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ID-5-O-2554 Following at high resolution the biodegradation of inorganic nanoparticles in the organism

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Given the increasing use of nanomaterials in industry and their tremendous potential in the biomedical field, human are expected to be more and more exposed to nanosized materials. A key concern raised by the development of nanotechnology is the long term fate of nanomaterials, and particularly the control over inorganic nanoparticles (NPs) full life cycle and related risks for human health. Most toxicology studies take the point of view of living organisms to examine the effects of exposure to NPs on biological functions. Here, we propose an original "Materials Science" approach to the nanotoxicology paradigm: we choose to take the point of view of nanomaterials in order to monitor the transformation and degradation of their atomic structure and physical properties in living environment and then unravel the mechanisms determining their fate. Our methodology is illustrated here with both in vivo and in vitro studies that provide new insights into the relation between the structure and the life cycle of inorganic NPs in the organism. [1,2,3] Iron oxide NPs with different forms (spherical, nanocubes, nanoflowers) and different inorganic or organic coatings (polymers, citrate, gold) were studied.

We have exploited the multifunctionality of TEM to follow the biodistribution and the structural evolution of iron oxide NPs injected into mice over a period of three months. These nanoscale investigations were complemented by the magnetic follow-up of the injected NPs to quantify iron oxide NPs at the macroscopic scale and follow the evolution of their magnetic properties. This multi-scale approach allowed characterizing for the first time, the structural and magnetic in vivo degradation of NPs and the intracellular pathway of iron transfer from NPs to endogenous ferritine [1,2] (fig. 1).

Concomitantly, we are exploiting liquid TEM to study in situ the biodegradation mechanisms of NPs in a medium mimicking the intracellular environment (fig 2), or directly into cell cultures. The use of micro-fabricated liquid-cells (Protochips) in an aberration-corrected microscope is a straightforward approach to understand how the structure of NPs and their organization in solution influence the mechanisms and kinetic of degradation. In that regards, we have already evidenced that both surface coating and aggregation state are key parameters, because they control surface reactivity in biological environment [2, 3]. Therefore, our works allows suggesting relevant strategies to modulate the degradability of NPs and to avoid the drastic annihilation of their technologically interesting properties in cells (fig 3).

[1] M. Levy et al. Biomaterials, 32, 3988 (2011), [2] L. Lartigue et al. ACS nano, 7, 3939 (2013)
[3] Y. Javed et al. Small, Accepted (2014).

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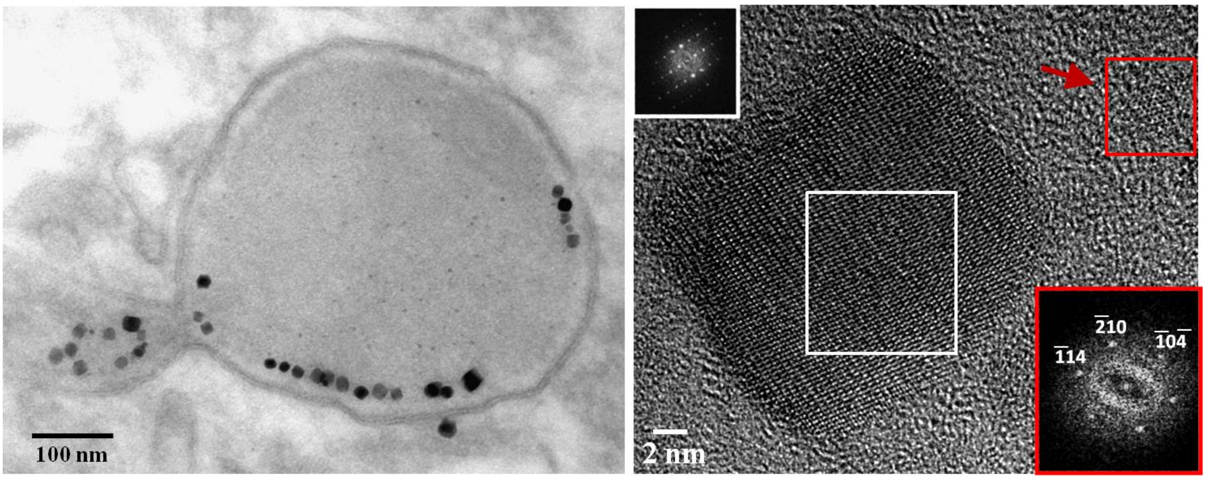

Fig. 1: In vivo study of the biodistribution and biotransformation of iron oxide nanocubes observed in lysosome of macrophage cells (right images). HRTEM investigations (right images) allows identifying the atomic structure of the degraded nanocubes (inverse spinel structure, FFT in white frame) and ferritine proteins (hematite structure, FFT in red frame)

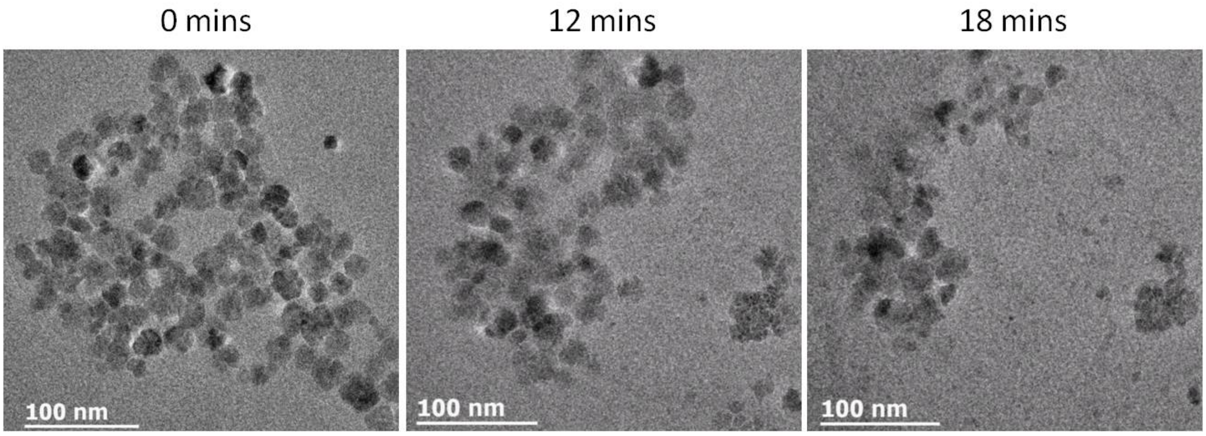

Fig. 2: In situ follow -up of the degradation of aggregated iron-oxide nanoflowers using liquid-TEM. The corrosion and dissolution of the NPs is directly observed in a solution mimicking the intracellular environment (ph = 4.7 + chelating agent). This experiment reveals that aggregated nanoparticles present a slower and non-linear kinetic of degradation.

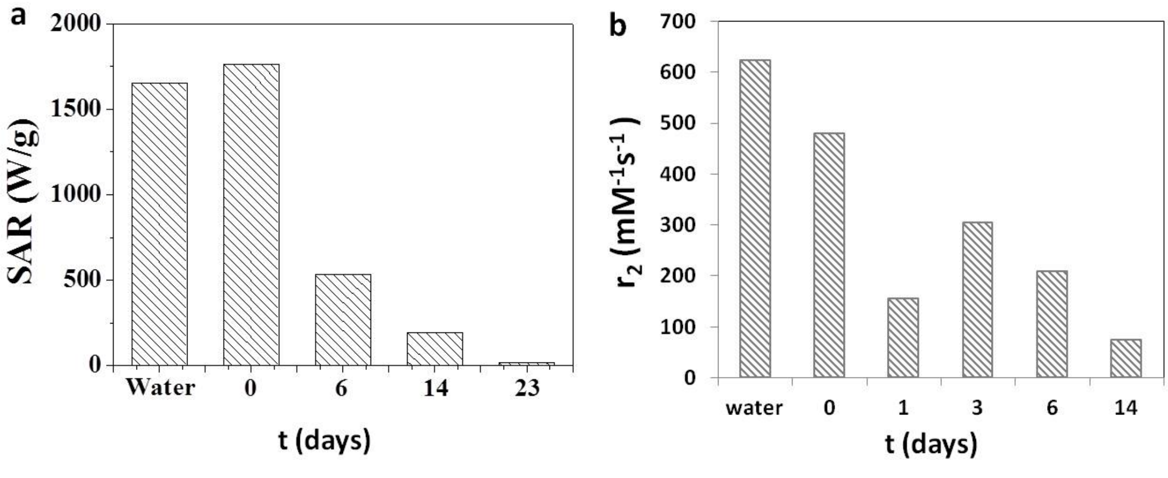

Fig. 3: The structural degradation of the nanoflowers in the lysosome like medium observed in fig.2, impairs their efficiency for magnetically induced hyperthermia and magnetic resonance imaging. Decrease of the specific absorption rate in a magnetic field of 24 kA/m and 520 kHz (a) and the transverse relaxivity r2 determined at 20 Mhz (b).