Amorphous iron nanoparticles: special structural and physicochemical features enable chemical dynamic therapy for tumors

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First draft submitted: 2 February 2016; Accepted for publication: 10 March 2016; Published online: 15 April 2016

Keywords: amorphous metals • chemical dynamic therapy • iron nanoparticles

Amorphous metals or alloys, also known as the metallic glasses with a disordered structure on atomic level, have attracted great attentions owing to their special physical properties and extraordinary prosperities [1–5]. In addition to the excellent plasticity upon heating for easy processing, the absence of grain boundaries leads the bulk metallic glasses (BMGs) to higher strength and better corrosion resistance than conventional metals or alloys, which stimulated widespread researches to hurry their potential as advanced structural materials. However, the severe synthesis conditions, typically the superhigh cooling rate (usually higher than 10^6 K s^{-1}) to freeze the molten metal and to suppress the nucleation of crystalline phases, have been being one of the main bottlenecks for the widespread applications of BMGs [6].

Compared with BMGs, nanosized amorphous materials such as amorphous nanoparticles, which combine the advantages of both random arrangement of atoms in amorphous state and nanodimension and are therefore expected to exhibit even more unique and diverse properties, have been rarely explored, most probably due to the difficulties in the successful syntheses of such materials which leaves rooms for researches and developments.

Taking amorphous iron nanoparticles (AFe-NPs) as an example, not to mention the possible specificities in electromagnetism such as soft magnetic characteristics and others, it is expected that the randomly arranged iron atoms are active enough to be ionized in mild acidic conditions for on-demand Fe (II) release and to initiate subsequent localized Fenton reaction under the presence of hydrogen peroxide. On the other hand, most solid tumors feature acidic nature ($\text{pH} = 6.5\text{--}6.9$) and overproduced hydrogen peroxide, and such a special microenvironment has attracted great interest for the exploration of so-called microenvironment-responsive cancer therapy [7–11]. In fact, acidic microenvironment in tumor has triggered the development of numerous strategies of pH-stimuli-responsible controlled drug releases, in which drug is expected to release in acidic tumor but not in neutral normal tissues or blood stream; while cumulative H_2O_2 in cancer has been exploited to implement specific therapeutic strategies, such as to act as a spontaneous trigger for responsive-drug-releasing chemotherapy or an endogenous O_2 producer for enhanced photodynamic therapy [12–14]. Thus, seemingly totally different fields of metallic glasses and cancer therapies find their common points for combination.

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Recently, we have presented a novel hubble–bubble approach to synthesize AFe-NPs, which show remarkable advantages over the corresponding nanocrystalline counterpart in serving as theranostic agents benefiting from their amorphous nature [15]. The successful synthesis is achieved by preventing the nucleation and growth of crystalline iron nanoparticles in an aqueous bubble film confined by the amphiphilic F-127 bilayers to suppress the long-range diffusion of the reduced Fe atoms. The unique advantages of such AFe-NPs have been evidenced for the theranostic applications in their report as follows. The amorphization of iron nanoparticles provide a potential but universal strategy to improve the biodegradability of inorganic biomedical agents such as drug carriers, MRI agents and so on, as the biodegradability of the inorganic agents has become one of the most concerned issues for their future clinical applications in comparison with the organic or polymeric ones, though these materials exhibit a number of attractive merits such as easy control of their dimensions and morphology, abundant strategies available for surface modification and multifunctionalization, high imaging performance or controlled drug release and so on; the amorphous state of iron nanoparticles show distinct magnetic properties, such as soft magnetism with a much lower coercivity ($H_c = 59$ Oe at 300 K) and remanent magnetic induction ($B_r = 12.1$ emu g⁻¹ at 300 K) but higher saturation magnetism than its crystalline counterpart, the absence of magneto-crystalline anisotropy in representative crystalline magnets, much improved dispersibility in aqueous solutions featuring much smaller critical dimension for aggregation and more attractively, significantly enhanced longitudinal (T_1^{-1}) and transverse (T_2^{-1}) relaxation rates for better performances of magnetic resonance imaging. The most outstanding advantage of AFe-NPs is its stimuli-responsible Fe²⁺ release, that is, AFe-NPs' ionization, in the mild acidic microenvironment of tumors benefiting from the active nature of the atoms in disorder state, which enables a tumor-specific intratumoral *in situ* Fenton reaction using the endogenous hydrogen peroxide in tumor tissues. Such an intratumoral Fenton reaction results in the efficient H₂O₂ disproportionation for efficient •OH generation which is one of the most toxic radicals to cells [16–18]. Based on this character of AFe-NPs which perfectly matches the microenvironmental features of tumors, a concept of chemical dynamic therapy has been proposed and demonstrated both *in vitro* and *in vivo*. Essentially different from the extensively explored photodynamic therapy which is highly dependent on the exogenous light irradiation of specific wavelength for ROS generation and therefore

suffers from the limited penetration of light in tissues and possible UV irradiation-induced tissue damage, the demonstrated chemical dynamic therapy is initiated by the on-demand release of ferrous ions in acidic tumor tissues, relying on the intratumoral microenvironment, but totally independent of external stimulations. Specifically, normal tissues or cells will hardly initiate such Fenton reactions due to the absence or insignificance of hydrogen peroxide overproduction or acidic microenvironment therein.

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Outstanding advantages do not gloss over the presence of some drawbacks. For example, the scalable synthesis of AFe-NPs, or other amorphous metal nanoparticles, is still difficult based on the present hubble–bubble strategy, which necessitates more facile approaches of material preparation; the easy oxidation of AFe-NPs in air will make its storage in protective media a prerequisite and surface modifications, for example, surface PEGylation for enhanced biocompatibility and dispersity, and specific moiety grafting for targeted drug delivery, is not so easy as on mesoporous silica nanoparticles.

Nevertheless, the defects cannot obscure the virtues, the reported AFe-NPs of amorphous nature, whose specific soft magnetic properties and microenvironment responsibility will be highly attractive to the researchers in the cancer theranostics, as revealed in the author's report. More meaningfully, the concept of amorphous metal/alloy nanoparticles may offer a novel pathway to explore the unique structural features, electric, dielectric and magnetic properties, electronic and/or energy transfer characteristics and the resultant performances, which may enable a bright future for a variety of practical applications in, for example, electromagnetic devices, adsorptions and heterogeneous catalysis, etc.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

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