Ultrasonic Interfacial Engineering of Red Phosphorous–Metal for Eradicating MRSA Infection Effectively

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DOI: 10.1002/adma.202006047

Sonodynamic therapy (SDT) is considered to be a potential treatment for various diseases including cancers and bacterial infections due to its deep penetration ability and biosafety, but its SDT efficiency is limited by the hypoxia environment of deep tissues. This study proposes creating a potential solution, sonothermal therapy, by developing the ultrasonic interfacial engineering of metal–red phosphorus (RP), which has an obviously improved sonothermal ability of more than 20 °C elevation under 25 min of continuous ultrasound (US) excitation as compared to metal alone. The underlying mechanism is that the mechanical energy of the US activates the motion of the interfacial electrons. US-induced electron motion in the RP can efficiently transfer the US energy into phonons in the forms of heat and lattice vibrations, resulting in a stronger US absorption of metal–RP. Unlike the nonspecific heating of the cavitation effect induced by US, titanium–RP can be heated in situ when the US penetrates through 2.5 cm of pork tissue. In addition, through a sonothermal treatment in vivo, bone infection induced by multidrug-resistant Staphylococcus aureus (MRSA) is successfully eliminated in under 20 min of US without tissue damage. This work provides a new strategy for combating MRSA by strong sonothermal therapy through US interfacial engineering.

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Non-invasive therapeutic strategies for treating cancers and bacterial infections have attracted significant attention. Although phototherapy, which includes photothermal and photodynamic therapies, has been widely investigated, its Achilles' heel of phototherapy is its limited ability to penetrate deep into tissues.

Ultrasound (US) therapy was developed to address the shortcomings of phototherapy as US can penetrate more than 5 cm under the skin without being affected by human skin or connective tissue. US is also a safe inspection imaging technology and has been widely used in the biomedical field. Until now, the most representative ultrasonic strategy is sonodynamic therapy (SDT), which can produce reactive oxygen species (ROS) using sonosensitizers under the cavitation effect. However, the therapeutic efficiency of SDT is limited by the hypoxic microenvironment of the deep tissues of tumors or infection sites.

Sonothermal therapy can be applied to address this issue. It is well known that the high-intensity focused ultrasound (HIFU) is an innovative and advanced technology using acoustic lens to focus ultrasound on a point. This focused ultrasound is then able to be deposited and converting the mechanical energy to heat (65–100 °C) in 0.5–1.0 s that can ablate lesions in vivo and save lives in clinical trials. However, HIFU cannot kill bacteria efficiently through high temperature in a short time. In addition to medical applications, the thermal effect of high-power US is also used for high-temperature sterilization in the food industry. Also, organisms have good absorption of US, indicating that the high-energy US can easily lead
to high temperature in biological tissue.\cite{9} The development of controllable sonothermal biomaterials has been rarely discussed in the literature so far. No effective way to achieve controllable ultrasound thermotherapy in vivo has been reported until now. Therefore, it is necessary to provide a facile strategy to realize the controllable sonothermal ability of materials for antibacterial treatment. For instance, red phosphorus (RP) is one stable and nontoxic allotrope of black phosphorus that can be obtained and degraded into biocompatible phosphate and phosphonate as time in vivo.\cite{10} In addition, an RP coating can be easily formed on the surfaces of metals through the mature chemical vapor deposition (CVD) methods.\cite{11}

Therefore, this biodegradable RP was chosen to address this gap through US interfacial engineering by constructing a heterojunction interface between semiconductor and metals with controllable sonothermal ability such as titanium (Ti), vanadium (V), chromium (Cr), iron (Fe), cobalt (Co), and nickel (Ni). Importantly, noninvasive medical imaging (frequency ≥ 1 MHz) with low-power (power ≤ 1 W) and continuous US (1 MHz, 1.0 W cm\(^{-2}\)) was applied to reduce the potential risk of thermal damage.\cite{8,12} The sonothermal mechanism was associated with US-induced electron motions which included vibration, relaxation, and phonon/lattice thermal vibration in the metal–RP interface. This sonothermal system was then combined with thermal responsive nitric oxide (NO) therapy and successfully treated bone infection induced by multidrug-resistant Staphylococcus aureus (MRSA) in vivo.

The heterojunction of Ti–RP was constructed by CVD; micro-morphology was observed by field-emission scanning electron microscopy (FESEM) and energy-dispersive spectrometry (EDS) (Figure 1 and Figure S1, Supporting Information). It can be observed via FESEM that there were many uniformly convex and compact structures on the Ti plate after deposition of RP (Figure 1a). The cross-sectional FESEM showed that the thickness of RP coating was around 1.15 µm and the corresponding mapping image illustrated that there was a clear boundary between the RP coating and the Ti substrate (Figure 1b,c and Figure S1a, Supporting Information).\cite{13} More concrete microstructures between Ti and RP were then revealed by high-resolution transmission electron microscopy (HRTEM). In the TEM image of Ti–RP that had been treated by a focused ion beam (FIB) (Figure 1d), it is clear that there were two regions with different contrasts, indicating the existence of two different matters. Additionally, the corresponding line-scan spectrum of EDS and mapping images showed the distribution of Ti and P elements on two different sides, which indicated that Ti and RP formed a heterojunction interface. There were two intersecting lattice fringes in region A and region B that formed a distinct demarcation line, as shown in Figure 1e. The d-spacings of the left lattice fringes (2.54 Å) and the right lattice fringes (2.46 Å) were consistent with the plane of α-Ti (100) and the plane of RP (104) in Figure 1f.\cite{13,14} In addition, the Raman spectrum obtained from Ti–RP showed characteristic peaks of fibrous RP from 320 to 480 cm\(^{-1}\) (Figure 1g and Figure S1b, Supporting Information).

The sonothermal abilities of Ti and Ti–RP were also tested using an ultrasonic device (Figure S1c, Supporting Information). Under continuous US (1.0 W cm\(^{-2}\), 1 MHz, 25 min), the temperature of Ti–RP increased from 22.30 to 44.90 °C, while an increase of only 7.53 °C was observed in the Ti group, 22.20 to 29.73 °C (Figure 1h). This indicates that the formation of a Ti–RP interface could endow Ti with sonothermal properties. The sonothermal heating curve was repeated in three on–off cycles, suggesting the stable and repeatable sonothermal property of Ti–RP under US (Figure 1i). Other parameters of the US were changed to observe their effects on the sonothermal performance of Ti–RP (Figure S1d, Supporting Information). An increase in intensity resulted in an increased final temperature of Ti–RP. Under the same intensity (1.0 W cm\(^{-2}\)) and duty cycle (100%), the changed frequency of the US did not result in any obvious difference in the heating performance of Ti–RP or Ti (Figure S1e, Supporting Information). The final temperature of Ti–RP also decreased significantly with the decrease of duty (Figure S1f, Supporting Information). These results suggest that the change of frequency (1 to 3 MHz) had no obvious influence on the sonothermal effect, but the change in output intensity or duty ratio was equivalent to the change of the effective time of US energy acting on Ti–RP. This revealed that the sonothermal effect of Ti–RP requires a continuous input of ultrasonic energy to accumulate and the mechanical energy can be converted into heat.

According to the theory of acoustoelectric effects, when ultrasonic transmission occurs in metals or semiconductors, the interaction of mechanical energy with electrons/carriers in the medium produces electron motion, current, attenuation, or amplification of sound waves.\cite{15} Therefore, it appears that the sonothermal effect is not only the result of the continuous input of external US energy, but also should be related to the transformation of mechanical energy into thermal energy by electron motion or phonons in the heterojunction (Figure 1j).

It is well accepted that the motion of electrons can lead to the production of phonons (quantization of lattice vibrations) and generate heat.\cite{16} US can also lead to electron motion in the solid mediums including metal and semi-conductors due to the acoustoelectric effect. The sono-electric properties of Ti and Ti–RP under US were investigated using the device of electrochemical test (Figure S1g, Supporting Information). The US current response over time was observed over five repeated cycles with or without US. The current in Ti–RP (≈0.022 mA cm\(^{-2}\)) was obviously far higher than that in Ti (≈0.012 mA cm\(^{-2}\)) (Figure 2a). In addition, Ti showed a small fluctuation in current while Ti–RP displayed regular and gradually increased US current, indicating the production of more US-excited electrons and rapid charge transfer at the interface of Ti–RP heterostructures in the presence of US. Electrochemical impedance spectroscopy (EIS) results showed that Ti–RP had a smaller semicircle arc while Ti–RP-US had the smallest arc in comparison with Ti and Ti-US, suggesting that Ti–RP-US had the lowest impedance, which is in accordance with US current results (Figure 2b). The US absorption coefficients of Ti and Ti–RP were measured by a Precision Acoustics UMS3 Test System with an Olympus 1 MHz transducer in a precision acoustic hydrophone. As shown in Figure 2c, at 1 MHz, the US absorption coefficient of Ti–RP (0.053352) was much higher than that of Ti (0.042563). The results of the absorption test suggested that the introduction of RP creates a heterogeneous junction interface and enhances the US mechanical energy absorption of Ti, which was consistent with the tendencies of

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the sonothermal effect. In addition, the direction of electron motion in Ti–RP was explored further. The bottom and profile of Ti–RP were polished and its sonothermal effect was tested (Figure 2d–f). Whether the unpolished Ti–RP was irradiated from bottom to top or from top to bottom by continuous US, it had sonothermal ability. However, the Ti–RP-Polished (US direction, from bottom to top) maintained a stable sonothermal ability and sonothermal ability of Ti–RP-Polished (US direction, from top to bottom) was significantly reduced (Figure 2d–f). These differences showed that when the polished Ti was exposed at the top, the sonothermal effect disappeared even if the Ti–RP heterojunction still existed.
The above results informed the sonothermal mechanism illustrated in Figure 2g. The weak sonothermal ability of Ti is due to the fact that US-generated electrons might escape from the surface of Ti and rarely participate in vibration to produce heat. Therefore, the US-excited electrons from Ti–RP–Polished (From top to bottom) escape, resulting in weak sonothermal ability. Although RP existed, the US-excited electrons of RP are easy to transfer to Ti because of the US direction and the electron-trapping ability of metal for semiconductor. As for Ti–RP–Polished (From bottom to top), it is important to consider that more US-excited electrons could transfer to RP and vibrate to convert ultrasonic energy into heat due to the limited motion of electrons in semiconductors. Additionally, the US-generated electrons in RP might participate in the relaxation of carriers or recombination of the electron–hole, which transfer the mechanical energy of US into phonons and results in the lattice thermal vibration.

To further investigate the influencing factors of Ti–RP on sonothermal ability, the temperature of different Ti–RP samples with various thicknesses of RP coating were measured under the same US treatment (Figure 3a and Figure S2a,b, Supporting Information). The samples with different thicknesses of RP coating 1.15 (the sample in Figure 1a), 1.04, 0.71, and 0.27 µm were labeled as Ti–RP–A, Ti–RP–B, Ti–RP–C, and Ti, whose corresponding final temperatures were 45.03, 45.10, 45.60, and 29.70 °C with similar RP coating coverages (100%). The samples with different coverages of RP coating, 100% (Ti–RP–A), 44.87% (Ti–RP–D), 10.63% (Ti–RP–E), and 3.44% (Ti)
showed gradually faded color (Figure S2c, Supporting Information) with corresponding final temperatures of 45.03, 36.73, 31.33, and 29.70 °C (Figure 3b and Figure S2d-c, Supporting Information). The results showed that the different thicknesses of RP coating with similar coverage did not change the sonothermal ability of Ti–RP. However, the sonothermal performance of Ti–RP was weakened if the coverage of RP coating on the Ti was changed or failed to form compact and dense microstructures. The data suggests that only when a dense and effective RP coating was formed and a complete Ti–RP interface constructed, could the sonothermal effect of Ti be significantly improved (Figure 3c). In terms of the sonothermal ability of pure RP, it has been noted that the final temperatures of RP dispersion in deionized H₂O and the deionized H₂O group are similar (Figure S3, Supporting Information). This indicated that pure RP cannot make a significant difference in temperature without forming a heterogeneous interface with the metal.

To investigate whether this sonothermal effect could be realized in other metal substrates with RP coating, several other kinds of metal (V, Cr, Fe, Co, and Ni) were chosen for testing. As shown in the Figure 3d-e, the color of all substrates became darker after the deposition of RP. In term of the sonothermal test (Figure 3d and Figure S2e–i, Supporting Information), there was a significant difference between the samples of metal and metal–RP. V increased by 78.3 °C (22.37 to 30.20 °C) and V–RP increased by 19.70 °C (22.27 to 41.97 °C); Cr increased by 7.53 °C (22.30 to 29.83 °C) and Cr–RP increased by 23.60 °C (22.53 to 46.13 °C); Fe increased by 6.67 °C (22.40 to 29.07 °C) and Fe–RP increased by 21.10 °C (22.30 to 43.40 °C); Co increased by 5.83 °C (22.50 to 28.33 °C) and Co–RP increased by 22.30 °C (22.27 to 44.57 °C); Ni increased by 6.56 °C (22.57 to 29.13 °C) and Ni–RP increased by 22.30 °C (22.33 to 44.63 °C). All of the final temperatures for the various metals–RP were over 40 °C. It indicates that the introduction of the RP coating is a universally applicable for endowing metal with sonothermal effects. In addition, as shown in Figure S4 (Supporting Information), a new type of P coating containing BP, which is in accordance with our previous work.[17] It was observed that the peaks of BP distributed around 17°, 26°, 34°, 35°, and 40° in the XRD.[17] The sonothermal ability of this new type of P coating was tested and a similar tendency of temperature changes compared with the Ti–RP was observed, indicating that other phosphorus allotropes also have sonothermal abilities.

The excellent sonothermal performance of Ti–RP led to an in vivo antibacterial application based on sonothermal therapy. Considering the fact that bacteria as a result of surgery can resist heat longer and even survive it,[9b,c,18] Thermal therapy at moderate temperatures alone cannot kill bacteria efficiently and excessive temperatures will damage the surrounding tissue in vivo.[11a] To facilitate the efficient sterilization of hyperthermia, an ultrasonically controlled NO release coating was introduced on the surface of Ti–RP to make the application of sonothermal effects more meaningful in antibacterial treatment.[13b] Therefore, the Ti–RP was further modified with a nanomessoporous silicon dioxide (MSN) coating with a thermally controlled release of nitric oxide (NO) on the surface of Ti to realize its synergetic antibacterial effect on a deep MRSA infection in vivo. The fabrication process of the NO-precursor-loaded MSN on Ti–RP (Ti–RP–SNO) was shown in Figure 4a. The Ti–RP–SNO was prepared through electrostatic bonding and the condensation reaction of MSN–SNO on the surface of Ti–RP.[19]

The FESEM images clearly showed that a uniform nanoparticles film with particle size of ≈100 nm was spread on the surface of RP coating (Figure 4b). The cross-sectional FESEM image of Ti–RP–SNO clarified that the thickness of the MSN–SNO film was around 10.17 µm. The EDS mapping further
showed the composition of the various components in the composite coating; the characteristic elements of Ti, P, and Si in the Ti substrate, RP film, and MSN–SNO coatings, respectively, were clearly observed (Figure 4c). The characterization of different MSN-based nanoparticles was shown in Figure S5a,b (Supporting Information).

The elemental changes in Ti covered with different coatings at each step or reaction were characterized by X-ray photoelectron spectroscopy (XPS). As shown in Figure 4d and Figure S5c (Supporting Information), the signal of C in Ti–RP at 285.3 eV disappeared and the signal of P appeared at 134.8 eV, indicating the decoration of RP on Ti. In terms of Ti–RP–SNO, a new signal of Si appeared at 103.4 eV and an increased C signal reappeared at 285.3 eV, indicated the formation of a MSN–SNO coating.[13a]

The surface hydrophilicity of the samples was then measured. The contact angle test showed that Ti has the highest contact angle (73.5°), while the angles for Ti–RP and Ti–RP–SNO were both 0° (Figure 4e).[20] These results were due to presence of PO₄³⁻ in RP and the –COOH and –NH₂ groups in MSN–SNO, leading to a prominent increase in the hydrophilicity of the samples which would be conducive to the growth and adhesion of cells. To carry out the antibacterial experiment reasonably, the size of the sample and the device were adjusted (Figure S5d, Supporting Information).

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The sonothermal effects of Ti, Ti–RP, and Ti–RP–SNO were tested under US (1.0 W cm⁻², 1 MHz, 20 min, continuous) (Figure S5e,f, Supporting Information). The final temperature of Ti–RP–SNO was 52.83 °C, indicating that the MSN–SNO film had little effect on the sonothermal effect of the Ti–RP (Figure S5e,f, Supporting Information). The release of NO under US was then tested by a NO testing kit. From Figure 4f, the amount of NO released from Ti–RP–SNO increased within 20 min under US, while Ti–RP–SNO without US only exhibited a slight release. The ultrasound responsive release of NO occurred because the –S–N– bond can be broken by the heating of US (1.0 W cm⁻², 1 MHz, 20 min, continuous) (Figure 4g). Therefore, it can be used to realize the controlled release of NO gas.[13b,21]

The Ti–RP–SNO was applied to test its synergetic antibacterial ability in vitro by attacking and killing MRSA (Figure 5). The samples for the antibacterial tests were divided into seven groups: Ti, Ti–RP, Ti–RP–SNO, Ti+US, Ti–RP+US, Ti–RP–SNO+US, Ti–RP–SNO+US (two cycles). After US irradiation for 20 min or silence, it was observed that MRSA grew well in the groups without US, while the bacteria colonies decreased in the groups with US (Figure 5a). As compared to the group of Ti, the antibacterial rates of different groups under US were: Ti+US (19.70%), Ti–RP–SNO+US, Ti–RP–SNO+US (two cycles) (99.99%) (Figure 5b). The antibacterial results showed, that the combination of sonothermal and NO treatments could efficiently kill MRSA and that repeated treatments could further elevate antibacterial performance. The morphology of the treated MRSA was further observed by FESEM. The cell membrane of the MRSA kept intact in the groups of Ti, US-treated Ti, Ti–RP, US-treated Ti–RP, and Ti–RP–SNO (Figure 5c). Conversely, the cell membrane of the MRSA was seriously damaged in the group of US-treated Ti–RP–SNO, which fit in with the results of antibacterial spread plate.

To verify whether the sonothermal effect of samples could be used for an in situ hyperthermia through deep tissue, a
pork tissue consisting of skin, fat, and muscle with an overall thickness of 2.5 cm was chosen and placed beneath the samples (Figure 5d). As shown in Figure 5e–h and Figure S5g (Supporting Information), the temperature of Ti (29.30 °C) showed only a slight increase even as surrounding tissue was heated to a much higher temperature (38.83 °C). Interestingly,
the temperatures of Ti–RP and Ti–RP–SNO were 49.70 and 50.20 °C, respectively, which were higher than the temperatures of the surrounding tissues (39.83 and 38.43 °C). The above results proved that the US could successfully penetrate the thick layer of pork tissue and heat the samples without thermally damaging the surrounding normal tissue. The biocompatibility of samples was then tested by methyl thiazolyl tetrazolium. The results showed that the cell viability of MC3T3–E1 samples treated by Ti, Ti–RP, and Ti–RP–SNO was similar, suggesting the nontoxicity of Ti–RP and Ti–RP–SNO after a 72 h culture (Figure S5h, Supporting Information).[22] The cell viability of MC3T3–E1 treated by US in the group of Ti, Ti–RP, and Ti–RP–SNO was also test (Figure S5i, Supporting Information). The cells in all three groups exhibited no significant difference after a 72 h culture, suggesting that the sonothermal effect of Ti–RP did not show obvious cytotoxicity.

Antibacterial tests in vivo were then carried out in a MRSA related bone infection model of rats. Considering that the sonothermal effect (45–50 °C) and NO release (62.12 × 10–6 μ) induced by continuous US (1.0 W cm–2, 1 MHz, 20 min) in vitro can effectively sterilize bacteria without obvious cytotoxicity, the infection in vivo was treated with ultrasound for 20 min (Figure 5i). The rats were implanted with different samples containing MRSA (Ti, Ti–RP–SNO) in their tibial plateau regions (Figure S6, Supporting Information), and the position of the implants in the bone tissue was further confirmed by Micro-CT (Figure 5j). After being fed for two days, they were treated by US for 20 min and the implants were then pulled out and tested to determine the number of remaining bacteria on their surfaces. As shown in Figure 5k, MRSA on the surface of the Ti–RP–SNO were efficiently killed by the synergism of sonothermal effect and NO. There was a lot of dense bacteria on the Ti plate, which proved the great antibacterial performance of this strategy in vivo. The tibial bone tissues, soft tissues around the implants, and the main organs were also examined through histopathology analysis. As seen in Figure 5l, there were many neutrophils (green arrows) in the Ti group, indicating the existence of serious bone infection induced by MRSA in the tibial tissues in vivo. In contrast, the number of neutrophils was significantly decreased due to the elimination of MRSA.

The in vivo thermal damage of tissues near the MRSA infectious site after US treatment in 3 days was also tested by H&E staining. In the H&E staining images of muscle tissues near the implants in vivo, the muscle tissues are clearly spaced and no significant inflammation, hematoma, or congestion can be observed (Figure S7, Supporting Information). The orderly arrangement of muscle fibers in these images of four groups proved that the soft tissues near the tibia were not damaged by the sonothermal effect. In the images of the skin tissues of the four groups, no cell vacuolization was observed and each layer of the skin, such as stratum basale and stratum corneum, is clearly visible (blue arrows). The blood vessels (red arrows) and hair follicles (green arrows) remained intact and normal in each group (Figure S7, Supporting Information). These results indicated that the skin and muscle tissues covering the bone were not seriously damaged by heat during ultrasound treatment, which are consistent with the conclusions of the cell viability test in vitro. H&E staining of rats’ main organs showed that they were not damaged after US treatment (Figure S8, Supporting Information), suggesting that this ultrasonic therapy could successfully treat MRSA infected bone infection in vivo without side effects.

In summary, a series of sonothermal materials was successfully designed through the construction of a metal/red phosphorus heterojunction interface. The sonothermal mechanism was found to be closely related to the activation of electron motion in heterojunction. Many other substrates can be endowed with sonothermal ability through introducing a metal/semiconductor interface, inspired by the special mechanism. Although this design is still limited to the surface modification of the water-insolusion implanted materials with a large size, the findings overcome the disadvantages of the traditional nonspecific heating of US treatment and illuminates a research direction for designing of sonothermal materials. This study can provide another strategy for ultrasonic therapy, especially in the field of biomedical materials.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

W.G. and L.T. contributed equally to this work. This work is jointly supported by the National Natural Science Foundation of China, Nos. 51801056, 51671081, 51871162, Natural Science Fund of Hubei Province, 2018CF064, and the National Science Fund for Distinguished Young Scholars 51925104, the National key R&D Program of China (2018YFA0703100), Hong Kong Innovation Technology Fund (ITS/287/17 and ITS/405/18), and Hong Kong Research Grant Council General Research Fund (17234516). The authors thank Wuhan Union Hospital also for their collaboration and assistance with this animal experiments research.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

antibacterial materials, interfacial engineering, red phosphorus, sonothermal ability, ultrasound

Received: September 4, 2020
Revised: November 11, 2020
Published online: December 22, 2020


