Review Article :

Biochemical and pharmacological properties of reporter systems and nanoparticles: For better tumors imaging and treatment

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Abstract

Reporter systems can analyze the biochemical and molecular processes in viable cells and organs and help imaging of cancer. That includes gene transcription activity, protein–protein interactions, sub-cellular localization and proteases activities. This helps studying the aspects of neoplastic transformation, drug development, monitoring specific cancer-related events and tracing complex pathological events (angiogenesis, apoptosis, proto-oncogene activity, oncongenes, tumor suppressor genes and tumor promoting signals). Resolution and sensitivity govern the choice of reporters. Nanoparticles have diverse uses (magnetic, catalytic, optical, thermodynamic, and electrochemical). Nanoparticles include aptamers, quantum dots, core-shell silica particles, gold nanoparticles, carbon nanotubes, liposomes, dendrimers, oligonucleotides and magnetic nanoparticles. Superparamagnetic iron oxide nanoparticles (SPIONs) have the advantages of easy visualization using Magnetic resonance imaging (MRI), easy cellular targeting, possibility of generating hyperthermia, and easy biodegradation into metabolizable iron particles. Magnetic nanoparticles can be used in chemotherapy, magnetic hyperthermia, photodynamic therapy and photothermal therapy. MRI is the most valuable noninvasive imaging techniques to overcome magnetic nanoparticles colloidal instability. In conclusion, SPIONs are among the best nanoparticles to date owing to their easy visualization using MRI, easy cellular targeting, possibility of generating hyperthermia, and easy biodegradation into metabolizable iron particles. Research regarding reporter systems and nanoparticles is quite interesting and challenging. More research efforts are needed to optimize in vivo cancer imaging and therapeutics monitoring.

Keywords:

reporter systems, nanoparticles, cancer imaging, SPIONs, aptamers, quantum dots.

Introduction

Research in biomedical imaging has benefited from important developments in electronics, information technology, and, more recently, significant developments in the creation of particles in the "nano" domain. With improved detection limits,

imaging modalities, and engineered biomarker functionality, the development of targeted contrast agents like fluorescent probes has made it possible to selectively view particular biological events and processes in both living and nonviable systems. Magnetic resonance imaging (MRI), positron emission tomography (PET), and ultrasound had revolutionized nanomedicine and therapeutics. In this review article, the author sheds light on the most medically important reporter systems and nanoparticles which carry a promise in future disease treatments particularly cancer management.

In this review, the research methodology included reviewing the relevant recent literature publications on reporter systems and nanotechnology and their related applications on cancer diagnosis and therapy. Inclusion criteria included: recent research studies, and focusing on both cancer diagnosis and treatment. Exclusion criteria includes using reporters and nanoparticles in other human diseases.

Reporter systems

It is a big hope to generate reporter mice models for proper cancer diagnosis and treatment. Non-invasive in vivo imaging techniques help tracing single molecular events. This also allows to spatio-temporally investigate the molecular events causing neoplasia.

The first reporter systems, now known as reporter gene systems, were created in the early 1980s and were based on monitoring the activity of an enzyme as a stand-in for promoter-driven transcriptional activity [1]. Analysis of a certain promoter's activity was the initial goal and use of reporter techniques (namely, the expression of a gene that is under the regulation of the specific promoter that is linked to the reporter gene). This technique enables highly sensitive imaging of particular promoter activity [2]. Two elements are normally included in a reporter system: a particular gene and regulatory complex and a particular substrate that interacts with the gene product. The reporter gene result is a protein, which can either be an enzyme or a protein [1].

Recently, imaging techniques progressed from detecting anatomical structures to dynamically analyse the molecular processes in viable organs [3]. After that, many reporter systems successfully studied reporter gene expression that could be traced using in vivo non-invasive imaging techniques to investigate many biological processes in complex living organisms. Studied biological targets include transcription of target genes, protein-protein interaction, signal transducers activation e.g. proteases, protein kinases and calcium

mobilization. Reporter mice giving those vital data may help studying the molecular modifications causing neoplastic transformation and growth for better studying of human cancers [4]. This allows a better molecular study of tumor development from normal state to metastatic diseases.

Imaging cancer cells and their environment in living organisms

In the beginning, in vivo imaging modalities studied cancer cells injected into immunodeficient mice. Many injected tumor cell types expressed reporter genes. Different radiological investigations used optical imaging, magnetic resonance imaging, positron emission tomography for imaging in vivo tumors. Reporters also include fluorescent proteins (Green fluorescent proteins) or luminescent (Luciferases) proteins [5]. Genove et al., reported also the use of protein-trapping paramagnetic compounds (as ferritin chains that promote intracellular iron accumulation) and radiotracer-binding proteins [6]. Such reporters were used for in vivo imaging. Tumor imaging usually aims at assessing mouse survival, tumor dimension and number of metastases. In addition, periodic serial imaging of tumors behaviour (subjected to different experimental treatments) in xenograft animal models is usually done. This also allows the early detection of micrometastatic secondaries and investigating the effects of given treatments. Assessing those parameters was not optimal using conventional imaging methods but improved so much after using reporter systems [1].

Biosensors of key genetic processes in cancer cells

Reporter-based biosensors can detect the following:

A. Gene transcription activity (via sensing the transcriptional factors or gene promoters).
B. Protein–protein interactions;
C. Sub-cellular localization.
D. Proteases activity.

These biosensors are available commercially for use in animal models [1, 7].

1. Reporters of target gene transcription factor activity

Transcription factors control gene transcription (RNA formation) when they bind to specific promoter region sequences. Reporter systems can detect precise transcription factors activities where related responsive elements bind to gene promoters (e.g. TATA box) responsible for gene transcription of the reporter genes. Ellwood-Yen et al., reported that the gene transcription reporters also include biosensors detecting nuclear receptors activities (as detecting receptors for oestrogen, androgen, progesterone, retinoic acid, and peroxisome

proliferators) to estimate tumor promotion [8]. Another study mentioned also that transcription reporters also detect oncogene activity (e.g. NFkB) or tumor suppressor genes (as P53) [9].

2. Reporters of cancer genes activities

A gene promoter includes a complex arrangement of responsive elements related to many alternative biological processes. The promoter activity of target cancer genes is quite vital as monitoring and controlling such activities may greatly help controlling cancer cells progression. Reporter-induced optical imaging (in a transgenic mouse model expressing green fluorescent protein (GFP) reporter gene controlled by VEGF promoter) can help monitoring and controlling tumor-directed neo-angiogenesis [10]. In addition, a reporter of propiomelanocortin promoter activity detects spontaneous tumorigenesis processes in pituitary cells [11]. Cancer cells proliferation can be monitored and subsequently controlled using in vivo imaging of telomerase promoter-dependent luciferase reporter system of the telomerase promoter activity [12]. Moreover, in prostate cancer cells, an in vivo biosensor reporting prostatic androgen receptor sensitivity was obtained by linking the activity of luciferase expression to prostate serum antigen promoter activity [13].

3. Reporters of protein–protein interactions

Target protein–protein interactions can be visualized and monitored using many different strategies. Bioluminescence resonance energy transfer or fluorescence resonance energy transfer can report protein–protein interactions [14]. Bioluminescent or fluorescent sources (donors) generate photons of a specific wavelength that reach nearby fluorophores (acceptors) to activate them to an excited state. Upon reaching the stationary state, acceptors transfer their energy by generating the photons of lower energy and wavelength that differ from the original fluorescent source. Both donor and acceptor must be brought in close proximity [15]. An example is the signal transduction cascade, including those occurring with receptor tyrosine kinases [13], G-protein coupled receptors [16], tyrosine and serine/threonine kinases [17] and small GTPases [18].

Moreover, functional complementation and reconstitution and two hybrid systems can also report protein–protein interactions [19]. Transcription factors activation can be monitored using resonance energy transfer techniques [20]. Using a single green fluorescent polypeptide with a high affinity for calcium ions, intracellular Ca2+ mobilization was monitored upon binding to produce monitorable fluorescent changes

[21]. Using a firefly luciferase or green fluorescent protein reporters, TOR (target of rapamycin) pathways were detected and reported.

4. Reporters of sub-cellular localization

That was monitored via attaching fluorescent reporter recombinant proteins to target proteins [22] or NF-kB to detect its translocation from the cytoplasm to the nucleus [23].

5. Reporters of proteases activity

Proteolytic events can be monitored and reported using recombinant reporter proteins carrying appropriate amino acids sequences targeted by specific proteases. Their intracellular activity can be detected using luciferase enzymatic activity [24]. Moreover, some specific proteases activities e.g. caspase-3 activity can be checked allowing real time assessment of the cells undergoing apoptosis [25].

The advantages of using reporter animals

- to study the aspects of neoplastic transformation in vivo
- for drug development [26].
- Reporter mice can be used for measuring the endpoints to monitor the specific cancer-related events.
- Using reporter mice, in vivo imaging can monitor complex pathological events (neo-angiogenesis, apoptosis, proto-oncogene activity, oncongenes, tumor suppressor genes and tumor promoting signals) during spontaneous tumor development [1, 27].

Side effects of reporter systems

Reporter systems and associated adjuvant chemicals may exert cytotoxic effects, and cause decreased intracellular glutathione and genotoxic effects. An example is the ToxTracker reporter system data showed comparability to conventional toxicity and oxidative stress [28].

How to choose the reporters?

Imaging modalities determine choosing a reporter applicable to the used animal model. Different properties of imaging modalities (resolution and sensitivity) often have different and complementary 3D image reconstruction and signal quantification abilities [3]. A combination of more than one reporter may be used when different imaging possibilities are needed [29].

Side effects of nanoparticles

Nanoparticles have the ability to cross specific biological barriers and harm vital organs like the kidney, liver, and brain. The danger of nanoparticles to reproduction has only recently come to light. The epithelial, placental, and blood-testis barriers—which guard reproductive tissues—may all

be breached by nanoparticles, which can then assemble in the reproductive organs. By destroying the Sertoli cells, Leydig cells, and germ cells, nanoparticles accumulation harms organs (testis, epididymis, ovary, and uterus), leading to reproductive organ dysfunction that adversely affects sperm quality, quantity, morphology, and motility or lowers the number of mature oocytes and interferes with primary and secondary follicular development. Additionally, nanoparticles have the ability to alter the quantities of hormones released, altering sexual behavior .[30]

Nanoparticles and nanotechnology may facilitate tumor imaging and targeting

Modern oncology is directed to an individual patient targeting specific tumor types using the virtue of specific cell surface antibodies and tumor markers. Nanotechnology includes designing nano-sized particles and devices at atomic, molecular and supramolecular levels, for theranostic uses (both diagnosis and treatment) for precise targeted drug delivery to specific cellular receptors for better targeting and minimal systemic side-effects sparing normal tissues and lessening the required drug doses.

Nanoparticles sizes range from 1 to 100 nm with distinct physical and chemical properties and diverse uses (magnetic, catalytic, optical, thermodynamic, and electrochemical) [31]. Nanoparticles less than 5 nm quickly exit the blood circulation. Nanoparticles less than 6 nm in size, undergo glomerular filtration and renal clearance. Nanoparticles over 8 nm, or having surface charges or hydrophobicity, are phagocytosed by the liver Kupffer cells and are cleared in the biliary system [32]. Small nanoparticles escape opsonisation by the reticulo-endothelial system and are retained in the systemic circulation. Taking enhanced permeability and retention (EPR) effect into account, the larger the nanoparticles size the longer their circulation times in the body [33]. EPR is due to producing vascular endothelial growth factor by tumors (having no effective lymphatic drainage) causing disorganized angiogenesis and formation of "leaky" blood vessels with permeable walls [34] causing retention and accumulation of nanoparticles (10–100 nm in size) at the tumor site.

In biomedical research and practice, nanoparticles have reported benefits as antimicrobial agents, imaging agents, drug delivery vehicles and others. Nanoparticles include superparamagnetic iron oxide nanoparticles (SPIONs) as Venofer® and Dexferrum® that are approved for treating anemia of chronic renal conditions. In addition, nanocrystals e.g. NanOss®, and EquivaBone® were approved as bone

substitutes (hydroxyapatite). FDA had approved polymeric nanoparticles e.g. poly lactic co-glycolic acid as an imaging as they are biocompatible, biodegradable and safe for delivery of drugs [35].

Currently used imaging nanoparticles

1. Aptamers
2. Quantum dots
3. Core-shell silica particles
4. Gold nanoparticles
5. Carbon nanotubes
6. Liposomes
7. Dendrimers
8. Oligonucleotides
9. Magnetic nanoparticles

Aptamers

Aptamers are nontoxic and non-immunogenic molecular theranostic agents (used for simultaneous imaging and therapy of cancer [36]. Aptamers are composed of short single stranded nucleic acids (DNA or RNA). Aptamers have 3D structures that can fit different biological targets. Aptamers can be used for forming oligonucleotides-based therapy e.g. antisense oligodeoxynucleotides that hinder genetic RNA formation (transcription), translation and protein formation of targeted cancer cells proteins [37]. Aptamers have the advantage of fast renal clearance rates i.e. aptamers have a relatively short time in the circulation and can be used for forming targeted radiopharmaceuticals.

Quantum dots

Quantum dots are spherical crystalline semiconductor particles (<10 nm in diameter) having about 200–1,000 atoms [38]. Quantum dots are quite small particles and can attach to cellular proteins causing energy packet that can be expressed as light emission. They have small sizes that attach to proteins able to penetrate the cell membrane. Quantum dots with MRI can show an excellent image of the tumor sites [39].

Polyethylene glycol-coated quantum dots have a longer availability in the circulation as coated quantum dots become large enough to escape the renal filtration. Unfortunately, quantum dots have minimal tissue penetration with no anatomical spatial resolution for imaging purposes [38], but their main drawback is toxicity (containing toxic heavy metal atoms e.g., cadmium, mercury, lead), the commonest being cadmium [40]. Quantum dots have the advantages of resistance to chemical modification, high quantum yield, intrinsic fluorescence emission spectra and ability to sense and release the anticancer drugs at the desired sites [41].

Lack of excretion is a catastrophic drawback facing cadmium-based quantum dots. In an interesting study, the concentration of cadmium in the kidneys and liv-

er reached 10% and 40% of the injected dose, respectively with no faecal or urinary excretion noted within the first 28 days suggesting permanent tissue binding. Quantum dots produce a better contrast picture compared to other chemical compounds. Unfortunately, although cadmium selenide is a source of excellent quantum dots that glows when exposed to UV light, cadmium toxicity is a big disadvantage [42]. Upon injecting the quantum dots in vivo, they go into the cancerous growth giving a clear and bright luminance that is better compared to chemically used organic dyes [43]. Kim et al., reported type II near infrared Quantum dots for the mapping sentinel lymph nodes in experimental animals [44].

Core-shell silica particles

Silica nanoparticles exert both bioimaging and biosensing properties and have the merits of being biocompatible, water dispersible and resistant to microbes. Upon swelling, silica has a transparent matrix (eases passage of emission light conferring photostability) that can lodge metal ions, fluorescent dyes, and drugs to attach the biomolecules [45]. Lee et al., reported using dual-mode nanoparticles (made of fabricated rhodamine dye-doped silica core with multiple magnetic nanoparticles satellites conjugated with HmenB1 antibodies) coupled with MRI and fluorescence for imaging neuroblastoma tumors [41]. Their fabricated "core satellite" structure specifically targets the cells expressing polysialic acids, a tumor marker of lung carcinoma, neuroblastoma, and Wilms tumor) where MRI imaging detected the targeted cells efficiently [46]. Moreover, targeting ligands and chemotherapeutic drug molecules can attach to mesoporous silicate for both concomitant imaging and treatment as well [47], as a simulation of "nanoclinics" (multiple function nanoparticles). Interestingly, Joshi et al., developed a handheld magnetometer that images sentinel lymph nodes in breast cancer via SPIONs injected subcutaneously [48]. Hence, there is no need for radioactive tracers or using blue dyes as lymph flow and the sentinel nodes can be visualized optically. Core-shell silica dots are made of silica (non-biodegradable). Silica dots are good alternatives to quantum dots in being more safe and producing more excellent images (multiphoton microscopy) for imaging sentinel lymph node [49].

Gold nanoparticles

Gold nanoparticles (<50 nm in size) are very versatile, biocompatible polymer-coated, non-toxic, non-biodegradable, and more flexible having different geometries e.g. nanoshells, nanorods, nanospheres, or nanocages [31]. They do many diagnostic and therapeutic applications

owing to biocompatibility, stability and easy decoration of gold nanoparticles with antibody for tumor-specific targeting [50], [51]. Gold nanoparticles are good CT contrast agent that can be coated with polyethylene glycol to prevent uptake by reticuloendothelial system organs and can be available in the blood stream for at least 4 hours without losing contrast. Even at high concentrations, gold nanoparticles are safe and can discriminate normal from hepatoma cells in rats [52]. Gold nanorods and nanocomposites were reported to be good T1 positive contrast-enhancing agents for MRI [53]. Such multifunctional nanocomposites are good candidates for both therapeutic and diagnostic features [54].

Carbon nanotubes

Carbon nanotubes are single- or multi-walled radiolabeled particles detected by PET scanning having both electrical and heat conduction properties. PEGylation of carbon nanotubes prolongs their half-life in the circulation making them escaping uptake by the reticuloendothelial system [55]. Conjugating carbon nanotubes with arginine-glycine-aspartic acid peptide maximized targeting integrin-expressing tumor cells in animal models.

Liposomes

Liposomes are self-assembling, spherical phospholipid vesicles (50–100 nm), utilized for drug delivery (of both hydrophilic and hydrophobic drugs) in oncology [31]. As prostate, adrenal, colon, breast, and lung tumors overexpress low density lipoprotein receptors, LDLR [56], gadolinium-diethylenetriaminepentaacetic acid chelate was conjugated to LDL liposomes to deliver gadolinium-diethylenetriaminepentaacetic acid to LDLR-expressing tissues e.g. human hepatoblastoma xenografts that showed significant contrast enhancement on MRI imaging 24 hours after intake. This suggests using gadolinium-diethylenetriaminepentaacetic acid-LDL as an MRI contrast agent for in vivo tumor detection [57].

Dendrimers

Dendrimers are non-immunogenic highly branched synthetic polymers (< 15 nm in size) and imaging agents [31] for imaging micro-magnetic resonance lymphangiography in both normal animals and animals bearing breast tumor xenografts [58]. Gold dendrimers attached to imaging molecules (fluorescein isothiocynate) and targeting ligands (e.g. antibodies or folic acid) maximized cancer imaging [59]. Tumors' thermal ablation via injecting nanoshell suspensions into tumors and then subjecting that to near infrared wavelengths and monitoring by MRI allows both imaging and guided therapy [60].

Oligonucleotides facilitate drug delivery.

Oligonucleotides were reported to facilitate drug delivery. 2 amino 2 deoxy glucose was conjugated to COOH modified cobalt ferrite magnetic nanoparticles to selectively kill the tumor cells as drug/gene delivery vehicle for cancer treatment [61].

Magnetic nanoparticles are promising cancer theranostics

With early cancer detection, the cure rate is greatly better helping decreasing both morbidity and mortality rates of patients. Tumor imaging helps cancer diagnosis and selecting the best clinical treatment options. Nanoparticles play vital roles in cancer imaging, diagnosis, drug delivery and treatment. Magnetic nanoparticles present in the superparamagnetic state [62] were extensively researched in cancer imaging. They have a lot of merits (table 1).

Table 1. Advantages and disadvantages of SPIONs:

Advantages of SPIONs	Disadvantages
• Monitored using MRI • Magnetic fields give contrast for MRI. • External magnetic field helps targeting the cells • Can give hyperthermia for treating cancer [63]. • No magnetism occurs if there is no magnetic fields [64, 65]. • Easily metabolized into nontoxic iron ions in vivo. • SPIONs' efficiency is not disturbed by the environment [64]	• Can cross specific biological barriers and harm vital organs as the kidney, liver, and brain. • May harm the epithelial, placental, and blood-testis barriers— • May harm the Sertoli cells, Leydig cells, and germ cells. • May harms reproductive organs (testis, epididymis, ovary, and uterus) causing dysfunction. • May affect sperm quality, quantity, morphology, and motility. • May decrease the number of mature oocytes and interferes with primary and secondary follicular development. • May alter the quantities of hormones released, altering sexual behavior

Using xenograft animal models (both orthotopic and ectopic), expressing a reporter system eases the imaging and measurement of tumor parameters [1]. Updating and optimizing the chosen reporter/imaging system accelerates the preclinical development of novel anticancer drugs. Magnetic nanoparticles are fine nanomagnetic materials having magnetic response, small particle size, large "specific surface area", and superparamagnetism [66]. Magnetic nanoparticles are constructed under a constant magnetic field, where heat is absorbed by the electromagnetic field.

Iron oxide nanoparticles

Commonly used nanopar¬ticles are derived from iron oxide, as magnetite (Fe3O4) and maghemite (γ Fe2O3) [67]. Tumor imaging facilitates early disease detec¬tion. Common imaging modalities include magneto acoustic tomography, magnetic resonance imaging, computed

tomography and near infrared imaging). MRI is currently among the best imaging techniques in the early diagnosis of cancer. SPIONs are the best representative contrast agents for MRI. Currently, feru¬moxil (GastroMARK), an iron oxide based magnetic nanoparticles are approved for use in clinical MRI, to enhance bowel imaging [68]. Magnetic nanoparticles' small size and the relatively large specific surface area facilitate their arrival to lesion's location [69]. Magnetic nanoparticles are excellent drug carriers for targeted cancer drug delivery in vivo when linked to binding antibodies and chemotherapeutic drugs as doxorubicin [70]. This is potentiated upon using the magnetic field [71]. For cancer therapy, Magnetic nanoparticles can be used in different ways including:

A. Chemotherapy [72]
B. magnetic hyperthermia [73]
C. photodynamic therapy [74].
D. photothermal therapy [75].

Iron oxide nanoparticles are good contrast agents for magnetic resonance imaging of colorectal cancer. Guanyl cyclase C receptors are enormous in colorectal micrometastases. Hence, they can be targeted by ligands linked to multifunctional nanoparticles [76] and so is prostate specific membrane antibody that targets and images antigen expressing prostate cancer cells using a fluroscein-labelled dendrimer [77]. Unfortunately, blood brain barrier hinders the contrast delivery to the central nervous system. The nanoparticles polysorbate solves the problems of blood brain barrier via attaching to the peptides capable of crossing the blood brain barrier and mimic LDLs and can be transported into the brain by endocytosis [78]. Dual imaging nanoparticles (detectable by both MRI and fluorescence microscopy) can distinguish normal tissue from malignant cells [79]. Functionalized gold dendrimer particles (Au DENPs) help intraoperative MRI tumor imaging being stable and can be retained for 24 hours in targeted cells. Veiseh et al., reported successful glioma MRI imaging using PEG iron oxide particles conjugated with chlorotoxin (a peptide binding to glioma nanoprobes) and Cy5.[5] (infrared fluorescing molecule)[78]. Interestingly, Montet et al., fabricated a nanoparticle composite formed of iron oxide particles, bombesin receptors ligand (to target normal acinar cells of the pancreas) to distinguish normal tissue from pancreatic duct adenocarcinoma upon using MRI for better imaging [80].

MRI is the most valuable noninvasive imaging techniques [81], to overcome magnetic nanoparticles colloidal instability, surface modification of nanoparticles are done via inducing magnetic dipole interaction and its intrinsic surface energy [82]. For example, water-dispersible polyethyl-

eneimine-coated iron oxide nanoparticles are prepared, and then sequentially modified with PEGylated folic acid and fluorescein isothiocyanate via polyethyleneimine mediated conjugation chemistry [82]. That helped early detection of glioblastoma multiforme in patients using sensitive imaging of SPIONs or aggregates [83].

Conclusion

Reporter systems can help cancer imaging by analyzing the biochemical and molecular processes in cells and organs using proteases, sub-cellular localization, protein-protein interactions, and gene transcription. Nanotechnology helps creating new drugs, studying neoplastic transformation, tracking specific cancer-related events, and investigating the complex pathological occurrences (angiogenesis, apoptosis, proto-oncogene activity, oncogenes, tumor suppressor genes and tumor promoting signals). SPIONs are among the best nanoparticles for cellular targeting, causing hyperthermia, and are simply biodegraded into metabolizable iron particles.

Future perspectives

Reporter systems and nanoparticles revolutionized oncology research and practice. It is hopeful in the near future to get better and more economic, easily tracked nanoparticles that can be loaded with chemotherapeutics and tracers for easy tracing inside the human body. Ligand-associated nanoparticles for precise tumor targeting is a promising hope that may be at hand in light of the fruitful published research work.

Conflict of interest

The author declares that there is no conflict of interest with anyone

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