Cyclodextrin polymers as versatile tools for innovation in the combination of chemo- and phototherapy under hypoxia

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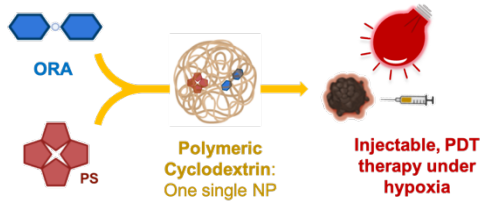
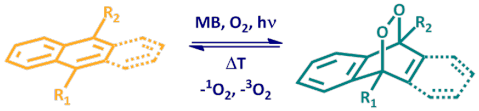
Solid cancer cells can be characterized by a low concentration of molecular oxygen in the tissues, a condition defined as hypoxia. This condition activates resistance mechanisms to standard chemotherapy and impairs photodynamic therapy (PDT) relying on the light-triggered production of singlet oxygen, $^1O_2$, a reactive oxygen species (ROS). In this context our aim is to develop new molecular systems aided by cyclodextrin (CyD) polymers to overcome the therapeutic limitations induced by hypoxic conditions. Biocompatible CyD polymers forming nanoparticles in water[1] were explored to implement the green synthesis of oxygen releasing agents (ORA) for the supply of O_2 in tissues and to load the ORA together with a photosensitizer (PS) to allow PDT also in hypoxic conditions.

Derivatives of anthracene and naphthalene have been selected as feasible ORA candidates. Visible light photocatalyzed conversion of the aromatic substrates in endoperoxides has been achieved in the presence of methylene blue in homogeneous aqueous environment thanks to the use of CyD polymers as inert reaction matrix solubilizing the aromatics.[2] Some of the endoperoxides obtained indeed act as ORA and release O_2 thermally either in its triplet state to feed the PS or as $^1O_2$. Next, co-encapsulation of the ORA and PS in the polymeric carrier has been achieved in dosage-consistent amounts as confirmed by UV-Vis and emission spectroscopies. The ability of the PS to generate $^1O_2$ and the tendency of the ORA to release O_2 upon thermolysis were unaltered upon complexation in the polymer loading the 2 components. These preliminary results forecast the use of this polymer as interesting, scalable platform for the production, and delivery of a combination of therapeutic agents operating under hypoxia.

PDT under hypoxia



Scheme of ORA synthesis



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References

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