Functionalizing polymers to align the redox state of tumour micro-environment: challenges, opportunities and perspectives

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Tailoring the features of natural polymers to target the redox state of tumour microenvironment is a valuable strategy to fight cancer. Tumour microenvironment, indeed, is characterised by a complex interplay between immunity and regulatory cell death, especially autophagy and apoptosis, which is crucially linked to the disruption of the oxidation-reduction homeostasis mechanism [1].

As a first approach for addressing this challenge, we proposed the conjugation of polyphenols such as Catechin and Curcumin to naturally occurring polymers (i.e. Dextran [2] and Gelatin [3]). Polyphenols showed interesting anticancer activity *in vitro*, although much debate has arisen about whether their supplementation alters the efficacy of cancer chemotherapy. Our approach is proved to enhance their stability and potentiate the efficiency of anticancer protocols. Moreover, an extensive investigation of the biological mechanisms underlying the therapeutic activity demonstrated the involvement of the cell redox balance and the chelation of essential metal ions, suggesting these pathways as a target for more accurate therapeutic interventions [4].

As a second approach, we investigated the insertion of redox-responsive elements in the polymer backbone as a tool to vectorize therapeutic agents within the tumour site, with a significant reduction of the adverse side-affects. More in details, the insertion of disulfide bonds makes the nanosystem responsive to the Glutathione concentrations, which are significantly higher in the tumour *vs* normal tissues. By means of lipoic acid and cystamine conjugation, we synthesized redox responsive derivative of Chondroitin [5] [1] and Human Serum Albumin [6], respectively, showing that the nanoparticle destabilization within the cancer environments is able to trigger the release of the bioactive agents, with a significant enhancement of their anticancer activity by increased cell internalization.

In conclusion, although more accurate in vivo investigation is needed to hypothesize a bench to clinic translation, the tailored functionalization of natural polymers with either polyphenols or redox-responsive moieties is proved as a promising strategy for cancer treatment.

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