1-11-6. Near-Infrared Photoimmunotherapy

Overview

Near-infrared photoimmunotherapy (NIR-PIT), developed by Dr. Kobayashi and colleagues at the U.S. National Institutes of Health, is a novel light-based cancer treatment (Mitsunaga et al.). In NIR-PIT, an antibody–IR700 conjugate, in which the water-soluble silicon phthalocyanine dye IR700 is linked to an antibody that specifically binds tumor cell surface antigens, is used as a photosensitizer. Following intravenous administration of the antibody–IR700 conjugate, irradiation with 690 nm light induces the therapeutic effect.

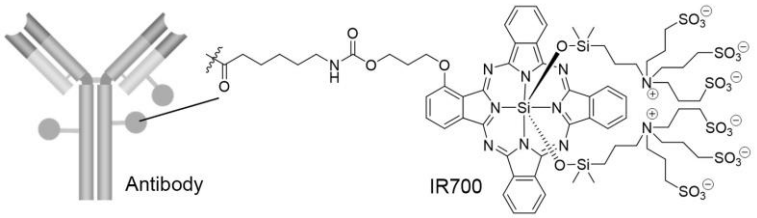

Figure 1. Antibody-IR700 conjugate.

Current Status and Frontiers

In 2015, a phase I/IIa clinical trial of near-infrared photoimmunotherapy (NIR-PIT) was initiated in the United States for patients with unresectable, locally recurrent head and neck squamous cell carcinoma. In 2020, Japan granted conditional early approval and became the first country worldwide to list NIR-PIT for reimbursement. The currently approved agent uses an antibody against the epidermal growth factor receptor (EGFR) conjugated with IR700. In Japan, clinical trials are ongoing for the anti-EGFR antibody–IR700 conjugate in esophageal cancer, vulvar/vaginal/cervical cancers, as well as in combination with anti-PD-1 antibody for gastric and esophageal cancers. In addition, a clinical trial is underway for the anti-CD25 antibody–IR700 conjugate in patients with advanced or recurrent solid tumors with liver metastases.

Upon binding of the antibody–IR700 conjugate to the target cell membrane, subsequent light irradiation induces membrane damage. It has been demonstrated that this membrane injury is initiated by the formation of insoluble aggregates on the cell membrane via a photochemical reaction (Ogawa, Sato, Nakajima et al.). Specifically, cleavage of the hydrophilic axial ligands of IR700 results in loss of water solubility. The planar π-electron system of the phthalocyanine ring promotes stacking of IR700 molecules, leading to insoluble aggregate formation. Antibody molecules conjugated with

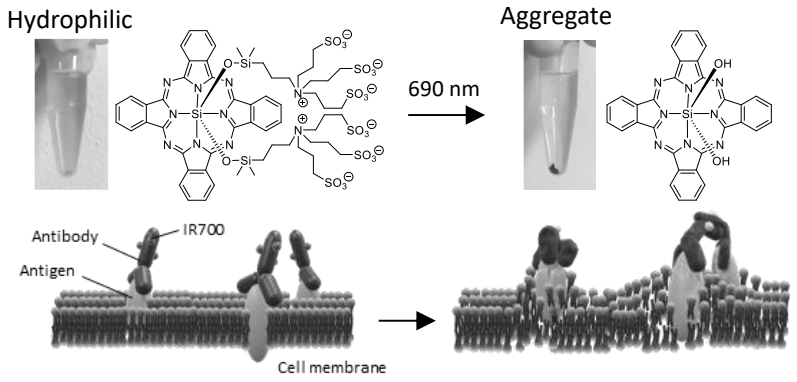

Figure 2. Mechanism of cell membrane damage.

IR700 are incorporated into these aggregates, forming clusters of multiple antibody–IR700 conjugates on the cell membrane. The resulting mechanical stress disrupts the membrane, leading to cracks and ultimately to cell death. Notably, this stacking also causes quenching of IR700 fluorescence, enabling monitoring of axial ligand cleavage through fluorescence imaging.

An important feature of NIR-PIT is its ability to activate anti-tumor immunity (Ogawa et al.). As described above, NIR-PIT selectively destroys the membranes of cancer cells expressing specific antigens upon light exposure. This mode of cell death induces the release of damage-associated molecular patterns (DAMPs) from the killed tumor cells. DAMPs stimulate the maturation of dendritic cells, thereby activating anti-tumor immunity and inducing immunogenic cell death (ICD). In mouse studies, it has been reported that not only irradiated tumors but also non-irradiated tumors can be eradicated following treatment (Nagaya et al.).

References

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2. M. Ogawa, et al., *Oncotarget*, **8**, 10425–10436 (2017).
3. K. Sato, et al., *ACS Cent. Sci.*, **4**, 1559–1569 (2018).
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Future Perspectives and Directions

Challenges to be addressed and goals to be achieved within the next 10 years include: expanding applicability to a wider range of cancers by altering the antibody, and developing more effective photo-reactive agents.

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