
	Non-enzymatic sensors	durable, reliable, and selective	Limited reports, only few able to achieve real-time *in-vivo* $O_2^{\bullet-}$ detections	[48]
$ONOO^-$	Unmodified electrodes	Simple, easy and robust	Poor sensitivity, selectivity and not applicable in *in-vivo* sensing	[49]
	Modified electrodes	Sensitive, selective, and reproducible	*in-vivo* sensing applications are not studied	[50]
NO_2^-	Enzymatic methods: Nitrite Reductase, hemoglobin, Cytochrome c, myoglobin	Highly selective	vulnerable to external conditions (pH & temperature), poor stability, reproducibility and durability, enzyme denaturation, and loss in shelf life	[51]
	Modified electrodes	Sensitive, selective, stable and reproducible, fast responses	*in-vivo* sensing applications are not explored	[51]

CySH	Unmodified electrodes	Simple, easy and robust	Poor sensitivity, selectivity	[52]
	Modified electrodes	Sensitive, stable, rapid response time	In-vivo real-time sensing is not explored	[53]
GSH	Enzymatic methods: glutathione reductase, horseradish peroxidase, glutathione peroxidase and glutathione oxidase	Highly selective	vulnerable to external conditions, poor stability and durability, enzyme denaturation, and loss in shelf life	[54]
	Modified electrodes	Sensitive, selective, stable and reproducible, fast responses	*in-vivo* sensing applications are not explored	[54]
UA	Enzymatic methods: uricase	Highly selective	vulnerable to external conditions, poor stability and durability, enzyme denaturation, and loss in shelf life, no reported *in-vivo* sensing	[55]
	Unmodified electrodes	Simple, easy and robust	Poor sensitivity and selectivity, *in-vivo* sensing is not achieved	[56]
	Modified electrodes	Sensitive, stable, rapid response time	*In-vivo* living cell study is not explored	[56]
NO	Enzymatic: Peroxidase, myoglobin, Cytochrome c, hemoglobin,	Highly selective	vulnerable to external conditions, poor stability, reproducibility and durability, enzyme denaturation, and loss in shelf life	[57]
	Clark type NO sensors	Sensitive, selective and reliable	Oxygen dependence and interference	[57]
	Electro-oxidation	Sensitive, durable	High overpotential (>0.6 V), potential interference from biological active species nitrite, ascorbate, and other (typically anionic) species	[57]
	Electro-reduction	durable, less interference from biological species	oxygen interference, reduced sensitivity, and pH dependence	[58]
H_2S	Ion selective electrode (ISE), Silver (Ag/Ag_2S)	Good selectivity, inexpensive, and easy operation	Need pretreatment and alkaline condition which is poor sensor for in-vivo detection, everyday electrode reconditioning.	[59]
	Polarography	Simple, sensitive, reproducible, fast	Easy to leak liquid electrolyte solution lead to dried up the electrodes	[59]
	Modified electrode	Fast response time and good sensitivity	Poor selectivity, in-vivo H_2S sensors scarcely reported	[59]

3.1. Hydrogen peroxide

H_2O_2, a renowned ROS is formed by oxidases and peroxidases mostly in mitochondria. It is commonly used as model to study the effects of ROS in cells due to its high stability [60]. Due to its good stability over other ROS, it can diffuse out freely through membranes to reach various cellular compartments [61, 62]. H_2O_2 plays essential roles as a mediator in regulating various signaling processes

in proteins metabolism, cell apoptosis, cellular proliferation, regulating DNA damage, tyrosine phosphorylation etc. [63]. Over the past years, many graphene based nanocomposites with metal, metal oxide nanostructures, conducting polymer and metal hexacyanoferrate have been developed as electrode materials for non-enzymatic H_2O_2 sensors. Some of our reported nanomaterials are, RGO-CNTs-Pt/myoglobin nanocomposite [64], graphene-CNTs-Prussian blue cubes [8], 3D graphene oxide (GO)-cobalt oxide polyhedrons [61], MoS_2 flowers grown on graphene/carbon nanotubes [41], and graphene/Cu nanoparticles [60]. Recently, there is a great deal of interest in the design of materials for monitoring *in-vivo* produced H_2O_2 in living cells that includes polydopamine/Prussian blue-coated microelectrode (rat brain) [65], Pt/graphene–CNTs hybrid paper (macrophages live cells) [24], nitrogen doped graphene (RAW 264.7 macrophage, MCF-7) [66], Graphene quantum dots/Au electrode (human breast adenocarcinoma cellvline MCF-7) [67], nickel cobalt sulfide/cobalt sulfide nanostructured arrays [68] and MoS_2 nanoparticles (Raw 264.7 cells) [33]. Prussian blue (PB) or ferric hexacyanoferrate known is a well-known electrocatalyst for specific H_2O_2 reduction at low potentials, away from oxygen and other biological interferences. The polycrystalline structure of PB allows only smaller molecules to penetrate into its lattice while larger molecules/ions such as ascorbate, uric acid, and dopamine were not efficiently catalyzed due to their inability to interact with PB crystals. PB alone, however, suffers from low electrochemical stability and requires acidic conditions in order to get to its specificity. [46].

Graphene-CNTs/Prussian blue ternary nanocomposite was demonstrated in the real-time quantification of endogenously produced H_2O_2 (Figure 3) [8]. The composite was characterized by analytical, spectral and electrochemical methods. The nanomaterial was used as a modifier on the working electrode surface and tested for its H_2O_2 sensing ability. The resulting amperometric sensor displayed nanomolar level sensitivity with detection limit of 13 nM. Furthermore, the assay was fast, sensitive, as well as robust. The method was demonstrated in *in-vivo* sensing of H_2O_2 release from mammalian cells Raw 264.7. The cultivated cells were induced with lipopolysaccharide (LPS) to produce H_2O_2, the electrochemical signal of as-produced H_2O_2 that was detected as a amperometric signal (potential –0.05 V vs. Ag/AgCl) by the ternary composite modified electrode. The H_2O_2 released from each cell was calculated to be 16.1×10^{-14} mol. If properly tuned, the method can be applicable to track other members of ROS family in living cells.

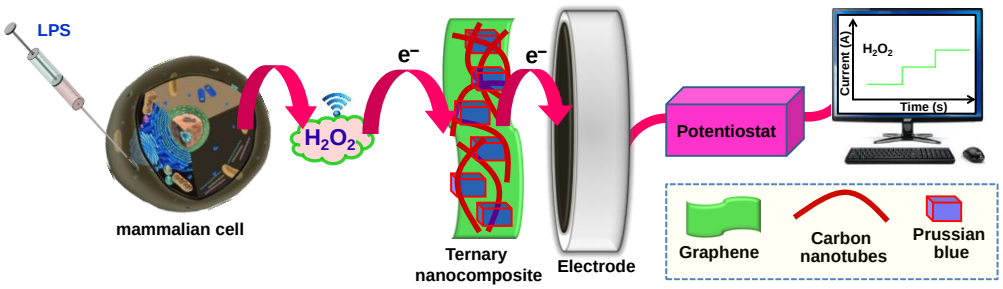

Figure 3. Real-time *in-situ* quantification of H_2S in Raw 264.7

More recently, a flexible electrode based on copper foam modified with $ZnCo_2O_4$ nanoflowers grown on spinal Co_3O_4 nanowire for real-time *in-situ* profiling of H_2O_2 secretions in live mammalian cells and biological media [69]. Two-step hydrothermal procedure was used to fabricate the modified

electrode and characterized by several characterization methods (Figure 4). The Cu foam surface provided significantly increased current densities at the solid state, which is considered beneficial for enriching the analytical sensitivity, by several order of magnitude for the same materials. In addition, the direct growth of nanostructures $ZnCo_2O_4/Co_3O_4$ on a Cu foam produced close proximity to the electrode surface, which improved stability.

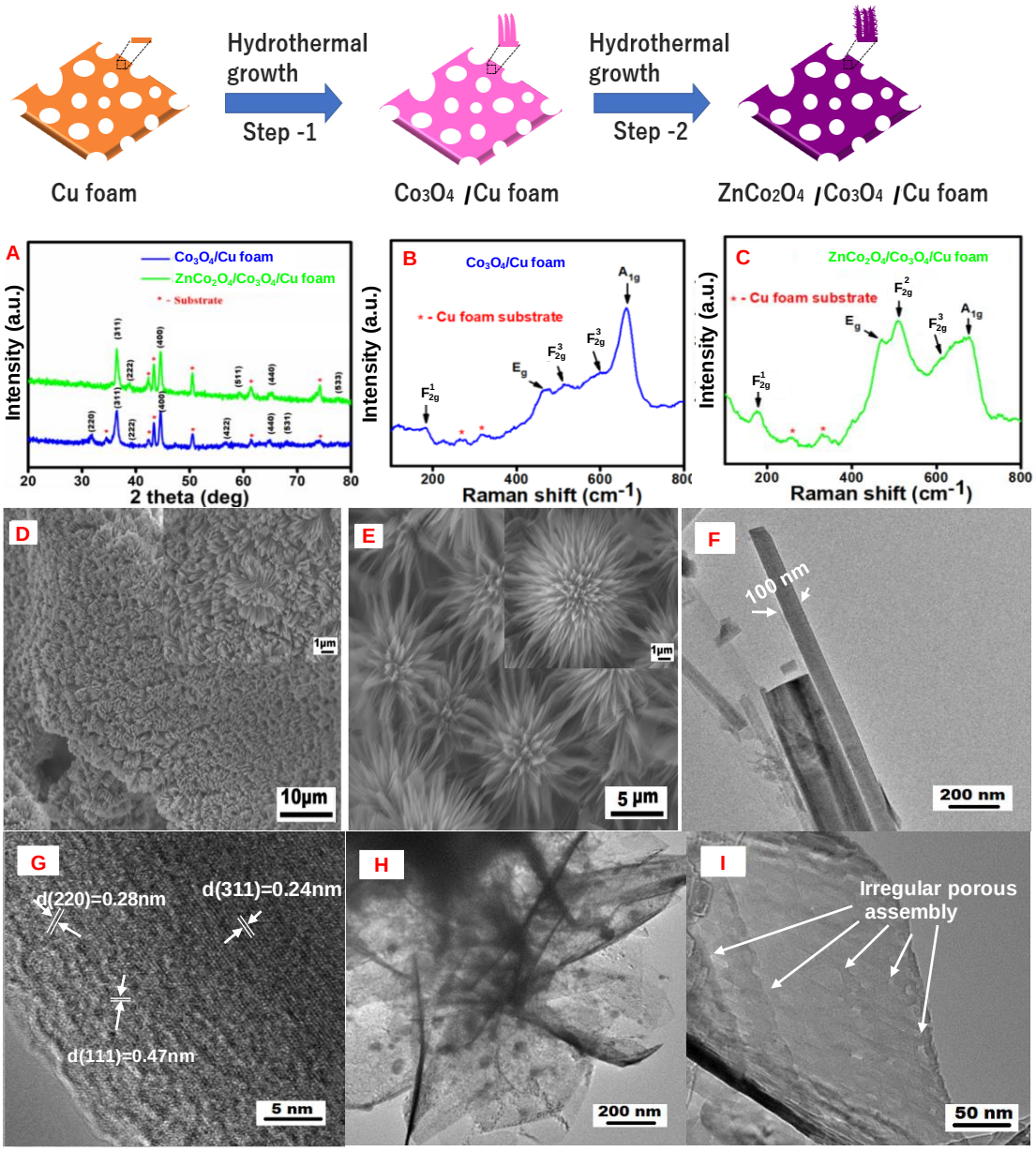

Figure 4. Hydrothermal synthesis of $ZnCo_2O_4/Co_3O_4$ on Cu foam. (A) XRD of Co_3O_4/Cu foam (blue curve) and $ZnCo_2O_4/Co_3O_4$/Cu foam (green curve). Raman spectra of Co_3O_4/ Cu foam (B) and $ZnCo_2O_4/Co_3O_4$/Cu foam (C). FESEM images of Co_3O_4/Cu foam (D) and $ZnCo_2O_4/Co_3O_4$/Cu foam (E). STEM images of Co_3O_4 nanowires (F and G) and $ZnCo_2O_4$ nanoflowers (H and I). (Reproduced with permission from Ref. [69] Copyright 2019 American Chemical Society)

3.2. Superoxide radical anion

$O_2^{\bullet-}$ plays a significant role in signaling processes as a regulatory mediator at physiological level, but causes cell damage at alleviated levels. The defense enzyme superoxide dismutase (SOD) produced to disproportionate $O_2^{\bullet-}$ to O_2 and H_2O. The *in-vivo* combination of $O_2^{\bullet-}$ and H_2O_2 produces $OH^{\bullet}$, paving way for heavy cell damages. Because, $O_2^{\bullet-}$ can inactivate NO, it is linked in endothelial dysfunction [70]. Studies indicates excessive $O_2^{\bullet-}$ generated in the circulating blood add excess harmful to patients who have traumatic brain injury, hypertension, and diabetes mellitus [71]. Methods such as electron spin resonance, spectrophotometry, chemiluminescence, chromatography, electrochemical, and fluorescence have been developed for its detection. Enzymatic electrochemical $O_2^{\bullet-}$ biosensors require the immobilization of expensive SOD onto electrodes [72]. SOD mimic electrocatalysts are attractive candidates for the development of robust $O_2^{\bullet-}$ sensors [73]. Nitrogen doped hollow mesoporous carbon spheres (L929 cells) [74], Ag nanoparticles/poly(amidoamine) dendrimers (PC12 cells) [48], Ag nanoparticles/L-cysteine functioned CNTs (PC12 cells) [75], and nanostructured cobalt phosphate nanorods (HaCat and A375 cels) have been developed for *in-vivo* sensing of $O_2^{\bullet-}$ [70]. Mugesh et al., discovered that V_2O_5 nanowires has the ability to efficiently scavenge $O_2^{\bullet-}$ by mimicking glutathione peroxidase [76]. Sadeghian et al., developed a highly sensitive $O_2^{\bullet-}$ biosensor using nanoporous Au immobilized cytochrome-c. The resulting sensor can be used for online monitoring of $O_2^{\bullet-}$ released from skeletal muscle tissue [47].

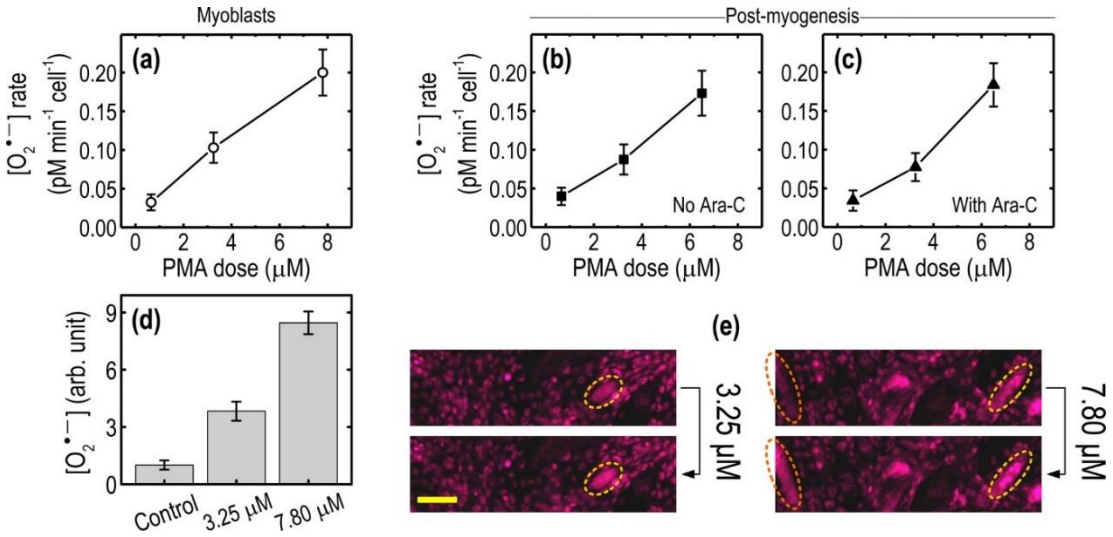

Figure 5. Generation of $O_2^{\bullet-}$ as a function of PMA dose. Electrochemically measured values using nanoporous Au/Cytochrome c based biosensor. The biosensor response for myoblasts (a), postmyogenesis cells (b), and postmyogenesis cells treated with cytosine β-d-arabinofuranoside Ara-C (antiproliferative selective DNA synthesis inhibitor) (c). (d) Normalized intensities of $O_2^{\bullet-}$ extracted from fluorescence snapshots observed 1 min after adding PMA. (e) Increase in the fluorescence basal intensity upon introduction of PMA. Fluorescent images from MitoSOX-dyed (pink) myotubes differentiated on polyester membranes were snapped 1 min after PMA was added. Encircled areas expose the relative increase in the brightness initiated by the surge of $O_2^{\bullet-}$. (Reproduced with permission from Ref. [47] Copyright 2016 American Chemical Society)

3.3. Peroxynitrite

$ONOO^-$, a powerful oxidizing and cytotoxic agent produced in cells by the recombination of NO and $O_2^{\bullet-}$ [50]. It is highly reactive. Right away after its production, $ONOO^-$ quickly reacts with biological targets, or reacts with other oxidants to produce different reactive species, thus create a major challenge for its quantification. The abnormal levels of $ONOO^-$ are linked to pathogenic effects, such as neurodegenerative, cardiovascular, diabetes, and inflammatory diseases. Numerous analytical tools such as, mass spectrometry, UV−visible spectroscopy, electron spin resonance spectroscopy, immunosensors, chemiluminescence, and fluorescence have been developed, however, many are not suitable for *in-vivo* sensing. Electrochemical methods are advantageous, some of the reported electrode materials for non-enzymatic $ONOO^-$ sensing are Hemin/RGO [77], conducting polymer−Mn ion complex [50], Mn (II), tetraaminophthalocyanine [78], and Mn porphyrins [79]. Many literature reports indicate Mn based materials specifically enhance the electron transfer reaction involved in the conversion of $ONOO^-$ to NO_2 and NO_3^- [79].

3.4. Nitrite

NO_2^- listed as a reactive nitrogen species, it is the source of non-enzymatic NO production in mammalian cells [80]. In addition, NO_2^- has been extensively used in food preservation and fertilizing agents, while its excess level in blood leads to the irreversible oxidation of hemoglobin to methemoglobin. Moreover, it can react with amines to form carcinogenic N-nitrosamine [81]. Electrochemical techniques provide rapid, highly selective and sensitive nitrite detections. Hence, several enzymatic and non-enzymatic NO_2^- sensors using wide variety of nanomaterials have been employed over the past years. However, electrochemical method for monitoring *in-vivo* NO_2^- is scarcely reported. Our group reported several graphene based nanomaterials for NO_2^- sensing; electrochemically RGO [81], GO/Mn_3O_4 microcubes [80], RGO-CNTs/myoglobin [64], and Fe nanoparticles/graphene-CNTs [82].

3.5. Glutathione and cysteine

Glutathione (GSH) and cysteine (CySH), are reductants play crucial roles in maintaining biological redox homeostasis and human pathologies [83, 84]. GSH is the most abundant cellular thiol (1–15 mM) [85]. *In vivo*, the antioxidant cellular defense mechanism is largely governed by GSH, which is oxidized continuously, generating oxidized form of GSH (GSSG), hence GSH and GSSG are constantly found in physiological fluids [12]. The ratio of GSH to oxidized GSH (GSSG) or the ratio of CySH to oxidized CySH (Cystine) can be used as indicators for monitoring oxidative stress [86]. Recently, an interesting platform for redox profiling of oxidative stress in biological fluids based on simultaneous electrochemical speciation of GSH to GSSG had been reported (Figure 6) [12]. They have used cobalt phthalocyanine (CoPc) and functionalized multiwalled carbon nanotubes modified glassy carbon electrode (CoPc/*f*-MWCNT/GCE), while differential pulse voltammetry (DPV) was used as a signal read-out. Cysteine deficiency is involved in slowed growth, hair depigmentation, edema, lethargy,

liver damage, muscle and fat loss, skin lesions, and weakness [87, 88]. Recently, a tetraamino cobalt phthalocyanine (CoTAPc) hybridized electrochemically reduced graphene oxide was reported for electrochemical determination of CySH [89].

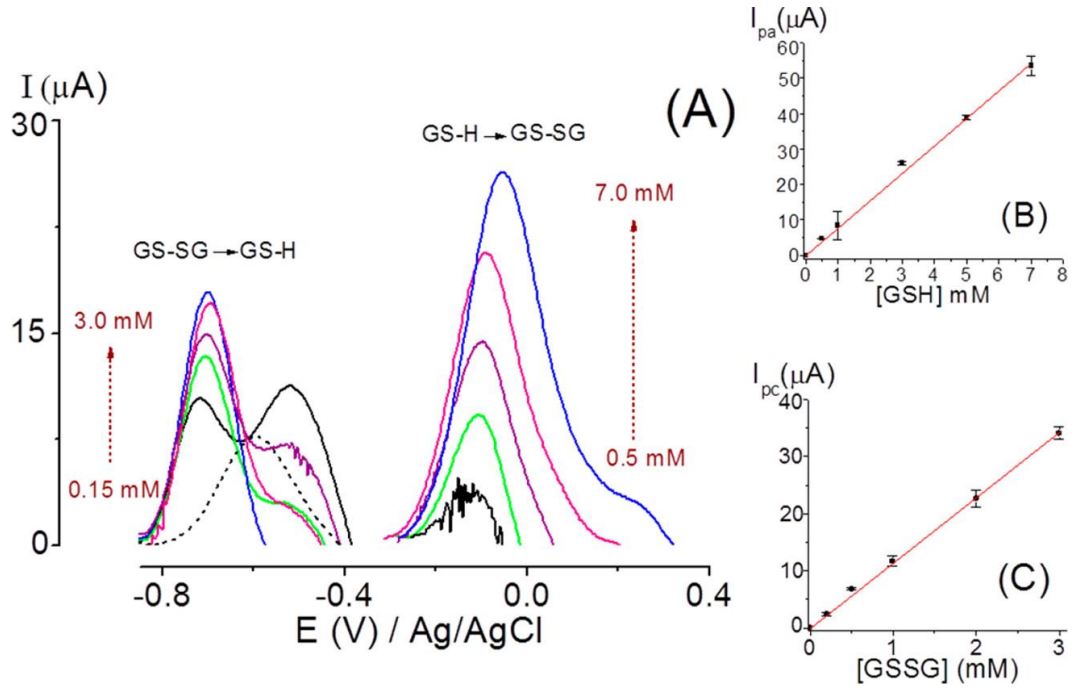

Figure 6 (A) DPV analysis at CoPc/*f*-MWCNT/GCE using various concentrations of GSH (0.5–7 mM) and GSSG (150 μM–3 mM). (B) Plot between anodic peak current (I_{pa}) and [GSH] and (C) calibration curve for GSSG: Cathodic peak current (I_{pc}) vs. [GSSG]. (Reproduced with permission from Ref. [12] Copyright 2016 American Chemical Society)

3.6. Uric acid

Uric acid is the primary end product of purine metabolism and its abnormal levels are symptoms of several diseases such as gout, hyperuricemia and Lesch-Nyan disease [90, 91]. In a healthy human, the average concentration of UA in urine is in the millimolar range (1.4–4.4 mM) and that in blood is in the micromolar (120−450 μM) range [92]. Numerous chemically modified electrodes have been reported for selective or simultaneous UA sensing. Cetyltrimethylammonium bromide–polyaniline/activated charcoal and polyaniline/Fe composites are reported from our lab as sensors for UA [90]. More recently, mounting experimental and clinical evidences indicate uric acid acts as a potent antioxidant and scavenges reactive species, thus its *in-vivo* monitoring can be a useful analytical tool for oxidative stress measurement [6, 93].

3.7. Hydrogen disulfide

H_2S plays significant roles in biological systems and hence it is classified as gasotransmitter [94]. In mammalian cells and tissues, H_2S has been biosynthesized using cystathionine β-synthase,

cystathionine γ-lyase, and 3-mercaptopyruvate sulfurtransferase. Its abnormal production heavily damages the cells and causes chronic kidney disease, liver cirrhosis, and Down's syndrome [95]. The conventional methods are not viable for *in-vivo* applications [96]. Recently fluorometric probes have gained substantial attention in H_2S real-time sensors. Nevertheless, its failure to calculate endogenous H_2S in biological samples is a common problem with most fluorescent sensors [97]. Ion selective electrodes are prevalent for H_2S detections; however, they require alkaline environment, and depends on every day electrode reconditioning [59, 98]. Recently, Huang et al., developed a facile electrochemical assay based on enzyme mimic redox substrates and GO modified electrode for H_2S detection in living cells of *E. coli* [99].

3.8. Nitric oxide (NO)

NO is most established gasotransmitter, it is identified as endothelial-derived relaxing factor (EDRF) [100]. It has vital roles in neurotransmission, cardiovascular systems and immune responses. NO is the most investigated gasotransmitter due to its vasodilation property which helps to treat heart related diseases [57]. Sensitive detections of NO release in living cells, will lead to the development of efficient diagnostic tools for early detection of several neurological diseases, and accelerate research in cancer therapies. Chemiluminescence, Griess method, electron magnetic resonance spectrometry, fluorescence, spectrophotometry, and bioassay are the common known NO methods. Electrochemical detection provides a suitable tool for direct NO monitoring in real-time with high sensitivity and ultrafast response time. Over the past years, enzymatic, Clark type electrodes, transition metal complexes, semiconductors, CNTs and graphene-based nanomaterials have been developed for NO detections, but scarcely achieve in-vivo NO sensing [57]. Particularly, Ni based metal complexes are found to exhibit the better electrocatalytic ability for NO. Recently, metal organic frameworks (MOFs) are emerging as a new class of porous rigid 3D materials composed of metal ions coordinated to organic ligands. They have unique properties such as, high surface area, high pore volume, and chemical tenability; as a result, they are extensively applied in electrochemical gas sensing applications [101].

4. CONCLUSIONS

Several nanocomposites developed for the electrochemical sensing of *in-situ* produced ROS, RNS, anti-oxidants and gasotransmitters have been reviewed. Electrochemical sensors are highly suitable candidate for in-situ analysis owing to their low-cost and simple analysis procedure. The nanocomposites modified electrodes appeared to be best candidates in providing high sensitivity, and good selectivity, and they are excellent analytical tools for monitoring endogenous redox chemicals that are involved with oxidative stress. Most of the in-situ sensors are focused on hydrogen peroxide and superoxide radical ion, very few efforts are made to develop in-situ electrochemical sensors for NO, H_2S, and uric acid. The short life span of the reactive species is one major limiting factor hindering the

production of *in-situ* electrochemical sensors. Nanocomposite of layered materials such as graphene, MoS_2 are excellent materials for oxidative stress based electrochemical sensors.

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