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Highlight Article (Invited)

Adjuvants that Empower the Action of Photodynamic Therapy†

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ABSTRACT

Compounds have been devised whose supportive actions make them important adjuvants in the priming of photosensitization to selectively target cancer cells. Here, we highlight the paper by Maytin and Hasan in this issue of *Photochemistry & Photobiology*, which describes adjuvants methotrexate, 5-fluorouracil, vitamin D and its analogs leading to improved photodynamic therapy outcome. These small molecule adjuvants act by different mechanisms to enhance the cytotoxicity in tumor cells and the therapeutic effect in cancers. These findings add to the list of strategies for enhancement of photodynamic therapy.

COMMENTARY

Maytin and Hasan have employed pharmacologic cell modifications that allow improved targeting of the photodynamic action. Pretreatment with certain adjuvants has been used to improve the response of the primed targets over unprimed ones. Specifically, adjuvants used in combination with exogenous ALA-based photosensitization are applied to ultimately enhance photodynamic therapy (PDT) for cancer. Such enhanced use of PDT has been carefully laid out in their paper (1) in this issue of *Photochemistry & Photobiology*. The authors have utilized adjuvants, including methotrexate, 5-fluorouracil, vitamin D, and its analogs that potentiate efficacy and selectivity for the photosensitized killing of cancer cells and ultimately malignant tumors (Fig. 1).

The use of adjuvants has opened up new avenues for PDT research and the development of novel protocols. By modifying the response of the target cell to exogenous ALA exposure, these molecules combine improved fluorescent imaging and enhanced photodynamic action. This approach helps surmount obstacles and limitations in PDT of cancers and potentially other targets. In the case of ALA-based PDT, adjuvant-treated cancer cells will fluoresce more brightly because of increased protoporphyrin IX (PpIX) concentrations. The increased porphyrin levels will also boost the cells' susceptibility to photodynamic action: In this process, cytotoxicity is caused by the interaction of light, photosensitizer and oxygen at the target cell. A quantitative change of any and each of these components can have a major impact on the desired therapeutic outcome. Over the past several years, Maytin, Hasan and their coworkers have systematically advanced the understanding at the molecular, cellular, tissue and organism level, of how adjuvant molecules act to enhance porphyrin formation and improve PDT.

Maytin and Hasan started exploring such ideas in their studies of adjuvants as compounds of importance in PDT studies more than 20 years ago. The initial finding of improved photodynamic action in primary murine keratinocytes that had been induced to differentiate triggered an investigation into several models of cellular differentiation (2,3). These findings led to studies with the adjuvant methotrexate, because at low doses this cytotoxic agent can also induce differentiation in certain cell types (4,5). Methotrexate led to greater PpIX concentrations from exogenous ALA exposure in keratinocytes and to enhanced phototoxicity. A subsequent study was with 5-fluorouracil, which also increased PpIX concentrations (6,7). Since PpIX levels increased not indiscriminately, but predominately in cancer cells and tumor sites, the virtue of adding these before exposure to exogenous ALA became apparent.

There is reason for optimism for future adjuvant use in everyday clinical applications of ALA-PDT. As there may be some hesitation to using cytotoxic drugs in a complex therapeutic regimen, Maytin and Hasan looked for other options and demonstrated that vitamin D leads to enhanced ALA-PDT efficacy (8-10). Small oral doses of vitamin D can avoid toxicity concerns while still inducing enhanced PpIX levels. The use of higher systemic vitamin D doses is limited by potential toxicity due to its effect on the calcium metabolism. Topical use of vitamin D instead of systemic administration reduces this concern. Calcitriol and its synthetic vitamin D analog calcipotriol have been approved by the FDA for topical use in the inflammatory skin disease psoriasis. Several investigations have demonstrated that calcitriol, including its topical application, enhances exogenous ALA-induced PpIX formation in malignant cell and skin cancers (11). The outcome of the use of cholecalciferol (vitamin D3)-PDT has also been reported (12,13). Androgens, vitamin A derivatives and other differentiation-modulating adjuvant use in cell lines and experimental tumors also have influenced the outcome of ALA-PDT in specific settings (3,14). There is also a recent report on capecitabine-enhanced ALA-PDT of experimental breast tumors (15). At this point, these latter adjuvant strategies are less well developed for clinical applications but may be useful in certain indications in the future.

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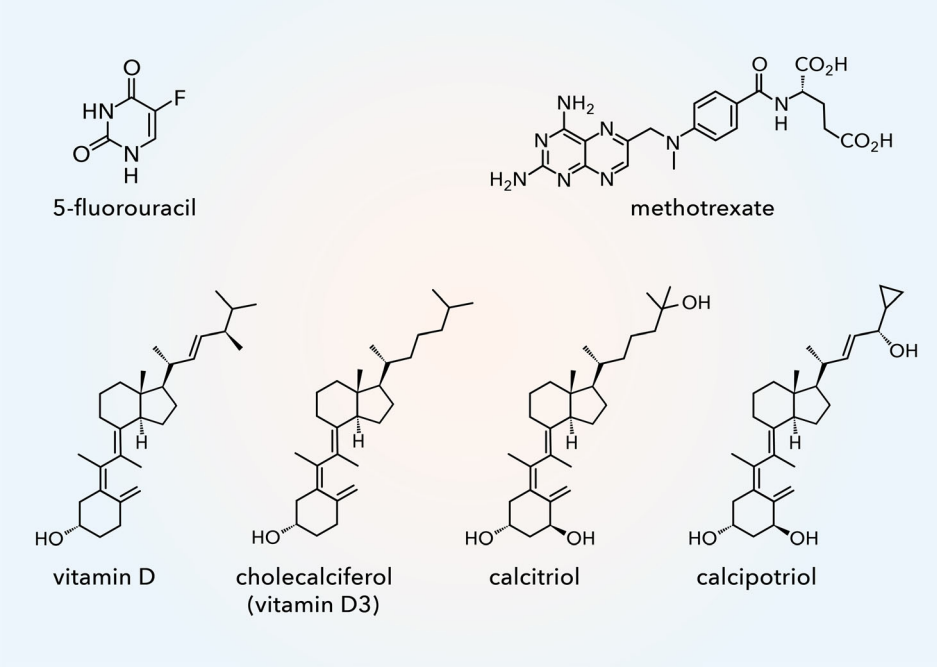

Figure 1. Molecular structures of adjuvants used for the enhancement of ALA-based PDT.

Mechanism of adjuvant-enhanced PDT

The investigation of the adjuvant-induced changes revealed a path that starts with transcriptional regulation of a heme enzyme that is critical in ALA-induced porphyrin synthesis (16). This change leads to enhanced production and accumulation of PpIX. The resulting increase in photosensitizing porphyrin within the cell is aided in its consequences and significance by two additional factors. First, the adjuvant effect appears to consistently favor malignant cells over cells with normal phenotype, thus not only enhancing efficiency of PDT but also its selectivity. Secondly, a threshold effect in photodynamic cytotoxicity that may be limiting for efficient therapy may be surpassed without increasing toxicity or other adverse events.

CONCLUSION

The variable response of human skin cancers to ALA-PDT was the initial motivation for the investigation into the action of adjuvants on keratinocytes. Maytin and Hasan have explored multiple levels and aspects of the adjuvant effects to ultimately return full circle to designing improved regimens for cancer treatment in patients. Thanks to the meticulous work along the way of their investigational journey, they have acquired and shared an impressive amount of knowledge, while always keeping their eyes on the target. Their review serves as a reference point for how rigorous research keeps advancing PDT. Their work has over the years also created a platform, on which young researchers will be able to build and further expand the use of adjuvant-enhanced photosensitization.

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