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Design of new nano-tools to target mitochondria and study the metabolic plasticity of cancer cells

Dorna Akbarzadeh^{1*}, Juan Carlos Calderón de la Rosa^{1,2}, Jolanda Spadavecchia³, Marie-Odile David⁴, François Treussart⁵, Nazanine Modjtahedi¹, Giorgia Urbinati¹

¹ University Paris-Saclay, CNRS, Gustave Roussy, Metabolic and systemic aspects of oncogenesis for new therapeutic approaches, Villejuif, France

² University Paris Cité, Faculty of Pharmacy, Paris, France

³ University Paris 13, Sorbonne Paris Nord, CNRS, Laboratoire de Chimie, Structures et Propriétés de Biomatériaux et d'Agents Thérapeutiques, Bobigny, France

⁴ University Paris-Saclay, Inserm, Univ Evry, Structure-Activité des Biomolécules Normales et Pathologiques, 91025 Evry, France

⁵ University Paris-Saclay, École Normale Supérieure Paris-Saclay, CNRS, CentraleSupélec, LuMh, 91190 Gif-sur-Yvette, France

Abstract:

The metabolic plasticity and mitochondrial functionality are crucial factors in tumorigenesis and response to anti-cancer therapy making the mitochondrion an attractive target for innovative anticancer therapies (1-2). Several bioactive molecules have been developed to modulate/perturb mitochondrial activity with the final aim of introducing alternative cancer treatment strategies. However, the efficacy of these biomolecules depends on their accumulation within mitochondria at the right dose, while preserving their activity (3). With this intent, nanovectors can be tailor-made to target mitochondria, to deliver these molecules sub-cellularly and therefore improve their bioavailability while reducing their off-target toxicity (4). Our team has developed a major interest for the mitochondrial import machinery AIF/CHCHD4, which regulates the mitochondrial import of proteins involved in cell survival and regulation of apoptosis, representing a potential therapeutic target in oncology (5). A peptide able to inhibit the *in vitro* interaction of AIF/CHCHD4 was identified by our team and represents a novel biomolecule with potential anticancer activity (6). Since this peptide is fragile, highly hydrophilic and negatively charged, two innovative nanovectors are developed in our laboratory with the aim of preserving the peptide's *in cellulo* functionality, while favoring its sub-cellular localization in the mitochondrion. The first strategy uses a classical liposomal-based system (Figure 1a). The second one is based on an innovative approach, using Fluorescent nano-diamonds (FND) for the tracking of the nanosystem down to the mitochondrion (Figure 1b). Five liposome formulations were prepared and characterized for their size, stability, release kinetics and cellular uptake. A chemical molecule with mitochondria tropism was grafted on the surface of these nanocarriers. The most promising liposomal formulation presented a size of ~200 nm with a homogenous distribution and a loading capacity of the peptide of ~20%. The peptide release kinetics was sustained over 72h in buffer conditions. In parallel,

the FND nanovector was loaded with the therapeutic peptide and functionalized with the mitochondria targeting peptide. The loading efficacy of the therapeutic peptide is 30% obtained after purification and the addition of the targeting peptide stabilized the complex, which tends to aggregate when in presence of the therapeutic peptide alone. We are now validating the mitochondrial localization of the nanovectors with imaging and biochemistry analysis. The study of the impact of AIF/CHCHD4 inhibition on the metabolic plasticity and survival of cancer cells is also under study.

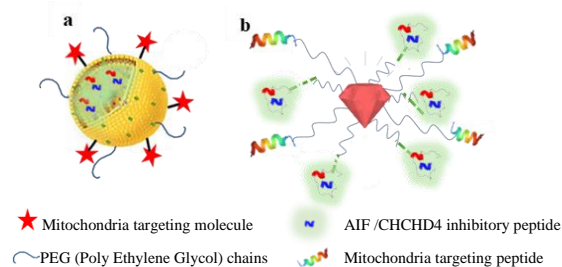


Figure 1. Schematic representations of two nanovectorization approaches for targeted delivery of the inhibitory peptide to mitochondria. (a) Liposome-based formulation encapsulating fluorescently labeled peptide and a mitochondria-targeting moiety. (b) Functionalized fluorescent nanodiamonds (FNDs) used to encapsulate the bioactive peptide and target mitochondria. Each approach offers distinct advantages and challenges in achieving efficient delivery to the mitochondrion.

Keywords: Nanovectorization, liposomes, fluorescent nanodiamonds, mitochondria-targeting, mitochondrial metabolism, metabolic plasticity.

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