DIRNANO

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Light-induced specific cell death in cancer therapy by nanoparticles

Nanoparticles (NPs) have emerged as a remarkable tool in the field of biomedical research offering myriad clinical applications that hold a great promise for improving clinical outcomes. Nowadays, NPs play an important role in cancer therapy with engineered to selectively accumulate in tumor cells, enabling localized treatment through techniques such as hyperthermia and photodynamic therapy.

Despite the efficient chemotherapeutic agents used to treat cancer, their low specificity often produces a range of dose-limiting side effects [2].

NPs have the potential to serve as vehicle for drugs to reduce the systemic toxicity and increase the specificity by targeting the tumor and the tumor environment. Several NP-based products have reached the market [3], and have demonstrated that drugs encapsulated in NPs might be a good solution to reduce the toxicity without losing the therapeutic effects.

Importance of cells death in cancer treatment

Cell death plays a crucial role in cancer treatment and is a main goal of basically all cancer therapies. It contributes to many aspects of anticancer therapy by eliminating cell growth leading to tumor reduction, preventing dissemination of cancer cells and creation of metastases or minimizing drug resistance.

Several cancer types may develop drug resistance to chemotherapy, therefore induction of cell death through various mechanism may help to overcome such a resistance and improve patients' response to the treatment [4] . With current progress in cancer immunotherapy, a medical approach that stimulates body immune response towards cancer cells, induction of specific cell death modality as a response to such a treatment gained even more attention. The release of tumor-specific antigens and other signalling molecules, may activate immune

cells and enhance their ability to recognize and kill cancer cells in the body providing long-term effect [5].

Apoptosis was described decades ago as a specifically programmed cell death by which the body removes damaged or abnormal cells including cancer cells and slow down creation of metastasis.
However, cancer cells can acquire mutations that disrupt the normal apoptosis, allowing them to evade cell death and continue to proliferate [6]. In the last decade, other cell death mechanisms such as pyroptosis, necroptosis and ferroptosis were described as distinctive cell death mechanisms.
Especially ferroptosis, a cell death modality relying on the presence of iron ions, characterized by creation of lipid peroxides and reactive oxygen species (ROS) was reported to have higher immunogenicity and playing a pivotal role in boosting immune response [4].
Additionally, it has been described that metastatic cancer cells, the ones which often acquired drug resistance, are more vulnerable towards ferroptosis making it even more interesting for clinical settings.

Photodynamic effect

Photodynamic therapy (PDT) is a medical treatment that uses a combination of light and photosensitizing agents to treat certain types of cancer. A photosensitizing drug is administrated to a patient and accumulates preferably in tumor tissue due to increased vascularization. Once enough of the photosensitizer has accumulated in the target tissue, a specific wavelength of light coming from various sources including lasers or light-emitting diodes (LEDs) is applied to the area [7, 8]. That leads to the activation of the photosensitizer and generation of singlet oxygen and other reactive oxygen species (ROS). ROS are toxic to cells and damage cellular components, including proteins, lipids, and DNA. It is considered as a minimally invasive approach and is used primarily for localized tumors and surface lessions. In contrast to chemotherapy, PDT has several advantages being minimally invasive, having low side effects and ability to selectively target cancerous tissues. Nowadays, there is significant emphasis on the integration of PDT and chemotherapy [8].

Photodynamic effect is also used for so-called photochemical internalization (PCI) a method developed by PCI Biotech ASA, a partner within DIRNANO consortium. Photochemical internalization (PCI) is a method to enhance the cytosolic delivery of macromolecules and avoid degradation of the active compound within the cell (M) [9].
The technology takes advantage of a photosensitizing molecule that, upon addition to cells, will be incorporated in the plasma membrane and entrapped in the membrane of endocytic vesicles.
Upon light exposure, the internalized photosensitizers produce ROS which disrupts the endocytic membrane and releases cargo (M) – Figure 1.

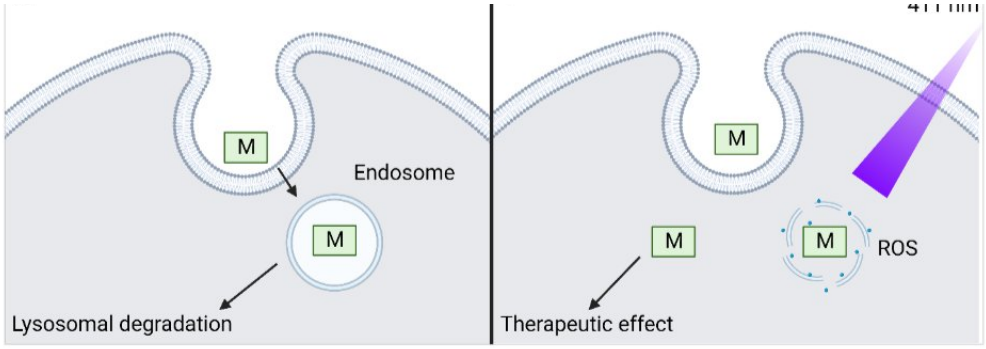

Figure 1: Principle of photochemical internalization. A: Uptake and processing a macromolecule without PCI treatment. Normally, a macromolecule is taken up by a cell and entrapped in endosomes where it is degraded. Using PCI technology (B), endosomes containing macromolecule are ruptured by ROS created by the photosensitizer and light exposure leading to the therapeutic effect by the macromolecule.

Currently, two distinctive anticancer approaches are being developed by the company, one to enhance T-cell induction for therapeutic vaccination called fimaVacc and the second to specifically deliver nucleic acids for therapeutic proposes. The company already conducted a clinical phase I study on 22 patients with advanced and recurrent cancer [10] and there has been also a Phase I dose escalation study to assess the safety, tolerability and immune response to adjuvanted peptide vaccines in healthy volunteers (ClinicalTrials.gov ID: NCT02947854) [11].

Our contribution

The project “Exploitation of immune cell infiltration for optimal nanoparticle-based cancer treatment” supervised by Gunhild Mari Maelandsmo, Kirsten Sandvig, Tore Skotland and Tore-Geir Iversen aims to use nanoparticles containing photosensitizer for the treatment of cancer. NPs are produced in the laboratory of Oslo University Hospital in collaboration with PCI Biotech ASA. We are particularly interested in their effect on immune cells recruited to tumour-microenvironment. In order to gain deeper insights into the therapeutic potential of these nanoparticles, our study is particularly focused on their impact on breast cancer. To this end, we employ two distinct phenotypic breast cancer cell lines as experimental models. These cell lines are exposed to the aforementioned nanoparticles, which are combined with a pharmaceutical agent with the intent of inducing ferroptosis.

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News in the consortium DIRNANO

- ESR01 Michele Tomaz has recently attended the IUPAC|CHAINS2023 'Connecting Chemical Worlds' Conference at The Hague presenting her work Lipid-coated Polylipoic Hybrid Nanoparticles.

- ESR05 Pedro Veloso is finishing his secondment at Paris Lodron University in Salzburg evaluating the interactions between nanoparticles and primary monocytes and dendritic cells.

- ESR12 Marek Feith is about to start his secondment in Logroño in the group of Dr. Alfredo Martinez with focus on the metabolic response of breast cancer cell lines to the combined treatment of nanoparticles containing photosensitizer and ferroptosis inducing drug.

- The DIRNANO team is meeting again at the end of September in Caparica (Portugal) for the 4th Regular Network Meeting.

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