Introduction to Hyperthermia

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1 HYPERTHERMIA AS THERAPEUTIC APPROACH

1.1 Short History of Hyperthermia

The term “hyperthermia,” derived from the Greek words “*hyper*” (meaning “rise,” “over,” or “above”) and “*therme*” (heat) refers to the increase in the temperature of the whole body or of specific body regions above physiological values with the aim of achieving a therapeutic effect.

The use of heat for the treatment of different diseases had been acknowledged since ancient times [1–3]. There are several references to hyperthermia in traditional Indian medicine (Ayurveda, c. 3000 BCE), as well as in ancient Egyptian medical texts, such as The Edwin Smith Papyrus (about 1700 BCE) and The Ebers Papyrus (about 1550 BCE). The Greeks and the Romans were also familiar with the healing potential of heat, many of the physicians of the era believing that the ability to control body temperature would allow them to cure practically any disease. Parmenides of Elea (c. 540–480 BCE) stated: “Give me the power to induce fever and I will cure all diseases,” while Hippocrates is well known for his aphorism “those who cannot be cured by medicine can be cured by surgery; those who cannot be cured by surgery can be cured by heat; and those who cannot be cured by heat are to be considered incurable.”

The first mention of hyperthermia in cancer treatment can be found in “De Medicina,” the work of the Roman doctor Celsus (c. 25 BCE–50 CE), who recommended the use of hot baths in incipient stages of cancer and acknowledged for the first time the enhanced thermosensitivity of tumors, vide infra. In the Middle Age there are also reports on tumor regression in patients with diseases accompanied by high fever (e.g., smallpox, malaria, or tuberculosis).

The first paper on hyperthermia was published in 1886, when the German surgeon Carl D. W. Busch reported sarcoma regression induced by fever in a 43-year-old patient suffering from erysipelas. He observed that, while cancer growth was stopped at temperatures above 42°C, healthy cells seemed to tolerate well the increase in temperature. The American surgeon William D. Coley confirmed these results in 1893; Coley is dubbed the father of modern hyperthermia and immunotherapy cancer treatment due to its approach of inducing fever in cancer patients by injecting pyrogenic toxins into tumors. Other types of hyperthermia treatment in the late 1800s and early 1900s included *hot baths*, *perfusion hyperthermia* (using the patient’s previously warmed own blood), *electrical cauterization*, and *surgical diathermy*, consisting in circulating high-temperature water (>42°C) through metallic coils. Nevertheless, all these approaches yielded irreproducible or mixed results and some were extremely invasive, resulting in severe pain.

This, together with the discovery of X-rays and radioactivity at the end of the 19th century (with radiotherapy emerging as a new therapeutic approach for cancer treatment), led to a decrease in the interest in hyperthermia. However, in 1912 a first clinical trial involving combined radiotherapy and hyperthermia in 100 patients demonstrated the potentiation of radiotherapy in the presence of heat.

The interest in the use of heat as therapeutic tool began to rise again after the first international conference on hyperthermic oncology, held in 1975. Much of the research carried out in this period was focused on understanding and unraveling the biological effects of heat, especially regarding the thermal radio- and chemosensitization of tumor tissues [1]. Despite this new enthusiasm, the widespread use of hyperthermia in the clinical setting was hampered by the lack of precise and noninvasive thermometry methods, unsatisfactory heat generation techniques, able to reach deep tumors, and the nonconclusive clinical outcomes as consequence of nonstandardized randomized trials.

Since 2000, the research in the field of hyperthermia has experienced a considerable growth, with more than 100 clinical trials involving hyperthermia as part of the therapy [4], and almost 30,000 scientific publications between 2000 and 2018, according to Web of Science. This can be attributed to several factors, including improvements in the heating infrastructure, the development of more accurate temperature measurement techniques, and a better understanding of the biological effects of heat. But perhaps one of the most important roles is the one played by the rise of nanotechnology, as detailed in Section 1.2.

1.2 The Cellular and Molecular Foundation of Hyperthermia

As mentioned before, the first investigations regarding the cellular effects of hyperthermia date from the 1970s [5]. There are many excellent

reviews covering the topic [5–8]; we particularly recommend the comprehensive overview that can be found in the work of Hildebrandt et al. Hereafter, we provide a short description of such effects in order to equip the reader with some basic concepts that will facilitate the understanding of the content of this book.

1.2.1 The Effect of Hyperthermia at Cellular Level

Hyperthermia affects a series of cellular functions at different cellular levels. Increased temperatures can lead to an increased fluidity and permeability of the cellular membrane and can induce cytoskeletal changes (e.g., alterations of cell shape and membrane blebbing, changes in membrane potential, etc.). At temperatures between 42°C and 45°C, it has been shown that mechanisms of protein and nucleic acid synthesis have slowed down. While ribonucleic acid (RNA) and protein synthesis resume quickly after the removal of the thermal stress agent, deoxyribonucleic acid (DNA) synthesis does not. This is because heat shock over a certain threshold thermal dose (which depends on the cell line) can induce protein denaturation and aggregation, impairing several cellular functions, including DNA synthesis and repair. This is the common explanation behind the mechanism of enhancement of chemo- and radiotherapy by hyperthermia [Note: A detailed discussion regarding chemo- and radiosensitization is outside of the scope of this book; the interested reader is referred to several literature revisions of the topic [3, 5, 9]]. Moreover, at moderate temperatures (<42°C), hyperthermia treatment can increase tumoral perfusion and oxygenation, sensitizing cancer cells toward radiotherapy; at temperatures exceeding 42°C, the decreased blood flow as consequence of tumor vasculature damage leads to hypoxia and a more acidic cellular environment. These effects are also considered to contribute to the radio- and chemosensitization of the cancer cells [10]. However, the process is far from being simple, as the sensitivity of cells to heat depends on the different phases of the cell cycle.

1.2.2 Heat Shock Proteins

Heat shock proteins (HSPs) are a group of proteins overexpressed under thermal stress conditions. They have different sizes—small HSPs (with molecular mass less than 40kDa), HSP 60, HSP 70, HSP 90, and HSP 100 families—and biological functions, having in common the chaperoning role (they prevent the loss of function of other proteins by assisting their correct folding/refolding). Although HSPs have been initially described in relation to thermal stress, nowadays it is known that they are involved in a series of other stress conditions (with HSP 27 and HSP 70 being called “general survival proteins”). In hyperthermia, the overexpression of HSP 27 and HSP 70 offers protection against lethal thermal damage by inhibiting programmed cell death mechanisms [11]. However, HSP overexpression in cancer cells has been associated with thermoresistance and cancer progression. This dichotomy and the fact that HSPs have immunogenic properties are being exploited for developing new cancer therapy solutions (inhibition of HSP 70 and anticancer vaccines) [11, 12].

1.3 Hyperthermia Modalities

There are three main methods for the application of hyperthermia in the clinical setting: local, regional, and whole-body hyperthermia [3, 13]. While local and regional hyperthermia are typically used as adjuvant therapy for local chemo- and radiotherapy, whole-body hyperthermia can also be used as a stand-alone methods for the treatment of metastatic cancers. Heat can be generated using capacitive, radiative (radio- or microwaves), or infrared-based systems [14].

Local hyperthermia is applied with the goal to heat small tumor areas using radio- and microwaves or ultrasounds, usually at a temperature of 42°C. Heat penetration depth in local hyperthermia generally does not exceed a few centimeters, and the application of this type of treatment is further restricted in areas with

irregularities (e.g., axilla, neck, and head). Thermal energy in local hyperthermia can be delivered by a variety of methods: *external* (a superficial or external applicator is used to heat a subcutaneous tumor), *intraluminal* (the applicator is placed inside the cavity, e.g., for esophageal cancer), *interstitial* (applicators or antennas are implanted directly in the tumor, as for prostate or head and neck cancers), and *endocavitary* (the applicator is inserted in the cavity of hollow organs, e.g., vagina, rectum, and esophagus).

In *regional hyperthermia*, used for the treatment of larger and deeply seated tumors, heat is applied using external arrays of antennas/applicators placed around the area of interest, or by regional perfusion using fluids (such as the patient’s own blood or chemotherapeutic agents). This type of hyperthermia is applied either alone or in combination with chemotherapy for the treatment of melanomas, lung, liver, gastric, and peritoneal cancers. When regional hyperthermia is used as a stand-alone therapy, higher temperatures (43°C) are generally tolerated well for a period of up to 2 h; the temperature must be reduced when used in combination with chemotherapeutic agents.

Whole-body hyperthermia is used to raise the temperature of the whole body to 41–42°C for about 1 h under anesthesia or sedation. The temperature can be achieved by different means: hot water blankets, hot wax, infrared, or hot water thermal chambers. When used in combination with chemotherapy, a slightly lower temperature (40°C) can be applied for a longer period of time.

2 HYPERTHERMIA AT THE NANOSCALE—WHY NANOMATERIALS?

2.1 Introduction

Current challenges regarding the traditional hyperthermia modalities described in the previous section include: (i) the uniform generation of

heat in the desired area (while minimizing the heating of the surrounding tissue), (ii) the development of methods for precise temperature control during the hyperthermia treatment, (iii) insufficient heating of the target tissue [10, 15, 16]. In this sense, nanotechnology can offer unique solutions. Several types of nanomaterials are able to convert the energy absorbed from external sources (such as magnetic fields or light) into heat (so-called “nanoheaters”); if such nanomaterials are suitably decorated with tumor-targeting ligands, they can be selectively delivered to the target tissue, thus ensuring that the generation of heat is limited to the area of interest and avoiding unnecessary heating and damage of healthy tissues. Moreover, the use of nanomaterials as platforms for controlled drug release can lead to the development of more efficient theranostic agents, combining diagnostics and therapy in a single multifunctional nanoplatform; this is often referred to as the “magic nanobullet” [17]. Furthermore, nanomaterials hold great promise for the development of accurate temperature probes (“nanothermometers”), able to monitor local temperatures generated by nanoscale hyperthermia [18, 19]. The possibility of joining nanoheating and nanothermometry in a single nanoparticle demonstrates the potential of nanotechnology for further developments in hyperthermia at the nanoscale [20].

In the past two decades, nanotechnology has witnessed a rapid development, and nowadays nanomaterials offer exciting possibilities for new developments in nanomedicine and nanobiotechnology. A major milestone reached in nanotechnology is represented by the current ability to synthesize nanomaterials with a high degree of control over their size, shape, composition, and surface chemistry. This, in combination with suitable surface (bio)functionalization techniques aiming at ensuring stability in physiological conditions, has led to the development of novel multifunctional nanomaterials capable of overcoming biological barriers. Often,

such systems integrate targeting ligands (e.g., antibodies, cell-penetrating peptides, proteins, aptamers) for *active targeting* of the nanomaterials to their desired site of action. Nanomaterials can be engineered to act also as smart drug delivery vehicles, accommodating the targeting, diagnostic, and therapeutic (hyperthermia and/or drug release) functionalities in a single multifunctional platform. The concept of “theranostic nanoparticle” is one of the most promising developments for personalized medicine [21]. Lastly, we would like to briefly introduce the concept of *passive targeting* of nanomaterials, especially relevant for cancer treatment due to the specific physiological features of tumors that result in the so-called “enhanced permeability and retention (EPR) effect” [22]. Solid tumors usually have a poorly organized vasculature, resulting in leaky blood vessels, with fenestrations of 20–2000 nm. This particular feature enables the delivery of nanoparticles, while the deficient lymphatic drainage of the tumor is responsible for their accumulation and retention at the tumor site [23].

This book will focus on two main types of nanomaterials, namely magnetic and noble metal nanoparticles, although some examples concerning the use of carbon-based nanomaterials as emerging optical hyperthermia mediators will be provided. To understand heat generation at the nanoscale in magnetic and optical hyperthermia, it is fundamental to grasp the idea that at nanoscale level, materials have unique properties, nonexistent in their bulk counterparts. Thus, the most important features of nanomaterials in view of biomedical applications, especially hyperthermia, are briefly discussed as follows; for in-depth literature revisions, the readers are directed to several comprehensive reviews [21, 24–35].

2.2 Magnetic Nanoparticles

Magnetic nanoparticles (MNPs), especially iron oxide-based ones (magnetite Fe_3O_4 and maghemite $\gamma\text{-Fe}_2\text{O}_3$) are particularly appealing

for biomedical applications including magnetic hyperthermia, biosensing, as contrast agents for magnetic resonance imaging (MRI) and as drug delivery vehicles. This is due to their magnetic properties, which can be tuned according to their size, as well as to the biocompatibility and biodegradability of iron oxide nanoparticles [36].

Small MNPs usually present *superparamagnetic behavior*, which means that at room temperature and in the absence of an external magnetic field, these MNPs have no net magnetic moment. In the presence of a magnetic field, there is a net magnetization resulted from the alignment of the magnetic moments with the field; however, the magnetization does not persist after the removal of the magnetic field. This lack of remanent magnetization is fundamental for biomedical applications, as it ensures the colloidal stability of the MNPs and prevents their agglomeration in vivo. The MNPs are able to generate heat upon exposure to an alternating magnetic field (AMF), provided that the field can lead to a reorientation of the magnetic moments. This phenomenon is the basis of *magnetic hyperthermia* and its fundamentals will be described in more detail in [Section 2.5.1](#). Another interesting feature of MNPs is their ability to produce small local magnetic fields that can impact the relaxation times of the surrounding hydrogen atoms; this is the principle behind the use of MNPs as *contrast agents* in MRI or as *magnetic relaxation nanoswitches* in biosensing applications. The unique magnetic properties of MNPs can be also exploited for the tracking of their fate and biodistribution in vivo, via magnetic measurements such as alternating current (AC) magnetic susceptibility [36].

2.3 Plasmonic Nanomaterials

This class of nanomaterials, including mostly noble metal nanoparticles (the commonest being gold, silver, and platinum) owes its name to the unique mode of interaction with light due to the

localized surface plasmon resonance (LSPR) phenomenon. When these nanomaterials are excited with a source of light at a certain wavelength, a collective oscillation of the electrons in the conduction band occurs; this collective oscillation is named plasmon [37]. The LSPR wavelength depends on the chemical composition, size, shape, and aspect ratio of the plasmonic nanoparticle, and this is of paramount importance for hyperthermia applications, as it allows working in the so-called “biological window” (near-infrared region, NIR), in which biomolecules such as hemoglobin and melanin have limited absorption [38]. For instance, in the case of gold nanoparticles, the most studied type of plasmonic NP in hyperthermia applications, spherical nanoparticles usually exhibit LSPR bands in the visible region of the electromagnetic spectrum (500–600 nm). In anisotropic gold nanoparticles (possessing nonspherical geometries, such as nanorods, nanostars, nanoprisms, nanocages, etc.), the LSPR band can be tuned to NIR wavelengths (700–1000 nm).

2.4 Carbon-Based Nanomaterials

Carbon-based nanomaterials, including carbon nanotubes (CNTs), nanodiamonds, graphene, and graphene oxide, have been recently investigated for diverse applications due to their properties: large surface area, excellent mechanical resistance, high electrical conductivity, lightweight, and NIR absorption [26]. These interesting features arise from the confinement of carbon atoms at the nanoscale (a honeycomb lattice of sp^2 hybridized carbon atoms). Due to their shape and high aspect ratio, CNTs show enhanced absorption of NIR radiation (700–1100 nm) and can effectively and rapidly convert the absorbed radiation into heat [39]. Graphene, the newest addition to the family of carbon-based nanomaterials, consists of a single layer of sp^2 carbon atoms disposed in a hexagonal arrangement. This two-dimensional arrangement and the unique electron band structure

of graphene results in a plasmonic behavior at NIR wavelengths, with the subsequent heat generation.

2.5 Fundamentals of Nanomaterial-Based Magnetic and Optical Hyperthermia

2.5.1 Heat Generation in Magnetic Nanoparticle Hyperthermia

Bulk magnetic materials present several magnetic domains; in each of these domains, individual magnetic moments have a certain orientation. When the size of the material decreases, the number of magnetic domains is also reduced until, eventually, a single domain is reached in the case of small MNPs (monodomain MNPs, smaller than approximately 25–30 nm in diameter), while larger MNPs (up to 100 nm in diameter) usually have several magnetic domains (multidomain MNPs). Upon exposure of MNPs to an AMF, the reorientation of the magnetic moments can produce energy in the form of heat by a variety of mechanisms. For monodomain MNPs, which are generally the object of magnetic hyperthermia applications, heat generation occurs mainly via two relaxation mechanisms: Brown relaxation [21, 36, 40]. *Néel relaxation* consists in the rotation of the magnetic moments inside the MNP and is the only relaxation process that can take place when the rotation of the whole MNP is physically restrained (e.g., when MNPs are inside tumors). Néel relaxation is also the prevalent heat generation mechanism in small MNPs (below 15 nm diameter). When MNPs are present in a suspension, the movement of the whole particle can generate frictional losses with the environment, provided that the viscosity of the medium allows the MNPs to rotate freely (*Brown relaxation*). A more in-depth discussion on heat generation mechanisms can be found in [Chapter 1](#) of this book; for further details, see also the references mentioned in this paragraph.

The heating capacity of MNPs is a fundamental parameter in magnetic hyperthermia and is typically defined as the *specific absorption rate* (SAR; it can be found in the specialized literature also as “specific loss power,” *SLP*, “specific power absorption,” *SPA*, or “specific heating power,” *SHP*). This is defined as the heating power (P) generated per unit of mass of MNPs (m_{MNP}), or

$$\text{SAR} = P/m_{\text{MNP}} = C \left(\frac{\Delta T}{\Delta t} \right) \left(\frac{1}{m} \right) \quad (1)$$

where C is the sample specific heat capacity, m the mass concentration of the MNPs, and $(\Delta T/\Delta t)$ is the increase in temperature over time. However, some researchers prefer to describe the heating capacity of MNPs in terms of *intrinsic loss power* (ILP) [41]. This figure of merit takes into account the parameters of the AMF [frequency, f , and amplitude, H , see Eq. (2)] and enables a better comparison of the heating efficiency of MNPs measured in different laboratories and under different conditions.

$$\text{ILP} = \frac{\text{SAR}}{fH^2} \quad (2)$$

To conclude this section, we would like to draw the attention to a fact that, although clearly of the essence, remained rather overlooked for a long period of time in the realm of magnetic hyperthermia research: the characterization of the heating capacity of MNPs in different biological environments. As mentioned above, Brownian relaxation depends on the ability of the MNP to rotate freely; this ability is hindered or even suppressed in media with high viscosity (such as the intracellular environment) or when nanoparticles are immobilized in tumors or on cell membranes [42, 43]. It thus becomes clear that a mere evaluation of the heating capability (by means of SAR or ILP values) of MNPs in water is not sufficient; researchers should incorporate into their characterization toolbox experimental measurements and theoretical simulations

resembling more closely the biological conditions (e.g., high viscosity solvents, three-dimensional gels) and take into account the AMF parameters used for in vivo applications.

2.5.2 Heat Generation in Optical Hyperthermia

In the case of *noble metal nanoparticles*, exposure to a light source (typically a laser) with a wavelength in resonance with the oscillation of the surface plasmons results in the generation of heat through a three-step electron–phonon relaxation process [15, 44, 45]. During the first step—*electronic absorption*—the free electrons present in the metallic nanoparticle absorb part of the incident laser pulse energy. In the second step, the *electron–phonon thermalization* occurs, in which an internal thermal equilibrium is reached; at this point though there is no heat transfer to the surrounding medium. For spherical nanoparticles larger than 5 nm, the electron–phonon relaxation time (τ_T) required for reaching a steady-state temperature distribution inside the particle is estimated to be around 2 ps. If the laser pulse duration is shorter than τ_T , the heat generated remains confined in the particle; however, in practice τ_T is much shorter than the laser pulse duration, which results in *external heat diffusion* from the nanoparticle to its surroundings, with the subsequent increase in the local temperature of the medium and decrease in the temperature of the nanoparticle.

The heat generated by an individual nanoparticle (Q_{NP}) can be described in a simplified way as

$$Q_{NP} = C_{abs} \times I \quad (3)$$

where C_{abs} is the absorption cross-section area of the nanoparticle (the effective area absorbing the light under resonance conditions) and I is the laser irradiance (power per unit of surface) [38, 44]. For a sample of nanoparticles at a certain concentration, the SAR can be defined as

$$SAR = Q_{NP} \times N = C_{abs} \times I \times N \quad (4)$$

The absorption cross-section area can be tuned by changing the morphology and aspect ratio of the plasmonic nanoparticles; however, a more appropriate way to compare the absorption of light by nanoparticles of different geometries is the use of the *absorption efficiency*, in which the absorption cross-section area is normalized by the geometric cross section. It is worth mentioning that, for example, the absorption efficiency of gold nanorods is much higher when compared to gold nanospheres of similar dimensions [38].

Due to their electronic structure, *carbon-based nanomaterials* can behave as plasmonic nanomaterial when irradiated at infrared wavelengths and efficiently convert the absorbed laser energy into thermal energy [26, 46]. However, to date the heat generation mechanisms for this class of nanomaterials have not been investigated in detail when compared to magnetic or noble metal nanoparticles.

3 ABOUT THIS BOOK

The present books aims at giving an overview of the current status of the use of nanomaterials for magnetic and optical hyperthermia. In Part 1 the main aspects related to the topic are introduced, while Part 2 covers the design, fabrication, and characterization of nanomaterials for in vitro and in vivo hyperthermia applications and the development of hyperthermia instrumentation and nanoscale thermometry. Part 3 is focused on the cellular response to heat, covering different aspects from mechanisms of cellular death to synergistic effect of hyperthermia and chemotherapy. Finally, Part 4 discusses the challenges related to nanomaterial toxicity, regulatory, and translational aspects, as well as standardization of hyperthermia experiments. The book closes with the point of view of the editors on the future of nanomaterial-based hyperthermia in terms of challenges, future developments, and new

potential applications (Part 5). We hope that these chapters, written by experts in the field, will provide useful insights for a broad academic readership, including researchers and postgraduate students in different areas (materials science/nanomaterials, chemistry/biochemistry, nanomedicine/bionanotechnology, biology). However, we expect that the book will also be of interest for oncologists, clinicians, translational researchers, and small nano/bio-tech companies.

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