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Nanomedicine: Photo-activated nanostructured titanium dioxide, as a promising anticancer agent

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ABSTRACT

The multivariate condition of cancer disease has been approached in various ways, by the scientific community. Recent studies focus on individualized treatments, minimizing the undesirable consequences of the conventional methods, but the development of an alternative effective therapeutic scheme remains to be held. Nanomedicine could provide a solution, filling this gap, exploiting the unique properties of innovative nanostructured materials. Nanostructured titanium dioxide (TiO_2) has a variety of applications of daily routine and of advanced technology. Due to its biocompatibility, it has also a great number of biomedical applications. It is now clear that photo-excited TiO_2 nanoparticles, induce generation of pairs of electrons and holes which react with water and oxygen to yield reactive oxygen species (ROS) that have been proven to damage cancer cells, triggering controlled cellular processes.

The aim of this review is to provide insights into the field of nanomedicine and particularly into the wide context of TiO_2-NP-mediated anticancer effect, shedding light on the achievements of nanotechnology and proposing this nanostructured material as a promising anticancer photosensitizer.

Contents

Abbreviations: BG, band gap; CB, conductivity band; HA, hyaluronic acid; MRI, Magnetic Resonance Imaging; nanoMIPs, Molecularly imprinted nanoparticles; NPs, nanoparticles; NSMs, nanostructured materials; PDT, Photodynamic Therapy; PEG, polyethylene glycol; PET, Positron emission tomography; PTT, Photothermal Therapy; RES, Reticulo-Endothelial System; ROS, generate reactive oxygen species; SASP, Senescence Associated Secretory Phenotype; SIPS, Stress Induced Premature Senescence; SPR, surface plasmon resonance; TiO_2, Titanium Dioxide; VB, valence band.

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1. Introduction

Nanotechnology is defined as the manipulation of matter with at least one dimension sized from 1 to 100 nanometers (Jeevanandam, Barhoum, Chan, Dufresne, & Danquah, 2018) and includes various fields of science, such as semiconductor physics (Tamirat, 2017), surface science, chemistry, biology, energy storage (Hübler & Osuagwu, 2010; Shinn et al., 2013), *microfabrication* (Lyon & Hübler, 2013; Martinez & Chaikof, 2011), molecular engineering (Nagamune, 2017) and many others. It is reasonable that various applications have been developed, in order to exploit the potential of this scientific field. The use of the achievements of nanoscience in medicine, pharmacology and biology has reasonably a great impact, aiming to improve the quality of life (Ventola, 2012).

The multivariate context of cancer has been addressed by various approaches (Bindels et al., 2018). Recent studies focus on personalized treatments by employing nanomaterials or composite materials, minimizing the undesirable consequences of the conventional methods, such as chemotherapy and radiotherapy, (Ketabat et al., 2019). Other strategies focus on the development of modalities for accurate cancer cell detection, fascilitating thus molecular imaging. Innovation of alternative effective therapeutic schemes remains to be held. Nanomaterials are promising candidates for filling this scientific gap, as a part of their extended range of applications. Particularly, nanostructured titanium dioxide (TiO_2) has a variety of applications of daily routine and of advanced technology. Due to its biocompatibility, it has also a great number of biomedical applications (Jafari et al., 2020). It is now clear that photo-excited TiO_2 nanoparticles, induce generation of pairs of electrons and holes which react with water and oxygen to yield reactive oxygen species (ROS) that have been proven to damage cancer cells, triggering controlled cellular processes (Zhou, Song, Nie, & Chen, 2016).

The aim of this review is to provide insights into the field of nanomedicine and particularly into the wide context of TiO_2-NP-mediated anticancer effect, shedding light on the achievements of nanotechnology and proposing this nanostructured material as a promising anticancer photosensitizer.

1.1. Nanotechnology

Modern nanoscience and nanotechnology seem to be quite new scientific fields (Pitkethly, 2004). However, nanoscale materials were used for centuries in various applications (Jeevanandam et al., 2018; Mody, Siwale, Singh, & Mody, 2010) and those techniques are probably the precursor of the modern processes of nanotechnology (Drexler, Peterson, & Pergamit, 1991).

The foundations of the modern nanotechnology were established by the physicist Richard Feynman (Hulla, Sahu, & Hayes, 2015). Actually, the main ideas and concepts behind nanoscience and nanotechnology started with his talk entitled "There's Plenty of Room at the Bottom", at an American Physical Society meeting, which was held at the California Institute of Technology on December 29, 1959 (Samir, Elgamal, Gabr, & Sabaawy, 2015). Then, Feynman described a new process which would give scientists the ability to manipulate and control individual atoms and molecules (Kumar, Kumar, Savadi, & John, 2011). Thus, this was the first reported approach to discuss his modern ideas and it was long before the term "nanotechnology" was widely used (Jeevanandam et al., 2018). In fact, over a decade later, Professor Norio Taniguchi, during his explorations of ultraprecision machining, used for the first time the term "nanotechnology". The development of the scanning tunneling microscope, at the early 80s, allowed to detect and observe individual atoms and this was the official launch of the modern nanotechnology (Fujita & Sagisaka, 2008).

It is now well-established that nanotechnology is a combination of science, engineering and technology (Kulkarni, 2007). This term is also referred to the study and application of extremely small materials, conducted in nanoscale. Nowadays this scientific field tend to be a part of modern physics, chemistry, biology, materials science, pharmacology and engineering (Institute of Medicine (US) Roundtable on Environmental Health Sciences, Research, and Medicine, 2005). The definition of nanotechnology, itself, reflects that, at this quantum-realm scale, the quantum mechanical effects are important (Valavanidis & Vlachogianni, 2016) and this interesting potential has to be exploited in various applications.

1.1.1. Nanomaterials and applications

Nanomaterials have at least one dimension that measures 100 nm or less, as it was previously mentioned. Since, in the past two decades, various nanostructured materials (NSMs) have been developed, the need of their classification was presented (Jeevanandam et al., 2018). The first categorization of NSMs was proposed by Gleiter in 1995 (Gleiter, 2000) and five years later a further explanation was given by Skorokhod (Tiwari, Tiwari, & Kim, 2012). These two first attempts were not fully considered, as they did not take into account some important categories of NSMs. Therefore, Pokropivny and Skorokhod (Pokropivny & Skorokhod, 2007) reported a modified classification scheme for NSMs, in which zero-dimensional (0-D), one-dimensional (1-D), two-dimensional (2-D) and three-dimensional (3-D) NSMs were included. Herein the most common classification of the NSMs is based on this scheme, until now. So, this classification of nanomaterials is considered the number of dimensions of an NSM, considered in nanoscale (Jeevanandam et al., 2018).

The last decades, scientists and engineers try to find a variety of ways to fabricate materials at the nanoscale, taking advantage of their unique properties, such as higher strength, lighter weight, control of light spectrum and greater chemical reactivity, which are extremely differ from those of their bulk and dissolved counterparts (Mourdikoudis, Pallares, & Thanh, 2018).

The great potential of NSMs allows them to be used in a variety of environmental applications, as sensors, for treatment purposes, remediation, or developing green manufacturing and engineering (Jeevanandam et al., 2018). To generalize, the environmental applications could be categorized in two main classes, these which are reactive to the existing environmental problems and those which are proactive in preventing future problems (Kim, 2018). Another use of NSMs is in food science and food microbiology. This approach includes food processing, packaging, functional development, safety and precise detection of foodborne pathogens (Bajpai et al., 2018). Actually, their unique size-dependent properties, make NSMs indispensable in various human activities.

The wide use of NSMs in cosmetics (Raj, Jose, Sumod, & Sabitha, 2012), pharmaceuticals (Fornaguera & García-Celma, 2017), dentistry (Ozak & Ozkan, 2013), veterinary (El-Sayed & Kamel, 2018), biology (Salata, 2004) and medicine (Mishra, 2016) led to the development of a specialized branch of science, named nanomedicine. Nanomedicine applies the fundamentals of nanotechnology to the prevention and hopefully to the treatment of many diseases (Boulaiz et al., 2011).

Hence, nanomedicine involves the use of nanostructured materials for diagnosis, delivery, detection or actuation purposes in a living organism (Patra et al., 2018).

1.2. Alternative cancer treatments and nanomedicine

Recent epidemiologic studies demonstrate that cancer is still one of the main factors of morbidity and mortality, worldwide (Bray et al., 2018; Momenimovahed & Salehiniya, 2019). Cancer disease is characterized by dynamic changes in many cellular processes (Fouad & Aanei, 2017) presented also in the genome (Hanahan & Weinberg, 2000). Cancer cells have various defects in their regulatory circuits, governing the normal cell proliferation and homeostasis (Hanahan & Weinberg, 2000). Hence, cancer cells become overactive, in growth and proliferation rate, aggressive as they invade and destroy adjacent tissues and metastatic, spreading to other organs (Hanahan & Weinberg, 2011).

The multivariate condition of cancer disease has been approached by scientific community in various ways (Goossens, Nakagawa, Sun, & Hoshida, 2015; Sallam, 2015). Recent research studies focus on individualized treatments in order to minimize the undesirable consequences of the conventional approaches (Agyeman & Ofori-Asenso, 2015). There are still aspects of the research field of alternative cancer treatments that remains to be unraveled (Galata, Georgakopoulou, Kassalia, Papadopoulou-Fermeli, & Pavlatou, 2019; Hu & Fu, 2012). Nanomedicine could be a very promising choice. Recent studies focus on personalized treatments, by employing nanomaterials or composite materials, minimizing thus the unfavorable effects of conventional methods, such as chemotherapy and radiotherapy, (Ketabat et al., 2019).

The application of noninvasive molecular imaging for cancer diagnosis and therapy has become mandatory in clinical routine. Current imaging tracers, which are widely used have well-known intrinsic limitations. Nanomedicine can allow the development of molecular diagnostic systems for accurate detection of cancer cells (Hu, Fine, Tasciotti, Bouamrani, & Ferrari, 2011). Molecular imaging allows for *in vivo* measurement of many critical processes, in neoplasms, such as metabolism, proliferation, hypoxia, and apoptosis. Therefore, these techniques can be employed in order to monitor the therapeutic response.

NSMs may overcome some of the limitations of cancer diagnosis, while allowing therapeutic applications. These theranostic or theragnostic approaches have great potential to use NSMs as therapeutic tools, loading targeted molecules for both imaging and therapeutic purposes. Lipid-based nanoliposomal imaging agents, CF800, polyethylene glycol (PEG) functionalized nanoparticles (NPs) of gold (Au-PEG) conjugated with specific antibodies, iodinated gold nanoclusters and various other nanosystems have developed for NIR fluorescence and CT imaging. Superparamagnetic iron oxide NPs coated with different chemical compounds and quantum dots can be used in Magnetic Resonance Imaging (MRI), providing molecular imaging of cancers cells (Wang et al., 2018). Nanodroplets with a perfluorocarbon (PFC) core and a solid shell, consisted of lipids or polymers are proposed for their use in an alternative ultrasound-mediated chemotherapy. Homogeneous multivalent lipid NPs are used can be used in Positron emission tomography (PET) imaging. Cumulatively, various approaches focus on the development of assays and systems, facilitating accurate detection of cancer cells.

The targeted suppression of cancer cells could be possible, maximizing the killing effect in the tumor area and leaving unaffected the healthy tissues (Moding, Kastan, & Kirsch, 2013) and this result could be achievable through innovative drug delivery systems, which are based on nanostructured materials with the potential to make a controlled release at the target-area (Goldberg, Langer, & Jia, 2007; Patra et al., 2018; Ulbrich et al., 2016). For instance, smart, polymerically embedded titanium dioxide (TiO_2) NPs have been designated to exhibit photo-induced anticancer properties under visible light (Galata et al., 2019).

2. Titanium Dioxide (TiO_2)

Titanium dioxide (TiO_2) is a naturally occurring oxide of titanium. It is usually found as an odorless and tasteless white powder with a molecular weight of about 79.87 g/mol (Shi, Magaye, Castranova, & Zhao, 2013). Its boiling point is at 2500-3000 °C, under the pressure of 760 mm Hg (Winkler, Notter, Meyer, & Naegeli, 2018). Its melting point is at 1855 °C and its density varies from 3.9 to 4.3 g/cm^3 (Hoang, 2007). TiO_2 is insoluble in water and in organic solvents (Llansola-Portoles et al., 2014). It can dissolve very slowly in hydrofluoric acid and in hot concentrated sulphuric acid (Hung, Lin, & Feng, 2017).

Nanostructured TiO_2 is considered as a well-characterized nanomaterial, which exists in three crystalline polymorphs: rutile (tetragonal crystal system), anatase (tetragonal crystal system), and brookite (orthorhombic crystal system) (Di Paola, Bellardita, & Palmisano, 2013). Rarely, at low temperatures, TiO_2 is also found as an amorphous material (Kulczyk-Malecka, Kelly, West, Clarke, & Ridealgh, 2013). Comparatively, rutile and anatase display higher catalytic performance and stability (Luttrell et al., 2014). Generally speaking, TiO_2 is among the most popular, commercially available, nanomaterials (Jacobs, van de Poel, & Osseweijer, 2010) with great applications in a variety of fields due to its wide availability, low cost and high chemical stability (Wang et al., 2016).

There are many synthetic procedures that may lead to the preparation of titania nanomaterials. Besides dimension, most of them are focusing on the effective control of nanoparticles morphology and well as their structure, crystallinity, porosity and surface area. It is now well established that dimensionality (1D, 2D, 3D) and nanomorphology (wires, sheets, belts, membranes, hollow spheres, rods, tubes, foams, photonic crystals, heterostructures and other architectures) are crucial parameters that determine their structural (anatase, rutile, brookite) and optoelectronic properties and therefore their photocatalytic activity (Arabatzis & Falaras, 2003; Arfanis et al., 2017; Diamantopoulou et al., 2019; Hung et al., 2017; Ibhadon, Greenway, Yue, Falaras, & Tsoukleris, 2008; Idakiev, Yuan, Tabakova, & Su, 2005; Kontos et al., 2010; Lagopati et al., 2014; Likodimos, Stergiopoulos, Falaras, Kunze, & Schmuki, 2008; Miranda et al., 2014; Pastrana-Martínez et al., 2013; Pelaez et al., 2012; Toumazatou et al., 2020; Takahashi, 2018).

2.1. TiO_2 and applications

TiO_2 is widely used in many fields of application of everyday routine (Kang et al., 2019). It is known as titanium white, Pigment White 6 (PW6), or CI 77891 (Weir, Westerhoff, Fabricius, Hristovski, & von Goetz, 2012). TiO_2 is also used in cosmetics and particularly in sunscreens, and in pharmaceuticals (Behnam, Emami, Sobhani, & Dehghanian, 2018), since it is absolutely biocompatible, according to World Health Organization (WHO) (Latha et al., 2013), providing whiteness and opacity. Furthermore, TiO_2 can be used in advanced technological applications and devices, such as in solar cells (Luceño-Sánchez, Díez-Pascual, & Capilla, 2019), in aeronautics (da Rosa, 2013) and in medicine (Wright et al., 2017).

Titanium dioxide is widely used in biomedical applications, since its mechanical and photocatalytic properties and biocompatibility make it the material of choice for various bone implants, dental prosthetics, vascular stents, valves and many more (Liu, Liu, & Wang, 2019; Özcan & Hämmerle, 2012; Prasad et al., 2017). In Fig. 1, the main fields of application of TiO_2 are being demonstrated.

2.2. Photocatalysis process

There are many definitions of the term “photocatalysis”. The most common of them is the following: “Photocatalysis is the acceleration

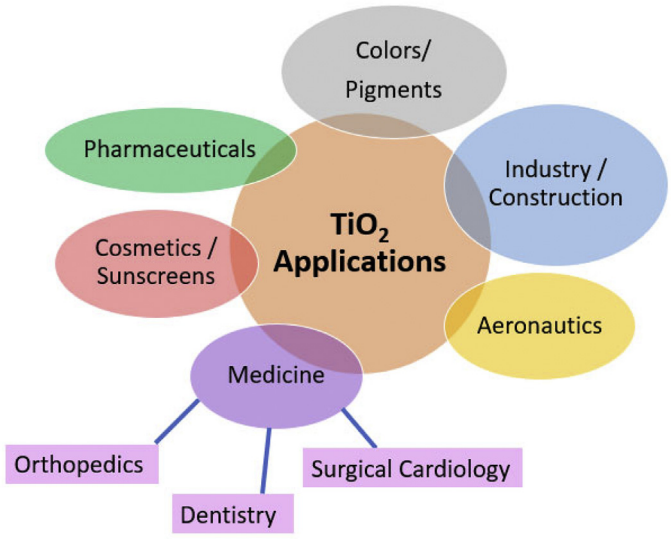

Fig. 1. The main applications of TiO_2. TiO_2 is widely used in colors and pigments, in pharmaceuticals, in aeronautics, in cosmetics, in industry and in the production of construction materials. It is also used in biomedical applications (in orthopedics for bone implants, in dentistry for dental prosthetics, in surgical cardiology for vascular stents, valves).

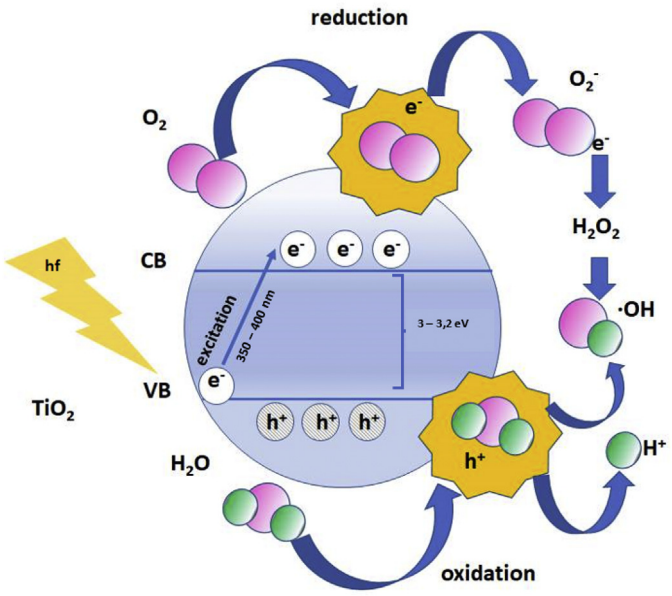

Fig. 2. Schematic representation of photocatalytic process. Following illumination with light of energy (hf) higher than the materials energy gap (3.0-3.2 eV), the photogenerated charge carriers, holes (h+) in the valence band (VB) and electrons (e-) in the conduction band (CB), react with water (H_2O) and O2 molecules and create hydroxyl radicals (·OH) and anionic oxygen radicals (O_2^{-}·), respectively. These radicals are short-leaving species with high activity for redox reactions and can thus decompose organic pollutants, bacteria, viruses and cancer cells.

of a photo-reaction in the presence of a catalyst" (Mills & Le Hunte, 1997; Seprone & Emeline, 2002). Another more enriched version is equally prevalent: "Photocatalysis is the process of ROS production by aquatic medium in the presence of a solid heterogenous catalyst and irradiation with light of specific and appropriate wavelength" (Bull, Gebra, & Trussell, 1990; Pickering & Owen, 1997). According to the International Union of Pure and Applied Chemistry (IUPAC), photocatalysis is "A catalytic reaction involving light absorption by substrate" (Schneider, Bahnemann, Ye, & Li, 2016).

2.2.1. Fundamentals of Photocatalysis

During photocatalysis, light with an appropriate wavelength, frequency and consequently energy, in order to overcome the energy gap of the band gap (BG) (Tseng, Lin, Chen, & Chu, 2010), comes by on the semiconductor photocatalyst, then the electrons from the valence band (VB) are excited and transit to the conductivity band (CB), leaving positive holes, in the VB (Fan et al., 2017) (Fig. 2).

Since the photocatalytic reactions are happening at the surface of the photocatalysts, the photo-induced carriers need initially to diffuse into the active sites of the surface (Hashimoto, Irie, & Fujishima, 2005). The relative positions between the redox potentials (RP) and the band edges of a photocatalyst, determine if the chemical reaction is possible to be undergone (Beranek, 2011). The following possibilities are distinguished, depending on the equilibrium of the RP of the substrate and the CB edge of the photocatalyst (Fu, Li, & Li, 2019; Zhu & Wang, 2017): i) if the RP is lower than the CB edge, then reductive reactions can be undergone, ii) if the RP is higher than the CB edge, then oxidative reactions can be undergone, iii) if the RP is higher than the CB edge, or lower than the VB, then neither reductive, nor oxidative reactions can be undergone and iv) if the RP is lower than the CB edge, or higher than the VB, then either reductive, or oxidative reactions can be undergone (Fan et al., 2017; Fu et al., 2019; Zhu & Wang, 2017).

If the reactants and the photocatalysts exist in the same phase, the photocatalysis considered as homogeneous, otherwise the photocatalysis is heterogenous (Seprone, 2018). Ozone and photo-Fenton systems are among the most commonly used homogeneous photocatalysts (Javaid & Qazi, 2019). The heterogenous photocatalysis includes a large variety of reactions, such as oxidations, dehydrogenation, hydrogen transfer, metal deposition, water detoxification, and many others (Colmenares et al., 2009).

The preferable characteristics of the photocatalysts that are used in the aforementioned applications is the photo-stability, the ability to be photoactivated by the excitation in a wide range of electromagnetic spectrum (ultraviolet (UV) and visible light), the low cost and the biocompatibility. TiO_2 is widely used as a photocatalyst, since it gathers these properties. The band gap is approximately 3-3,2 eV, thus pure TiO_2 can be activated only upon irradiation with UVA light (350 3–2 400 nm).

2.2.2. Photocatalytic applications of titanium dioxide

It is well known that photo-activated TiO_2 can trigger various chemical reactions, since it possesses strong oxidizing and reducing potential. In recent studies, regarding the use of TiO_2 nanoparticles, it is demonstrated that the photocatalytic technology has a great impact and high potential for restoring and keeping the living environment clean and safe (Binas, Venieri, Kotzias, & Kiriakidis, 2017; Hashimoto et al., 2005). The most important environmental photocatalytic applications of TiO_2 include the removal of pollutants either from air (VOCs, NOx and odors) (Binas et al., 2017; Burton, 2012; Choi, Stathatos, & Dionysiou, 2006) or water (pesticides, phenols, textile azo-dyes) (Bratovčić, 2019; Das, 2014; Muhd Julkapli, Bagheri, & Bee Abd Hamid, 2014; Zhang et al., 2019). Due to the combination of photocatalytic, superhydrophylic and magnetic properties, in parallel with its high refractive index (Chemin et al., 2018), TiO_2 can decompose harmful substances, prevent stains formation and kill pathogen microbes (Tsuang et al., 2008). Thus, is can be used for self-cleaning, as well as for self-sterilization, as a doping component of existed materials, such as cement or metallic surfaces (Bogdan, Jackowska-Tracz, Zarzyńska, & Pławińska-Czarnak, 2015).

The pandemic, which is named Coronavirus disease 2019, COVID-19 (Wang et al., 2020) is associated with the infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is well established that the fast and worldwide COVID-19 pandemic outburst has caused a

serious public health problem. This situation emerged the mass production of masks and uniforms. Photocatalysts, like TiO_2, could be used as a coating of the conventional materials, in order to provide protection against SARS-CoV-2, through the mechanism of auto-sterilization. According to our experience the efficiency of TiO_2 is significant, indicating that TiO_2 might be a promising candidate, transforming conventional textiles and fabrics into an impermeable barrier for biological fluids, offering bactericidal and virucidal activity.

TiO_2 nanoparticles (NPs) might also be an interesting choice for biomedical applications, including the drug delivery systems, for various anti-cancer drugs, such as doxorubicin, daunorubicin, temozolomide, and cisplatin (Behnam et al., 2018). Particularly, multidrug resistance of breast cancer cells might be overcome if TiO_2 NPs could be used as carries, transferring doxorubicin (Ren et al., 2013). The electrostatic interactions link the drug with the NPs. Drug accumulation was increased and enhanced anticancer activity was observed compared the effect of doxorubicin alone. The hypothesis was that the nanocomposite led the drug into cells via internalization, thus bypassing the P-glycoprotein mediated doxorubicin pumping system (Ren et al., 2013). Another interesting approach was implemented by Liu and colleagues, who developed TiO_2-NPs modified with hyaluronic acid (HA), acting as a pH-responsive drug release system, loading cisplatin for potential neoadjuvant chemotherapy of ovarian cancer. This drug delivery system increased the accumulation of cisplatin in A2780 ovarian cancer cells through endocytosis, presenting significant anticancer activity *in vitro* (Liu et al., 2015).

TiO_2 NPs can also be used in cell imaging, in biosensors for biological assay and in Photodynamic Therapy (PDT) (Abdal Dayem et al., 2017; Behnam et al., 2018; Çeşmeli & Biray Avci, 2019; Ziental et al., 2020). Since they have super hydrophilicity, low-toxicity, thermal conductivity, high optical absorption, chemical and thermal stability in vivo, TiO_2 NPs can be utilized as agents in converting photon energy into heat in the Photothermal (PTT) therapy (He et al., 2016).

There are many studies which focus on increasing the biocompatibility of TiO_2 NPs, with polyethylene glycol (PEG), attached to their surfaces, because PEGylated NPs can escape the Reticulo-Endothelial System (RES) (Parhiz et al., 2018). Other studies introduce the use of stimuli responsive polymers, with the ability to respond to slight environmental changes, such as temperature, pH, ionic strength, light, electric and magnetic field (JagadeeshBabu, Kumar, & Maheswari, 2011; Li, Hou, Qu, Dai, & Zhang, 2018), in order to develop smart drug delivery systems (Karimi et al., 2016). Poly (N–isoprpopylacrylamide)–pNipam microgel can promote the embedding of TiO_2 NPs, operating in human body environmental conditions (Galata et al., 2019).

The photocatalytic properties of TiO_2-mediated toxicity have been shown to eradicate cancer cells (Thevenot, Cho, Wavhal, Timmons, & Tang, 2008). It is now well established that when TiO_2 nanoparticles are excited by light of energy (hf) higher than the materials energy gap (3.0-3.2 eV), the photon energy generates pairs of electrons and holes (Xiong et al., 2013). The photogenerated charge carriers, holes (h^+) in the valence band (VB) and electrons (e^-) in the conduction band (CB), react with water (H_2O) and O_2 molecules which exist in vast amounts in any biological system, creating hydroxyl radicals ($^{\cdot}OH$) and anionic oxygen radicals ($O_2^{-\cdot}$), respectively. These radicals are short-leaving species with high activity for redox reactions and can thus decompose organic pollutants, bacteria, viruses and cancer cells (Stefanou, Evangelou, & Falaras, 2010; Zhou et al., 2016). Therefore, TiO_2 NPs are one of the promising photosensitizers against cancer (Lagopati et al., 2010; Lagopati et al., 2014; Zhang, Shan, & Dong, 2014). Fig. 3 sums up the main photocatalytic applications of TiO_2.

3. TiO_2 and apoptosis

NSMs are chemically very reactive. This could be considered as a desirable property or an undesirable situation (Skocaj, Filipic, Petkovic, & Novak, 2011). For example, it is desirable to develop a catalyst which is highly reactive, or a drug delivery system with high carrier capacity and penetration of cellular barriers for therapeutics but is it totally undesirable for an NSM to present uncontrolled toxicity, induction of oxidative stress or cellular dysfunction (Wang, Santos, Evdokiou, & Losic, 2015).

Some of the physical and chemical properties of NPs, such as their size, charge, specific surface area, crystallinity, shape, solubility and aggregation state, play important role, from a toxicological point of view (Khan, Saeed, & Khan, 2017; Xia et al., 2006). The active sites of the surface may render NPs hydrophilic or hydrophobic, lipophilic or lipophobic and active or passive, regarding to their catalytical performance (Yu et al., 2016). These properties can regulate the cellular uptake, the subcellular localization and the cytotoxicity of the NSMs (Xia et al., 2006). There are two main pathways of the NP uptake in the cell, the active uptake by endocytosis and the passive one, characterized by free diffusion (Behzadi et al., 2017). The size of the NSM is responsible for triggering either the active or the passive choice. Thus, depending on the size, NPs can be found totally cleared by macrophages (very small NPs)(Geiser et al., 2008), or free within the cytoplasm of epithelial and endothelial cells and fibroblasts (20-50nm) (Geiser et al., 2005), or bound to membrane (big NPs) (Rothen-Rutishauser, Schurch, Haenni, Kapp, & Gehr, 2006).

Pure TiO_2 can cause cyto- and geno-toxicity, inducing apoptosis, upon irradiation with ultraviolet (UV), since the band gap of ultrafine TiO_2 allows photo-excitation only in this limited spectrum range (Skocaj et al., 2011). Thus, through UV-induced photocatalysis, TiO_2 NPs can generate reactive oxygen species (ROS), such as superoxide anions and hydroxyl radicals (Li, Zhang, Niu, & Chen, 2012). It is well known that ROS can damage cellular components and macromolecules causing cell death if produced in excess or if they are not neutralized by innate antioxidant defense mechanisms (Manke, Wang, & Rojanasakul, 2013; Redza-Dutordoir & Averill-Bates, 2016). ROS, derived from the photocatalysis of NPs, are cytotoxic to a variety of cell types (Braydich-Stolle et al., 2009; Coccini, Grandi, Lonati, Locatelli, & De Simone, 2015; Serpone, Salinaro, & Emeline, 2001; Uchino, Tokunaga, Ando, & Utsumi, 2002; Xue et al., 2010; Yu et al., 2015).

In the presence of ROS scavengers or antioxidants (Setyawati, Tay, & Leong, 2015; Xiao, Liu, Chen, & Yang, 2016) NP-induced cytotoxicity could be prevented, indicating that oxidative stress plays central role in NP-induced cell death induction pathways. The use of coating material (polymer, silica, vitamins etc.) can regulate the oxidative behavior of NPs (Carlotti et al., 2009; Fisichella et al., 2012; Tran & Salmon, 2010).

It has been proven that the biochemical and cell signalling events, which are related to the induction of ROS, DNA damage and cell death mediated by TiO_2 NPs, include the activation of NF-κB, (Setyawati et al., 2015), the disruption of calcium homeostasis (Yu et al., 2015), the secretion of the proinflammatory cytokine (De Angelis et al., 2013), the activation of executioner caspases (Wang et al., 2015; Wang, Santos, et al., 2015) and caspase 12 (Yu et al., 2015) and the disruption of mitochondrial membrane potential (Filippi et al., 2015). These biochemical changes were not reported on all the examined cell types (Miyani & Hughes, 2017). The expression of β-catenin and E-cadherin did not change (Wright et al., 2017).

On the other hand, it has been already reported that TiO_2 NPs possess cell-specific toxicity on breast cancer epithelial cells of different metastatic rate (Galata et al., 2019; Lagopati et al., 2010; Lagopati et al., 2014) (Fig. 4). According to our previous studies, the process that leads to cell apoptosis is executed by the family of caspases, including caspase-3. One of the main cleavage targets of caspase-3 is PARP, a 113 kDa nuclear poly (ADP-ribose) polymerase. PARP is involved in DNA repair in response to environmental stress. Cleavage of PARP facilitates cellular disassembly and characterizes cells undergoing apoptosis. Thus, PARP cleavage was examined by immunoblot analysis in cells treated with UV-activated TiO_2. UV-A light (without TiO_2 NPs) slightly up-regulated PARP cleavage (Fig. 4A and B). PARP cleavage was significantly increased in the presence of TiO_2 NPs or photoexcited TiO_2 NPs

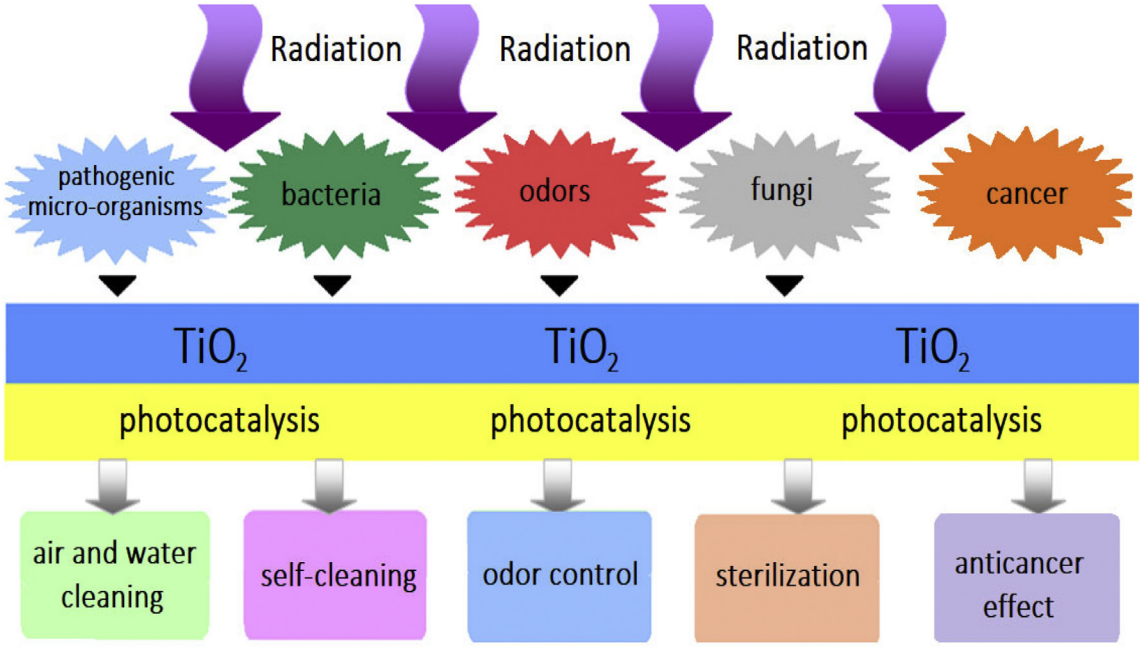

Fig. 3. The main photocatalytic applications of TiO_2. The most important environmental photocatalytic applications of TiO_2 include the removal of pollutants either from air (VOCs, NOx and odors) or water (pesticides, phenols, textile azo-dyes). Due to the combination of photocatalytic, superhydrophylic and magnetic properties, in parallel with its high refractive index, TiO_2 can decompose harmful substances, prevent stains formation and kill pathogen microbes. Thus, is can be used for self-cleaning, as well as for self-sterilization, as a doping component of existed materials, such as cement or metallic surfaces. TiO_2 can also be used as an anticancer agent alone or in combination with other drugs, as a drug carrier.

(Fig. 4A and B), indicating that TiO_2 NPs induces apoptosis in MDA-MB-468 cells, while MCF-7 cells were unaffected under the same conditions (Fig. 4C and D).

The phototoxicity is potentially mediated by ROS production that initiates programmed death of the cancer cell. Various studies support this hypothesis, since oxidative stress is known to induce cellular death by apoptosis and the production of ROS is increased with the photo-excited nano-TiO_2 concentration. The photogenerated charge carriers lead to the formation of ROS such as hydroxyl radicals, superoxides and hydrogen peroxide which are highly reactive with cell membranes and the cell interior, including DNA. The relevant oxidative reactions may affect the cell rigidity and the chemical arrangement of surface structures, with a significant cyto-toxic effect. Series of experiments were held in the presence of molecular scavengers of both hydrogen peroxide and hydroxyl radicals, such as catalase and N-acetylcysteine which diminished cell death. Hence, hydroxyl radicals and hydrogen peroxide may play a role in cell death mediated by TiO_2 NPs (Lagopati et al., 2010).

Also, further analysis showed that Bcl-2 family proteins seems to play a key role in the regulation of cell apoptosis in the presence of two different crystal forms of TiO_2 NPs. Bcl-2 family proteins can induce (proapoptotic members) or inhibit (antiapoptotic members) the release

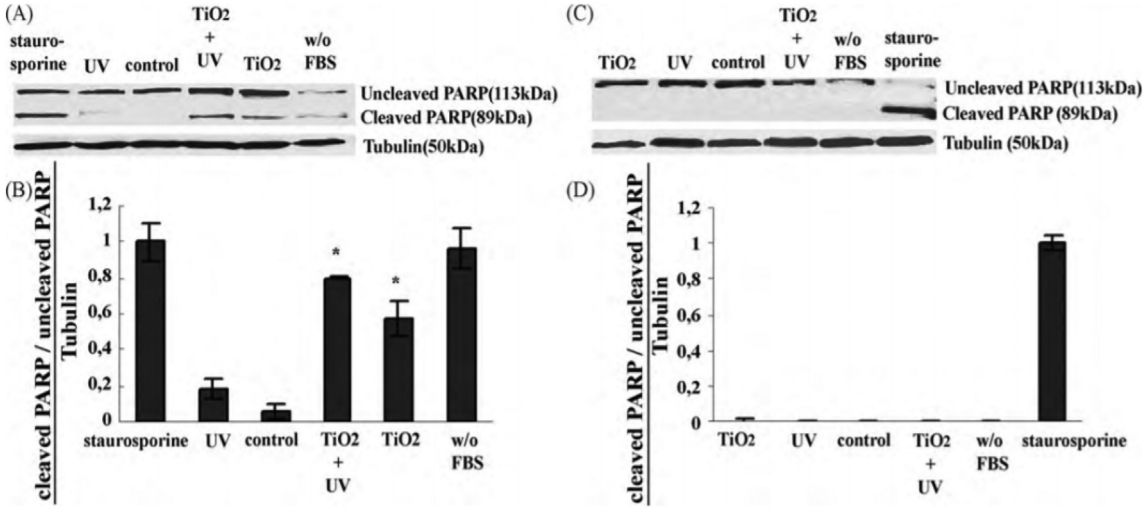

Fig. 4. Photoexcited TiO_2 NPs induced caspase-3-mediated PARP cleavage. MDA-MB-468 (A) and MCF-7 cells (C) were treated with 15 M TiO_2, UV-A-irradiated for 20 min and incubated for 48 h. Representative Western blots (A and C) of uncleaved and cleaved PARP. Cells treated with 200 nM staurosporine for 24 h or serum-depleted cells were used as positive control for induction of PARP cleavage. Blots were stripped and re-probed with anti-tubulin antibody to normalize the blots for protein levels. (B and D) Densitometric quantification of cleaved/uncleaved PARP to tubulin levels. Data represent the means ± SD from three independent experiments. *$P < 0.05$ as compared to cleaved/uncleaved PARP/tubulin levels of untreated cells (Lagopati et al., 2010-Copyright License Number: 4923600353001).

of cytochrome C into the cytosol, which activates caspase-9 and caspase-3, leading to apoptosis. Photo-activated TiO_2 NPs increased the expression of Bax in MDA-MB-468 cells (Fig. 5A and B), leaving Bcl-2, Bcl-xL, and Bad at the same levels as the control sample. Upregulation of Bax expression was one more apoptosis index. There was no significant effect in Bcl-2, Bcl-xL, Bax and Bad expression (Fig. 5C and D) under the same treatment in MCF-7 cells.

Furthermore, the effect of TiO_2 NPs on DNA damage in breast cancer epithelial cells was qualitatively evaluated applying the DNA-laddering assay. There was a significant DNA damage (fragmentation) induced after treatment of MDA-MB-468 cells with photoexcited TiO_2 NPs (Fig. 6).

Moreover, other studies indicate that TiO_2 NPs exert remarkable effects on cellular functions, such as cell proliferation and viability, in human skin-derived cells (Kiss et al., 2008) and induce apoptotic cell death in human non-small cell lung cancer cells (Wang, Cui, et al., 2015), in human colon carcinoma cells (De Angelis et al., 2013), in cervical cancer cells (Cai et al., 1992; Cai, Hashimoto, Itoh, Kubota, & Fujishima, 1991), in sarcoma cells but were not toxic to cultured fibroblasts MCR-5 (Stefanou et al., 2010). Also, Stefanou et al. tested UV-irradiated TiO_2 NPs on human platelets, by considering and evaluating important factors stimulating the aggregation effect, including: platelet activating factor (PAF), arachidonic acid, diphosphate adenocine (ADP) since it is well known that platelets are involved in the haematogenous process of cancer metastasis. There are also various reports of phot-killing effect of TiO_2 NPs in cancer cells (Fujishima et al., 1993; Fujishima, Hashimoto, & Watanabe, 1999; Kubota et al., 1994; Thevenot et al., 2008). Other studies support that there is an enhanced effect of nano-sized TiO_2 on drug uptake, by drug-resistant leukaemia cells, under UV light irradiation (Song et al., 2006). This could be very promising, considering that the appearance of multidrug-resistant tumor cells is a one of the major obstacles to the success of a chemotherapy. There are also interesting attempts, including the use of X-rays, in order to photo-activate TiO_2 NPs (Schmidt-Stein et al., 2009) and others which exploit the photocatalytic effect of TiO_2 and the electroporation, in combination with monoclonal antibodies in order to target cancer cells (Sette et al., 2013). The monoclonal antibodies may enable the targeting of the cancer cells, while the photoinduction can trigger the generation of radicals, locally, and the electroporation may accelerate the tranfer and perhaps the entrance of TiO_2 NPs into the cancer cells (Jia, Omri, Krishnan, & McCluskie, 2017; Xu et al., 2007). Representative anticancer applications of TiO_2 on cancer cells are summed-up in Table 1.

These results and many other derived from intensive studies, show that photo-excited TiO_2 NPs can be proposed as an anticancer agent, under controlled conditions (Behnam et al., 2018). The use of TiO_2 NPs might allow the targeted cancer cell attack, but there is the need of a protection system of the surrounding healthy tissues (Zhang, Guo, Ding, Xiong, & Chen, 2016). This kind of regulation can be achieved with the development of a system of directed beams of light, which can focus on the target-area, allowing the triggering of the photocatalysis and the ROS production only in the area of interest (Nita & Grzybowski, 2016). Thus, this cell population will face oxidative stress-mediated cell death, leaving the healthy cells unaffected (Davalli, Mitic, Caporali, Lauriola, & D'Arca, 2016).

There are many hypotheses about the way, through TiO_2 NPs lead to cell death or to the inhibition of cell proliferation (Huerta-García et al., 2018). TiO_2 particle-mediated cell toxicity could potentially be the result of the cell-particle interactions. Actually, although the relationship between physicochemical parameters and potential toxicological effects is not totally clear, it seems that cell toxicity is related to the surface properties of the TiO_2 NPs (Warheit, Webb, Reed, Frerichs, & Sayes, 2007) playing a critical role on the efficacy of NPs (Oberdörster, Oberdörster, & Oberdörster, 2005; Sayes et al., 2006). The size and the surface area seem to be very important parameters, affecting the ROS

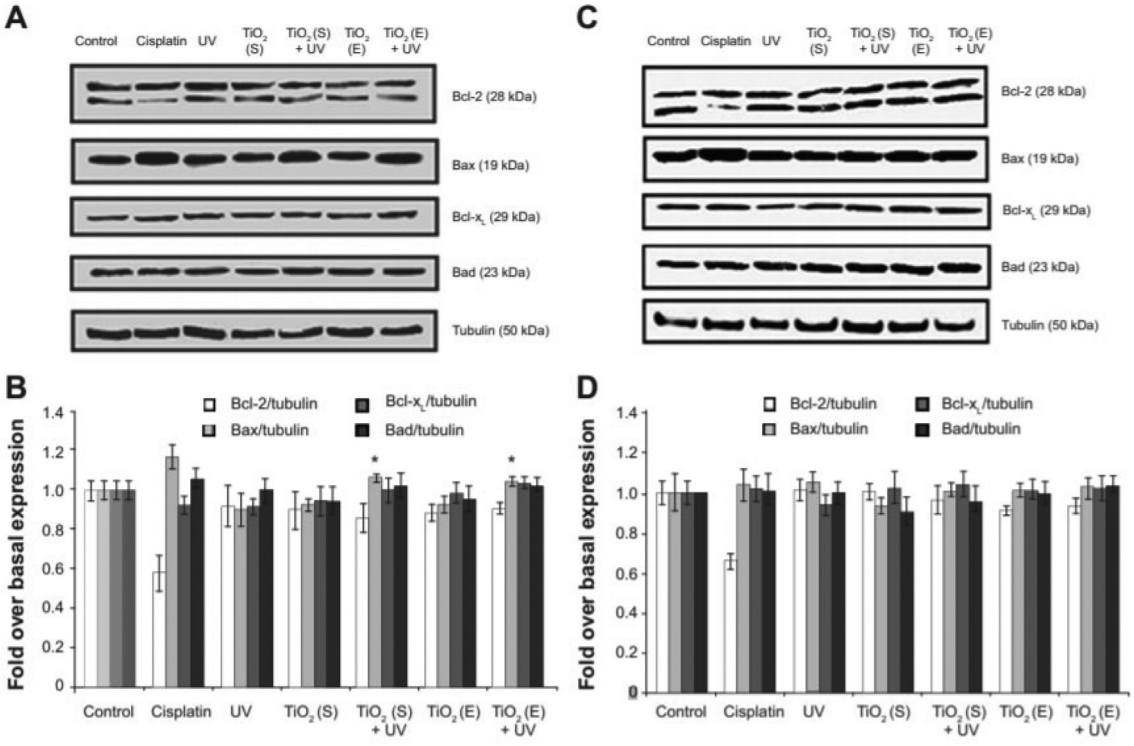

Fig. 5. Photoexcited TiO_2 NPs increased Bax expression in MDA-MB-468 cells. Representative Western blots of Bcl-2, Bax, Bcl-xL, and Bad expression in (A) MDA-MB-468 cells and (C) MCF-7 cells. Blots were stripped and reprobed with anti-tubulin antibody to normalize the blots for protein levels. Densitometric quantification of Bcl-2/tubulin, Bax/tubulin, Bcl-xL /tubulin and Bad/tubulin as fold over basal rate (control cells) in (B) MDA-MB-468 cells and (D) MCF-7 cells. *P<0.05 versus control cells. Lysates of cells treated for 24 hours with cisplatin (1 mg/mL) were used as positive control for induction of Bcl-2 family protein expression. Data represent means ± standard deviation from three independent experiments (Lagopati et al., 2014 – Copyright License by Dove Press).

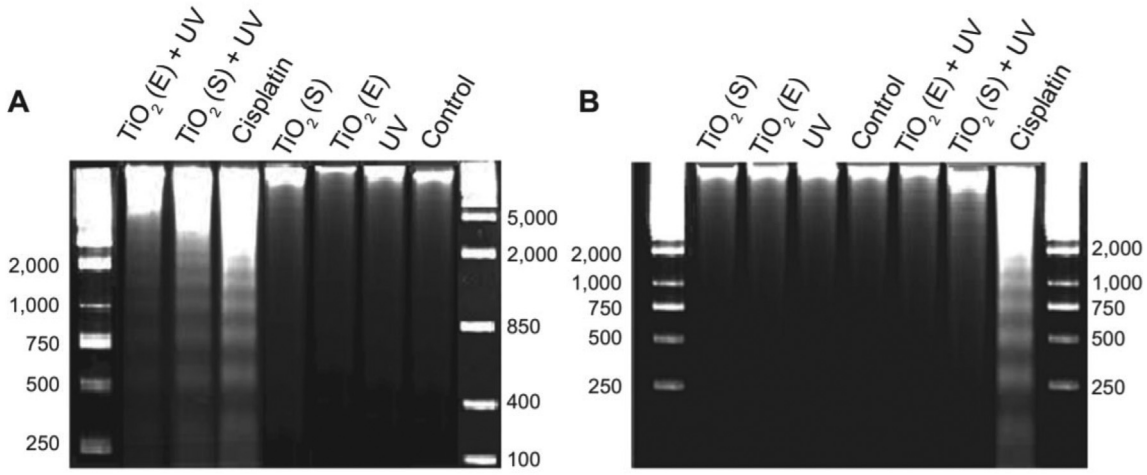

Fig. 6. Photoexcited TiO_2 NPs induced DNA fragmentation (laddering) in MDA-MB-468 cells. Representative images of DNA laddering in (A) MDA-MB-468 and (B) MCF-7 cells, showing the number of base pairs. Cells treated for 24 hours with cisplatin (1 mg/mL) were used as positive control for induction of DNA fragmentation (Lagopati et al., 2014 – Copyright License by Dove Press).

production and the biological effect of TiO_2 NPs (Jiang et al., 2008; Oberdörster et al., 2005) (Fig. 7). Furthermore, the cytotoxicity of TiO_2 NPs is affected by the ratio of the different crystal isomorphs. In fact, the cytotoxicity of TiO_2 NPs of similar size, but of different crystal structure gradually decreases, as their composition changed from pure anatase to anatase–rutile mixtures.

Other studies reveal that TiO_2 NPs have a negative charge (at pH 7) and can bind selectively to amino acids containing –OH, –NH, and $–NH_2$ in their side chains (Topoglidis, Discher, Moser, Dutton, & Durrant, 2003; Tran, Nosaka, & Nosaka, 2006). Hence, TiO_2 NPs may react with cell membrane proteins and contribute to cell-particle interactions (Lagopati et al., 2010). It seems that the cytotoxicity against cancer cells, depends on the cell type, the particle concentration and the surface properties.

4. TiO_2 and senescence

Cellular senescence is considered a cellular stress response that normally acts towards preservation of cellular/tissue homeostasis. It is activated upon the occurrence of numerous stressors (exposure to genotoxic agents, nutrient deprivation, hypoxia, mitochondrial dysfunction, and oncogene activation) and is implicated in various physiological processes as well as in a wide spectrum of age-related diseases, including cancer (Gorgoulis et al., 2019; Myrianthopoulos et al., 2019). Initially, it was described as replicative senescence that is related to telomere length shortening (Hayflick & Moorhead, 1961) while stress induced premature senescence (SIPS) that can be induced independently of telomere attrition by a variety of stress signals was later (Gorgoulis et al., 2019; Munoz-Espín & Serrano, 2014; Myrianthopoulos et al., 2019). Oncogene induced senescence is a well described representative of SIPS (Gorgoulis & Halazonetis, 2010) and in the earliest stages of cancer, senescence inhibits the propagation of incipient cancer cells, l similarly to apoptosis; thus, acting as an additional anti-cancer barrier (Bartkova et al 2006, Halazonetis et al 2008, Gorgoulis et al., 2019). Apart from its beneficial effects during carcinogenesis, senescence exerts also tumor promoting properties via a specialized secretory activity termed Senescence Associated Secretory Phenotype (SASP) (Gorgoulis et al., 2019). Other main hallmarks of the senescent cell are cell cycle withdrawal/tolerance against apoptosis, deregulated metabolism and macromolecular damage reflected by lipofuscin accumulation (Gorgoulis et al., 2019). Moreover, increased lysosomal senescence-associated β-galactosidase (SA-β-gal) activity, nuclear $p16^{INK4A/ARF}$ and $p21^{WAF1/Cip1}$ positivity, loss of Lamin B1 and senescence associated heterochromatin foci (SAHF) have been used to verify the senescence phenotype (Gorgoulis et al., 2019; Myrianthopoulos et al., 2019). Altogether these approaches have to some extent allowed the recognition of senescent cells. The latter has emerged as a critical issue given the increasing evidence of the role of senescence in human diseases and the rapidly expanding field of senotherapeutics, as well (Gorgoulis et al., 2019; van Deursen, 2014). For example, in primary human malignancies (Hodgkin's lymphomas) senescence has been shown to be related with poor clinical outcome, suggesting a putative role of senolytics in the treatment of this disease (Myrianthopoulos et al., 2019). In this context, the development of innovative therapeutic and diagnostic applications based on nanotechnology might allow the accurate targeting of senescent cells (Muñoz-Espín, 2019).

As it is already reported, NSMs are characterized by high specific surface area that correlates with high interfacial chemical and physical reactivity, being, in turn, biologically reactive in various ways either by inducing cell death or by binding and stimulating other cellular responses, like cellular senescence (Schosserer, Grillari, & Breitenbach, 2017). Magnetic nanoparticles (NPs), for MRI, or NSMs for PET, SPECT and other imaging devices have been developed in order to optimize the detection of senescent cells for diagnostic purposes (Thomas et al., 2019). Coated mesoporous silica nanoparticles, zinc oxides and titanium dioxide are among the most famous NPs, interacting with senescent cells and focusing on clearance, tissue repair and regeneration either as a monotherapy or in combination with conventional treatments (Hackenberg et al., 2017; Muñoz-Espín, 2019). Molecularly imprinted nanoparticles (nanoMIPs) could target surface proteins in senescent cells. NanoMIPs can use as epitopes, specific membrane proteins with extracellular domains which are particularly induced in these cells (Ekpenyong-Akiba et al., 2019). Thus, when the nanoMIPs are tagged with fluorescent probes, they can provide a novel tool for the detection of senescent cells (Althubiti et al., 2014), while when these nanoMIPs are loaded with the appropriate drug, for controlled release, they can be used to destroy senescent cells (Childs et al., 2017).

Cytoplasmic lipofuscin aggregation is an established hallmark of senescence and reflects deregulation of metabolism and macromolecular damage that characterizes as previously mentioned senescent cells (Georgakopoulou et al., 2013, Evangelou et al., 2017; Gorgoulis et al., 2019; Myrianthopoulos et al., 2019). GL13 is a biotinylated Sudan Black-B (SBB) chemical analog, commercially available as "SenTraGor™", that specifically interacts with lipofuscin. The reagent allows of precise recognition of senescent cells *in vitro* and *ex vivo,* by applying an

Table 1
Representative anticancer applications of TiO_2, related molecular mechanisms and experimental outcomes.

TiO_2 (Type)	Cell Type - Animal type	Method	Effect - possible mediated mechanism	Author
Commercially available TiO_2 – emulsion	• Human immortalized HaCaT keratinocyte cell line, Human dermal fibroblasts (HDFs), obtained from de-epidermized dermis, Human immortalized sebaceous gland cell line SZ95, Primary human melanocytes	• MTT Assay • Flow Cytometry - Annexin V • Nuclear microanalysis • Western Blotting • Calcium imaging	Effect on cell proliferation, viability, apoptosis and differentiation • Not reaching 'living' cells layers in human skin xenografts. • Inducing changes in the calcium-handling. • Decreased expression of the keratinocyte differentiation marker involucrin and the levels of the cell adhesion molecules desmoglein-1 and P-Cadherin.	Kiss et al., 2008
Commercially available TiO_2 NPs (anatase)	Human non-small cell lung cancer cells (A549 cells)	• MTT Assay • DAPI staining • Comet Assay • Cell cycle analysis – Flow Cytometry • Measurement of mitochondrial potential ($\Delta\Psi m$) • qRT-PCR	Apoptotic cell death, Inhibition of Cell proliferation, Morphological changes • Dose-Dependent DNA damage • G2/M cell cycle arrest • Alterations in the mitochondrial membrane potential • increased mRNA levels of caspase-3 and caspase-9 genes	Wang, Cui, et al., 2015
Commercially available TiO_2 NPs (anatase)	Human colon carcinoma cells (Caco-2 cells)	• Neutral Red Uptake and Colony Forming Efficiency (CFE) assays • Determination of ROS production • Tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6) and interleukin-8 (IL-8) cytokine release	Apoptotic cell death, • No effect on cell viability • Higher level of ROS in a dose-dependent manner after 6 h • IL-8 release	De Angelis et al., 2013
Commercially available TiO_2 NPs (anatase)-P25	Cervical cancer cells (HeLa cells)	• Surviving Fraction • Distribution of NPs via TEM microscopy	Photokilling effect • Photokilling effect under UV light irradiation • TiO_2 NPs are found on the cell membrane and on cytoplasm • ROS production	Cai et al., 1991; Cai et al., 1992
Commercially available TiO_2 NPs (anatase)-Degussa P25	Drug-resistant leukaemia cells (K562 cells)	• Confocal fluorescence microscopy	Enhancement of drug (daunorubicin) uptake TiO_2 NPs act as anti-MDR (MultiDrug Resistance) agent	Song et al., 2006
PEG-TiO_2 colloids	Pancreatic ductal adenocarcinoma (PDAC) cell lines, Panc-1 and MIA PaCa-2	• ELISA Assay against S5-P peptide • WST-1 assay • Immunofluorescence • TEM	Electroporation in combination with monoclonal antibodies against the Kv 11.1 potassium channel protein No effect on cell viability Kv 11.1-Mab-PEG–TiO2 NPs recognized the whole antigen	Sette et al., 2013
Sol-gel TiO_2	Breast cancer epithelial cells MDA-MB-468 and MCF-7	• DNA quantification: propidium iodide (PI) staining and flow cytometry (FACScan) • MTT assay • Western blotting	Effect on the cell cycle, on cell viability and apoptosis MDA-MB-468: decrease in the percentage of cells in G1 phase Dose-dependent decrease in cell viability Significant increase of PARP cleavage MCF-7: No significant effect	Lagopati et al., 2010
Commercially available TiO_2 P25 (anatase 75%–rutile 25%) and TiO_2 (100% anatase)	Breast cancer epithelial cells MDA-MB-468 and MCF-7	• MTT assay • Western blotting • DNA Laddering	Cyto-toxicity, Apoptosis MDA-MB-468: Dose-dependent reduction in cell viability Significant increase of PARP cleavage Upregulation of Bax expression No effect on Bcl-2, Bcl-xL and Bad expression DNA fragmentation MCF-7: No significant effect	Lagopati et al., 2014
Commercially available TiO_2 NPs anatase)-Degussa P25	Sarcoma cells, fibroblasts MCR-5, leiomyosarcoma cell line, platelet rich plasma (prp)	• Cell Growth Rates • Platelet aggregation • Enzymatic kinetics of 2,3-lipoxygenase	Inhibition of cell proliferation on sarcoma cells • No toxicity on MCR-5 • No effect on PAF platelet's aggregation for low TiO_2 concentrations • Important PAF and Arachidonic acid triggered desegregation • Significant alterations in the enzymatic activity	Stefanou et al., 2010
Colloidal TiO_2 NPs/Doxorubicin	MCF-7 Cells and multidrug resistant (MCF-7/ADM) cells	• Drug release • MTT Assay • Elemental Fluorescence mapping • Confocal laser scanning microscopy	pH controlled drug release system No effect on cell viability Endocytosis of TiO_2 NPs / Dox Accumulation of TiO_2 NPs / Dox in the nucleus	Ren et al., 2013

(continued on next page)

Table 1 (*continued*)

TiO_2 (Type)	Cell Type - Animal type	Method	Effect - possible mediated mechanism	Author
		• In vitro reversal of drug resistance		
Commercially available TiO_2 NPs (anatase)- PEG - TiO_2 NPs	metastatic murine melanoma cell line, B16/F10 /inbred mice	• Photo-Thermal Therapy • Histopathological examination	Induction of hyperthermia and necrosis in malignant tumor cells Destruction of solid tumors	Behnam et al., 2018
Commercially available TiO_2 NPs (anatase)-P25	T-24 cells	• colony-forming cyto-toxicity assay • Microscopical observation	Photokilling effect Dose and irradiation time-dependent photokilling effect Endocytosis: TiO_2 NPs are found on the cell membrane and on cytoplasm.	Kubota et al., 1994
Thin films. Commercially available TiO_2 NPs (anatase)-P25 enhanced by pulsed plasmas	LLC cells, JHU prostate cancer cell line, B16F10 and B16F1 are skin melanoma cells, 3T3 fibroblasts.	• Live/Dead staining • MTS assay • Lactate dehydroge-nase (LDH) Assay • FM1-43 Staning	Cytotoxicity Significant cytotoxicity on LLC cells. Lower toxicity on B16F10 and JHU cells. No effect in 3T3 and B16F1 cell viability Increase LDH activity Broken Membranes, Leakage of cytoplasm	Thevenot et al., 2008

antibody mediated detection method (Evangelou et al., 2017; Myrianthopoulos et al., 2019; Gorgoulis et al., 2019). The assay can also be implemented for the quantitative determination of soluble or extracted lipofuscin levels in cell culture supernatants, body fluids and tissue homogenates, (Rizou et al., 2019). However, the mapping of senescent cells *in vivo (particularly in living organisms)* still remains an attractive challenge. The novel GL13 compound could be enriched, by the incorporation of titanium dioxide quantum dots (also gold or carbon quantum dots might be used) or another appropriate nano-carrier and a hydrophilic hull to encapsulate the whole system. These modifications could renderGL13 a promising candidate for molecular imaging *in vivo*, employing a PET or a PET Hybrid System.

There are several studies that highlight the concern about the possible negative effect of TiO_2 NPs due to their potential for ROS formation (Li, Yina, Wamera, & Lo, 2014; Shukla et al., 2011). More specifically, high levels of generated ROS promoting oxidative stress and DNA damage which primarily affect mitochondrial function (Tucci et al., 2013) and are manifested as mitochondrial "common deletion" in HaCaT

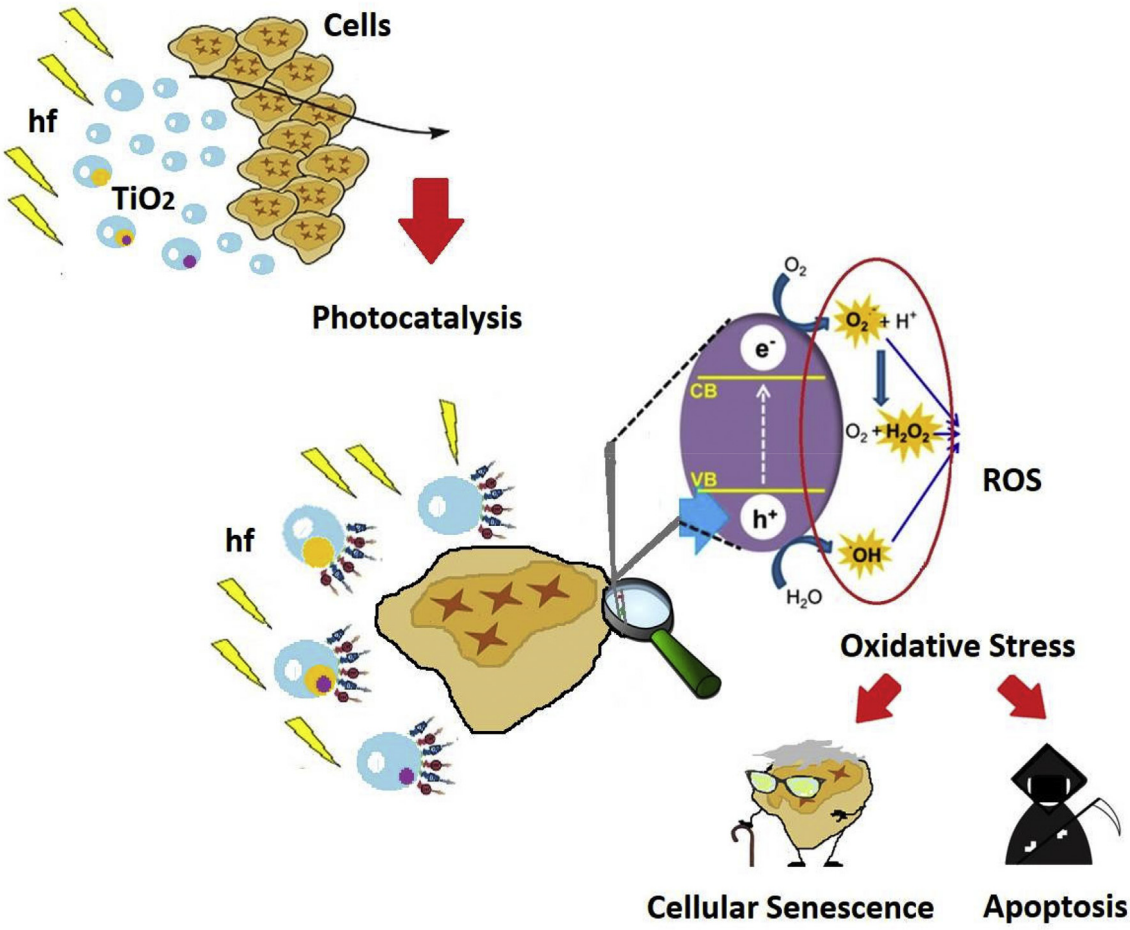

Fig. 7. Schematic representation of the proposed mechanism and the biological effect of photocatalytic activation of TiO_2 on cancer cells.

keratinocytes exposured to TiO_2 NPs (Jaeger, Weiss, & Jonas, 2012) reveal their cytotoxic and genotoxic ability. Since ROS are implicated in cellular senescence, thus, the oxidative stress-induced senescence triggered by TiO_2 nanoparticles could be exploited in order to induce in a controlled and dose dependent manner ROS-mediated cellular senescence in cancer cells. This could be an alternative "chemo" treatment avoiding the undesirable side effects (Abdal Dayem et al., 2017; Davalli et al., 2016), while the effectiveness of eliminating cancer cells could be significantly increased if the NPs are conjucated with Ag or folic acid (Bogdan, Pławińska-Czarnak, & Zarzyńska, 2017). In a second level, the development or the use of another type of NPs or the same, but after a chemical modification, could be proposed in order to trigger the clearance mechanism which could allow the transformation of the phenotype of these cells, allowing cell repair.

5. Need of chemical doping

As it was previously mentioned, during photocatalysis, the charge separation is short-lived, and the light absorption is limited (Xu, Anusuyadevi, Aymonier, Luque, & Marre, 2019). Thus, the performance of the semiconductor photocatalysts are relatively unsatisfactory and sometimes these are not suitable for practical applications, especially in clinical routine (Zhang et al., 2019). Several strategies have been proposed by researchers to improve the properties of the photocatalysts, such as doping, dye-sensitization and coupling, each of them with its own pros and cons (Fu et al., 2019).

Toward the strategy of dye-sensitization, light-sensitive dyes are selected in order to maximize the light absorption (Balasingam, Lee, Kang, & Jun, 2013). But, although the light-sensitive dyes can absorb light efficiently and transfer the photo-excited electrons to the photocatalyst, these dyes are proven to be susceptible to chemical corrosion, resulting in the poor stability of the developed dye-sensitized semiconductor photocatalysts (Wang et al., 2014).

Regarding the coupling, it is considered a strategy with a relatively short history and for this reason has aroused great interest among researchers. Coupling with metals and particularly with noble metals, leads to the improvement of the semiconductor photocatalyst (Fu et al., 2019). This is achievable, partly due to the enhanced charge separation at the metal–semiconductor interface and also due to the enhanced absorption of the visible light, caused by the surface plasmon resonance (SPR) of metals (Kumar, O'Donnell, Sang, Maggard, & Wang, 2019). The main disadvantages of the method are the high cost of noble metals as well as the poor control of the process of coupling with metals (Ola & Maroto-Valer, 2015).

Pure TiO_2 NPs can be photo-activated by UV light (Galata et al., 2019). Because of the harmful effects of UV in medical applications, which are reported to be related to DNA damage (mutations, single strand breaks (SSBs), double strand breaks (DSBs) etc.), UV is usually preferable to be avoided and replaced by other alternatives (Rastogi, Richa Kumar, Tyagi, & Sinha, 2010). The photocatalytic response of TiO_2 in visible light, can be achieved, by chemical doping with metals, or non-metal chemical elements. Novel surface modification strategies can lead to bio-interactive interfaces (Colmenares et al., 2009).

The most common dopant is nitrogen, as recent studies highlight its quite important anticancer properties (Ansari, Khan, Ansari, & Cho, 2016). Nitrogen leads to the reduction of the energy gap at 2.7 eV, allowing the phot-excitation with visible light (Preethi, Antony, Mathews, Walczak, & Gopinath, 2017). According to our experience, applying photo-activated nitrogen-doped TiO_2 NPs leads to a significant decrease in cell proliferation of the highly malignant breast cancer epithelial cells MDA-MB-231. In the presence of photo-activated N-doped/TiO_2 with visible light, there is also an obvious PARP cleavage, indicating that MDA-MB-231 cells are apoptotic. Photo-excited N-doped/TiO_2 did not affected the non-metastatic breast cancer epithelial cells MCF-7 (Fig. 8).

Iron, fluorine and sulfur are also among the prevalent candidates for chemical modification. Another choice is the doping with silver, focusing on minimizing the reconnection between of the photoelectrons of conduction zone with the holes of the semiconductor valency, in order to promote reactive oxygen species (ROS) generation and thus up-regulating the TiO_2 biological activity (Ahamed, Khan, Akhtar, Alhadlaq, & Alshamsan, 2017). Moreover, the co-doping with two or more dopants is selected it order to maximize the performance of the photocatalyst. For instance, co-doping with nitrogen and silver allows both the decrease in size and the photo-excitation in visible light (Williamson et al., 2019).

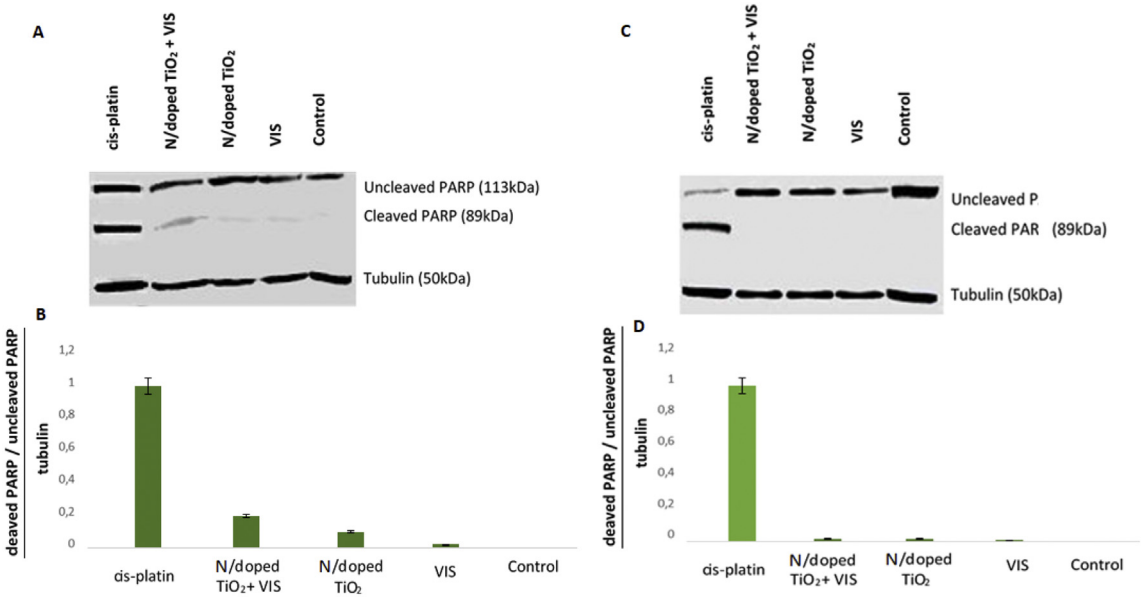

Fig. 8. Photoexcited N-doped TiO_2 NPs induced caspase-3-mediated PARP cleavage. MDA-MB-468 (A) and MCF-7 cells (C) were treated with 0,8 mg/ml N-doped TiO_2, irradiated with visible light and incubated for 48 h. Representative Western blots (A and C) of uncleaved and cleaved PARP. Cells treated with 1mg/ml cis-platin for 24 h were used as positive control for induction of PARP cleavage. Blots were stripped and re-probed with anti-tubulin antibody to normalize the blots for protein levels. (B and D) Densitometric quantification of cleaved/uncleaved PARP to tubulin levels. Data represent the means ± SD from three independent experiments. *$P < 0.05$ as compared to cleaved/uncleaved PARP/tubulin levels of untreated cells.

It is important to highlight the necessity of full characterization, utilizing techniques like, micro-Raman, XRD, SEM, FT-IR, XPS, TEM, DLS. This phase is absolutely imposed and necessary in order to confirm that the produced nanoparticles gather the desirable features and the appropriate physical and chemical properties, with regard to crystal phase, size, z potential, homogeneity, band gap and other important factors. Optimization is the key process for every scientific study, which focuses in the development of novel nanomaterials, particularly if these nanoparticles are designed in order to be applied as anticancer agents in a biological system *in vitro* or *in vivo*.

6. Conclusions

Nanomedicine is a specific scientific field medicine that applies the fundamentals of nanotechnology. Due to their potential, various nanostructured materials can be selected for diagnostic or therapeutic purposes. TiO_2 is considered as a well-characterized popular, commercially available, nanomaterial with great applications of everyday routine and of advanced technology. It is also used in biomedical applications, due to the mechanical and the photocatalytic properties as well as its biocompatibility. It is well established that photoactivated TiO_2 NPs, induce reactive oxygen species (ROS), damaging cancer cells. Giving a sense of the properties of this material and the increased interest around its applications, this review article focused on providing insights into the field of nanomedicine and particularly into the wide context of TiO_2-NP-mediated anticancer effect, shedding light on the achievements of nanotechnology and proposing this nanostructured material as a promising anticancer photosensitizer.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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