TMDC Nanozymes: Application Perspective

Subjects: Cell & Tissue Engineering | Immunology | Toxicology

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Applications of TMDC NZs in different fields—starting from biosensing to different treatment fields like antibacterial, anti-inflammation activity and cancer therapy—are discussed in more details.

nanozymes | transition metal dichalcogenides | biosensing | anticancer | antimicrobial | cytoprotection

1. Biosensing Applications

A biosensor is an analytical system that can detect a specific biological analyte and translate presence and/or concentration information into analytical data, such as electrical, optical, and thermal signals, using a simple, low-cost, and time-effective operation [1][2][3]. With the advent of nanotechnology, NZ biosensors, including TMDC-based, have witnessed enormous applicability in biomedical domain, particularly diagnostics, due to their intrinsic enzymatic capabilities [1]. To date, TMDC NZs have been used to detect a variety of biochemical analytes, including tiny biomolecules (such as glucose, cholesterol, glutathione (GSH), and cysteine) as well as macromolecules (e.g., proteins).

TMDC NZ-based biosensing strategies primarily take advantage of their POD-like activity, in which they can oxidize chromogenic substrates (such as TMB, ABTS, and OPD) in the presence of H_2O_2 to produce colored products that can be measured colorimetrically [4][5][6]. This NZ-based H_2O_2 biosensing is frequently coupled with analyte-specific oxidases such as glucose oxidase (GOx), cholesterol oxidase (ChOx), xanthine oxidase (XOx), and uricase to detect glucose, cholesterol, xanthine, and uric acid, respectively, in biological samples. First, a specific oxidase enzyme metabolizes the bioanalyte in the presence of oxygen to produce a specific acidic product and H_2O_2 as a byproduct. This H_2O_2 is further sensed colorimetrically by NZs as mentioned above. Notably, within the linear detection range, the intensity of color correlates directly with the amount of bioanalyte present in the samples. The GOx/WS_2 biosensor system, for example, was used to detect glucose with a linear range of 5–300 μM and a detection limit of 2.9 μM [7]. Similarly, cholesterol was successfully detected at concentrations as low as 15 μM using a ChOx/Au nanoparticle-laden MoS_2 nanoribbon system [8], whereas uricase/MoS_2 nanoflakes sensor could detect uric acid within a range of 0.5–100 μM in human serum samples [9].

On the contrary, the detection regimes for cysteine and glutathione (GSH) differ substantially. The ability of these materials to prevent oxidation of colorimetric substrates or revert the oxidized colored product (produced via POD-/OD-like activity of NZs) to its pristine unoxidized form is the basis for their sensing [10]. The color intensity of

the reaction mix is inversely proportional to the amount of cysteine or GSH present. Previously, WS_2 nanomaterial with POD-like activity was used to estimate GSH levels as low as 0.061 nM and a linear detection range of 0.1–10 nM. GSH levels in human serum samples could be measured easily and without interference from other substances [10]. Similarly, cysteine was quantified using Hg^{2+} stimulated OD-like activity of MoS_2 QDs-Ag NPs in the 1–100 µM range [11].

TMDC NZs can also be used to detect biomacromolecules, such as proteins, in a simple and label-free manner. To date, protein biosensing has been approached in a variety of ways. For instance, lipase was found to prevent POD-like activity of MoS_2, allowing its detection at concentrations as low as 5 nM [12]. Other TMDC NZs-based protein detection strategies utilize nucleic acid aptamer probes due to their target (proteins or other biomolecules) selectivity, chemical stability, and ability to be synthesized in vitro [13]. ssDNA aptamer probe/MoS_2 nanosheet system was used to detect carcinoembryonic antigen (CEA). In comparison to bare MoS_2 nanosheets, the POD-like activity of aptamer/MoS_2 was ~4.3 times higher, enabling greater oxidation of TMB substrate and consequently higher color intensity. However, when the target analyte, CEA, is present, the attached aptamer probe releases from the MoS_2 nanosheet's surface and binds with the protein, showing a reduced TMB oxidation. This drop in color intensity can be measured and is inversely proportional to the CEA concentration. Using this method, CEA could be detected in a linear range of 50–1000 ng/mL with the detection limit of 50 ng/mL [14]. Aptamer-anchored MoS_2/PtCu nanocomposites with strong OD-like activity were used to detect mucin 1 positive cells with high sensitivity and selectivity. Cells such as MCF-7 and A549, which have mucin 1 overexpression, could be detected even in populations as small as 300 cells. The use of NZs with OD-like activity, as in this case, is often advantageous because it surpasses the use of cytotoxic H_2O_2, thus improving the biocompatibility and allowing the biosensor to be used in conjunction with living cells [15]. Besides, protein-specific antibodies [16] or antibody/aptamer probes [17] were also physically/chemically conjugated onto TMDC NZs to detect *Salmonella typhimurium*-specific surface proteins and human epididymis-specific protein 4 (HE4) proteins, respectively.

Table 1 summarizes some of the recent TMDC-based NZs that have been used for molecular and macromolecular biosensing so far.

Table 1. TMDC NZs for biosensing applications.

Analyte Detected	Nanozyme System	Activity	Assisting Enzyme	Detection Type	Substrate Employed	Linear Range	Detection Limit	Stability	Biological Samples	Ref.
H_2O_2	MoS_2	POD-like		Colorimetric	TMB	0.125–1.75 µM	0.08 µM		Lake water	[18]
H_2O_2	N-Doped MoS_2	POD-like		Colorimetric	TMB			6 months		[19]
H_2O_2	Au NRs-anchored MoS_2/C	POD-like		Colorimetric	TMB	10–200 µM	1.82 µM		Cancer cells	[20]
H_2O_2	MoS_2/Ppy	POD-like		Colorimetric	TMB	50–2000	45 µM			[21]

Analyte Detected	Nanozyme System	Activity	Assisting Enzyme	Detection Type	Substrate Employed	Linear Range	Detection Limit	Stability	Biological Samples	Ref.
						μM				
Glucose	MoS_2	POD-like	GOx	Colorimetric	TMB	5–150 μM	1.2 μM		Human serum	[22]
Glucose	MoS_2 QDs	POD-like	GOx	Fluorometric		10–1500 μM	5.16 μM		Fetal bovine serum	[23]
Glucose	PTCA-MoS2	POD-like	GOx	Colorimetric	TMB	20–800 μM	18.3 μM	2 months (at 4 °C)	Human serum	[24]
Glucose	MoS_2-MIL-101(Fe)	POD-like	GOx	Colorimetric	TMB	0.01−15 μM	0.01 μM	1 month	Human serum	[25]
Glucose	MoS_2@$MgFe_2O_4$	POD-like	GOx	Colorimetric	TMB, ABTS	5–200 μM	2 μM	1 month	Human serum	[26]
Glucose	Cysteine- MoS_2 NF	POD-like	GOx	Colorimetric	ABTS	50–1000 μM	33.51 μM		Human serum	[27]
Glucose	Dextran-$MoSe_2$	POD-like	GOx	Colorimetric	TMB	40–400 μM	28 μM	10 days	Human serum	[28]
Glucose	Chitosan-$MoSe_2$	POD-like	GOx	Colorimetric	TMB	5–60 μM	0.71 μM	>1 month	Human serum	[29]
Glucose	SDS–MoS_2	POD-like	GOx	Colorimetric	TMB	5–500 μM	0.57 μM		Human serum	[30]
Glucose	AuNPs@MoS_2 QD	POD-like	GOx	Colorimetric	TMB	20–400 μM	0.068 μM	12 days	Human serum, tear and saliva	[31]
Glucose	PVP-MoS_2 NPs	POD-like	GOx	Colorimetric	TMB	1000–10,000 μM	320 μM		Fetal bovine serum	[32]
Glucose	WS_2	POD-like	GOx	Colorimetric	TMB	5–300 μM	2.9 μM		Human serum	[33]
Glucose	WS_2 NS + Ag NCs	POD-like	GOx	Chemiluminescence	Sodium bicarbonate	0.03–20 μM	0.0013 μM		Human serum	[34]
Glucose	Hemin-WS_2	POD-like	GOx	Colorimetric	TMB	5–200 μM	1.5 μM		Human serum	[35]

Analyte Detected	Nanozyme System	Activity	Assisting Enzyme	Detection Type	Substrate Employed	Linear Range	Detection Limit	Stability	Biological Samples	Ref.
Glucose	WSe_2	POD-like	GOx	Colorimetric	TMB	10–60 µM	10 µM			[36]
Glucose	VS_2	POD-like	GOx	Colorimetric	TMB	5–250 µM	1.5 µM			[37]
Cholesterol	MoS_2 NS	POD-like	ChOx	Colorimetric	TMB	2–200 µM	0.76 µM		Human serum	[38]
Cholesterol	MoS_2 nanoribbons–AuNPs	POD-like	ChOx	Colorimetric	TMB	40–1000 µM	15 µM		Human serum	[39]
Cholesterol	Oxidized GSH-modified MoS_2 NSs	POD-like	ChOx	Colorimetric	TMB	5.36–800 µM	5.36 µM		Mouse serum	[40]
GSH	WS_2 NSs	POD-like		Colorimetric	TMB	0.1–10 nM	0.061 nm		Human serum	[41]
Uric acid	MoS_2 QDs	POD-like	Uricase	Colorimetric	TMB	0.5–100 µM	0.3 µM		Human serum	[42]
Xanthine	$MoSe_2$	POD-like	XOx	Colorimetric	TMB	10–320 µM	1.964 µM		Human serum	[43]
Cysteine	MoS_2 QDs-Ag NPs (stimulated by Hg (II) ion)	OD-like		Colorimetric	TMB	1–100 µM	0.82 µM	1 month	Human serum	[44]
CEA	Aptamer/MoS_2 NSs	POD-like		Colorimetric	TMB	50–1000 ng/mL	50 ng/mL		Human serum	[45]
Lipase	MoS_2 NPs	POD-like		Colorimetric	TMB	5–200 nM	4.8 nM			[46]
Mucin 1	Aptamer-MoS_2/PtCu	OD-like	NA	Colorimetric	TMB	NA	300 cells of MCF-7		MCF-7, A549, HEK293, and HepG2	[47]

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modified silk fibroin based wound dressing exerted considerable antibacterial effects on *Escherichia coli* and *Bacillus subtilis* due to their POD-like activity. The studies were conducted both in vitro and in vivo in *E. coli*-infected full-skin defect mice model in the presence of low amounts of H_2O_2 [52]. Another study used lysozyme, an enzyme capable of hydrolyzing bacterial cell wall peptidoglycan, as an exfoliating agent to generate MoS_2 nanosheets. These nanomaterials demonstrated enhanced antibacterial activity against ampicillin-resistant *E. coli* and *B. subtilis*, which was attributed synergistically to the antibacterial activity of lysozyme and the POD-like activity of MoS_2 nanosheets [53].

Another intriguing study was conducted by Niu and his colleagues, who used a combination of citraconic anhydride-modified polyethyleneimine (PEI)-MoS_2 nanosheets and a photoacid generator molecule, 2-nitrobenzaldehyde (2-NBA). When 2-NBA was exposed to 365 nm light, the pH of the solution decreased, which activated the POD-like activity of the NZs to produce ROS and impart antibacterial effects. Furthermore, the irradiation time changed the charge of the nanomaterial from negative to positive, thanks to the photoreactive characteristics of citraconic anhydride, allowing Gram selectivity for the developed antimicrobial system [54].

Multimodal therapy is usually considered to be more efficient and effective at imparting antibacterial effects. NZs were combined with photothermal and chemotherapy in a study by encapsulating WS_2 quantum dots (WS_2 QDs) and vancomycin in a thermal-sensitive liposome. The use of WS_2 QDs benefited in two ways: (i) their POD-like activity allowed the generation of ROS and (ii) their photothermal property resulted in heat generation (via 808 nm NIR laser irradiation), causing liposomal rupturing at the targeted site, resulting in a reduction in drug doses required. This anti-biofilm agent demonstrated excellent anti-biofilm activity, eradicating both *E. coli* and Mu50 (vancomycin-intermediate *Staphylococcus aureus* strain) both in vitro and in vivo [55]. Owing to POD-like activity and photothermal properties, PEG-functionalized MoS_2 nanoflowers imparted an efficient antimicrobial effect and improved wound healing rate in ampicillin-resistant *E. coli*-infected full-skin defect mice models [56]. Another study used mesoporous ruthenium nanoparticle that was loaded and capped with ascorbic acid prodrug and hyaluronic acid, respectively. Ciprofloxacin-coated MoS_2 nanosheets were further bound to the outer surface of the nanocomposite. Post-administration, hyaluronidase enzyme (produced by bacteria) would reduce the hyaluronic acid capping degradation and release of ascorbic acid and MoS_2 at the infected wound site. Ascorbic acid/MoS_2-mediated reactive radical generation, and ruthenium nanoparticles-mediated photothermal therapy, could synergistically eliminate multidrug-resistant bacterial strains in vitro. Furthermore, this therapeutic agent demonstrated promising efficacy in *S. aureus*-infected mice models (tested for biofilm dispersion inhibition) and *S. aureus* and *Pseudomonas aeruginosa* infected mice models (tested for wound healing). On the other hand, Ciprofloxacin loading did not affect the antibacterial potency of these nanocomposites [18].

2.2. Cancer Therapy

Cancer is one of the leading causes of death due to its late diagnosis and insufficient effects of currently available treatments (e.g., chemotherapy, radiation therapy, and surgical treatment) [29]. NZs, including those based on TMDC, have recently gained prominence in cancer treatment. NZ-mediated cancer therapy, like antibacterial systems, uses POD-/OD-like activities to generate ROS and cause cancer cells to die [57].

NZ-mediated cancer therapy is often limited by the lower availability of intra-tumoral H_2O_2. To address this challenge, recently, $MoSe_2$/$CoSe_2$@PEG nanosheets were synthesized. Using dissolved O_2 and photoexcited electrons, this system was able to produce H_2O_2 via a sequential single-electron transfer mechanism. Furthermore, this NZ system showed potent dual POD- and CAT-like activities, which ensured efficient generation of $^{\bullet}OH$ and O_2, respectively. $^{\bullet}OH$ caused mitochondrial damage, whereas O_2 alleviated hypoxia and served as a source of H_2O_2. The anticancer effects were amplified by the nanomaterial's excellent photothermal characteristics, as well as redox disruptions (through intracellular GSH reduction). Besides, biodegradability and urinal/fecal elimination (within two weeks post-administration) are other notable features of this therapeutic system [58].

In another study, a glucose-responsive, H_2O_2 self-supplying nano-catalytic reactor was developed by self-assembly of GOx, tirapazamine (TPZ) and chitosan on the surface of MoS_2 nanosheets. The catalytic mechanisms involved in the cascade are as follows: (i) catalysis of intra-tumoral glucose by GOx (in the presence of O_2) to produce H_2O_2 and lower the pH; (ii) utilization of H_2O_2 by POD-like activity of MoS_2 nanosheets to produce ROS—to damage the cancer cells. Meanwhile, depletion of O_2 would activate TPZ, whereas MoS_2 could utilize GSH to

disturb cellular redox balance, further amplifying the anticancer effects. This therapeutic agent demonstrated potent anticancer effects on A549 cells in vitro and A549 tumor-bearing mice models in vivo. In contrast, even at concentrations as high as 100 g/mL, no cytotoxicity was observed in normal human umbilical vein endothelial cells (HUVEC). Furthermore, under in vivo conditions, these nanomaterials did not accumulate in normal organs, but instead degraded and were cleared out of the body, indicating minimal toxicity to normal tissues [59].

Another significant challenge in the field of nanomedicine is the development of advanced theranostic platforms with both therapeutic and diagnostic capabilities. In this regard, 3D porous MoS_2 nanoflowers were synthesized, then loaded with doxorubicin and coated with PEG-PEI (conjugated with LIM Kinase 2 protein (LMP) nucleolar translocation signal peptide). LMP peptide improved the nanomaterials' nuclear targetability in cancer cells. Thus, these materials were able to specifically target the cancer cells and could exert potent anticancer effects both in vitro (4T1 cells) and in vivo (4T1 tumor bearing mice model) through pH-responsive/NIR-enhanced doxorubicin delivery into the tumor cells, NIR-induced photothermal effects along with ROS generation due to POD-like activity of MoS_2 nanoflowers. Furthermore, the excellent photoacoustic properties of these materials allowed for real-time tracking post-intravenous in the 4T1 tumor bearing mice models [60]. A smart hybrid NZ based on MoS_2-coated bipyramidal gold nanostructure was developed for anticancer therapy and two-photon bioimaging. This hybrid nanomaterial produced considerable ROS due to the POD-like activity of MoS_2, which was augmented further by irradiation with 808 nm NIR laser due to localized plasmonic effects. Such synergistic ROS generation exerted significant anticancer effects in HeLa cells, as confirmed by two-photon luminescence imaging [61].

2.3. Anti-Inflammatory Effect

Apart from the applications listed above, TMDC NZs, particularly those with CAT/SOD-like activity, have also been used as antioxidant materials to provide cytoprotective effects and treat inflammatory diseases/conditions such as osteoarthritis and neurodegeneration [62][63][64]. For example, MoS_2 nanosheets with CAT/SOD-like activity were synthesized those were able to quench and reduce the levels of free radicals like nitric oxide ($^{\bullet}NO$), $^{\bullet}OH$, and nitrogen-centered free radicals ($^{\bullet}DPPH$). Furthermore, treating H_2O_2-exposed A549 cells with these nanomaterials dramatically reduced oxidative stress [63]. Fullerene-like MoS_2 (F-MoS_2) is another interesting TMDC-NZs with CAT-/SOD-like activities under physiological settings that appropriate it for using for the non-surgical treatment of osteoarthritis. F-MoS_2 was able to catalyze $^{\bullet}O_2^-$ into H_2O_2 and then produce water and O_2. Interestingly F-MoS_2 was used to protect HUVEC cells from oxidative stress induced by H_2O_2. Besides, F-MoS_2, when coupled with hyaluronic acid (HA), could reduce the excess of ROS and prevent the depolymerization of HA in artificial synovial fluid [64]. TMDC NZ with CAT-/SOD-like activity was used to mitigate the pathology of Alzheimer's disease by targeting neuronal mitochondria with (3-carboxypropyl)triphenyl-phosphonium bromide-conjugated 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[amino(PEG)-2000]-functionalized MoS_2 QDs. When tested in vitro in murine-derived microglia BV2 cells, this nano-formulation dramatically decreased oxidative stress, downregulated pro-inflammatory cytokines, and elevated anti-inflammatory cytokines. Furthermore, in vitro (in BV2 cells) and in vivo (in an Alzheimer's disease mouse model) tests revealed that these nanomaterials were able to reduce amyloid-beta (Aβ) aggregation-mediated neurotoxicity and eliminate Aβ aggregates. These were attributed

to switching microglial polarization from pro-inflammatory M1 to anti-inflammatory M2, presenting a novel pathway to mitigate Alzheimer's disease pathology [28].

Table 2. TMDC NZs for therapeutic applications.

Applications	TMDCs Material	Activity Mimics	Targeting Molecule (if Any)	Therapeutic Mechanism	Therapeutic Mediators	Light Characteristics (if Involved)	Activity Assessed Against		In Vivo Evaluation	Ref.
							Microbial Cells	Mammalian Cells		
Disinfection and wound healing	MoS_2/rGO	POD-like, OD-like, CAT-like		ROS-mediated	H_2O_2	Xenon lamp (100 mW/cm^2)	Chloramphenicol-resistant *E. coli* and *S. aureus*		*S. aureus*-infected full-skin defect mice models	[50]
	Fe_3O_4@MoS_2-Ag	POD-like		Ag+ ion-mediated toxicity, ROS-mediated, PTT	H_2O_2, Ag^+ ions	NIR (808 nm, 1 W/cm^2)	*E. coli*			[43]
	citraconic anhydride modified PEI-MoS_2	POD-like		Disruption of surface charge, ROS-mediated	H_2O_2, 2-nitrobenzaldehyde	UV light (365 nm)	*E. coli* and *S. aureus*		*E. coli* and *S. aureus*-infected full-skin defect mice models	[54]
	WS_2 QDs-Van@lipo	POD-like, OD-like		ROS-mediated, PTT, Chemotherapy	H_2O_2, vancomycine	NIR (808 nm, 1 W/cm^2)	*E. coli* and Mu50 (vancomycin-intermediate *S. aureus* strain)		Mice models with Mu50-infected abscess	[55]
	Cu NW-supported MoS_2 NS	POD-like		ROS-mediated, PTT	H_2O_2	NIR (808 nm, 1 W/cm^2)	*E. coli* and *S. aureus*		MRSA-infected full-skin defect mice models	[36]
	N-doped MoS_2, N-doped WS_2	POD-like		ROS-mediated	H_2O_2		Ampicillin resistant *E. coli* and *B. subtilis*		Ampicillin resistant *E. coli*-infected full-skin defect mice models	[65]
	Lysozyme exfoliated MoS_2 NSs	POD-like		ROS-mediated	H_2O_2		Ampicillin-resistant *E. coli* and *B. subtilis*			[53]
	PEG-MoS_2 NFs	POD-like		ROS-mediated, Photothermal therapy (PTT)	H_2O_2	NIR (808 nm, 1 W/cm^2)	Ampicillin-resistant *E. coli* and *B. subtilis*		Ampicillin resistant *E. coli*-infected full-skin defect mice models	[56]

Applications	TMDCs Material	Activity Mimics	Targeting Molecule (if Any)	Therapeutic Mechanism	Therapeutic Mediators	Light Characteristics (if Involved)	Activity Assessed Against Microbial Cells	Activity Assessed Against Mammalian Cells	In Vivo Evaluation	Ref.
	CMSF-$MoSe_2$ NSs	POD-like		ROS-mediated	H_2O_2		*E. coli* and *B. subtilis*		*E. coli*-infected full-skin defect mice models	[52]
	Glucose responsive, TMZ-loaded chitosan-MoS_2	POD-like		ROS-mediated, GSH depletion, hypoxia induced TPZ activation	H_2O_2 and TPZ			A549 cells	A549 tumor-bearing mice models	[59]
Anticancer therapy	AuNBPs@MoS_2	POD-like		ROS-mediated, PTT	H_2O_2	NIR laser (808 nm, 2.0 W/cm^2)		HeLa cells		[61]
	LNP-PEG-PEI coated, Dox loaded MoS_2 NFs	POD-like	LNP nucleolar translocation signal peptide	ROS-mediated, CT, PTT, PDT	Dox	NIR laser (808 nm, 3.0 W/cm^2)		4T1 cells	4T1 tumor-bearing mice models	[60]
	$MoSe_2$/$CoSe_2$@PEG	POD-like, CAT-like		ROS-mediated, GSH depletion, PTT	H_2O_2	NIR laser (808 nm, 1.0 W/cm^2)		HepG2 cells	Tumor-bearing mice models	[58]
Cytoprotection	MoS_2 NS	CAT-like, SOD-like, POD-like		Scavenging oxidative stress species			*E. coli* and *S. aureus*	A549 cells		[63]
Neurodegeneration	TPP-MoS_2 QDs	CAT-like, SOD-like	TPP (mitochondrial targeting)	Scavenging oxidative stress species				BV-2 cells	Amyloid precursor protein/presenilin 1 (APP/PS1) double transgenic mice	[28]
Osteoarthritis	Fullerene-like MoS_2	CAT-like, SOD-like		Scavenging oxidative stress species				HUVECs		[64]

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