Immune stimulation and tumor cells escape - the two sides of the coin of protoporphyrin IX-based photodynamic tumor therapy

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Objective: Photodynamic therapy (PDT) uses the combination of a photosensitizing drug and light to cause selective damage to solid tumors. For early or localized disease, PDT can be a curative therapy with many advantages over available alternatives. For more advanced or metastatic disease curative therapy is usually not possible. However, there is increasing evidence that PDT can also induce systemic anti-tumor immunity, indicating that PDT can become a rational therapeutic option, even if not all tumor cells are primarily eliminated by PDT. One prerequisite to minimize tumor relapse in these settings is to counteract repair mechanisms of PDT-induced damage and to aid PDT-triggered immune stimulation.

Material and methods: Here we have characterized the immune-stimulatory and rescue response of human prostate cancer (PC-3, Du145) and glioblastoma cells (U87, U373) in vitro and in murine TRAMP-C2 prostate tumors grown subcutaneously in albino C57BL/6-Tyr\textsuperscript{c-2J} mice exposed to sublethal low dose PDT after 5-aminolevulinic acid-induced protoporphyrin IX sensitization at the transcriptome level using Affymetrix oligonucleotide microarrays. Cells and tumors were irradiated with laser light at a wavelength of 635 nm adjusted to an irradiance of 100 mW/cm\textsuperscript{2} with irradiations varying between 0.5 and 3 J/cm\textsuperscript{2} and 75-100 J/cm\textsuperscript{2}, respectively. The normalized expression data were analyzed by comparing matched samples and by Gene Set Enrichment Analysis (GSEA). Selected cytokines secreted by PDT-treated PC-3 cells were quantified using a bead-based immunoassay (CBA).

Results: The early response was characterized by the upregulation of early stress response genes like FOS, JUN, EGR1, ATF3, DUSP, heat shock protein genes as well as histone and metallothionein genes, therefore, resembling the early response of tumor cells to high dose PDT but without signs of irreversible cell damage. Twenty-four h after PDT the cells still express high levels of early response genes but additional probe sets/genes were now significantly upregulated. The most prominently up-regulated genes belong to gene families encoding Hsp40 related proteins and aldo-keto reductases. The latter being probably involved in detoxifying processes and might aid tumor cell survival. In terms of a possible anti-tumor immune response it is noteworthy that also a multitude of chemokines and interleukin genes, including CXCL2, CXCL3, IL1A and IL6, were upregulated by the tumor cells upon PDT. Most of them are involved in granulocyte attraction and activation and indeed, the most significantly upregulated sets of functionally coupled genes belong to inflammatory and granulocyte and mast cell activation pathways.

Conclusion: In conclusion, the global molecular characterization of the response to PDT of tumor cells indicates that PDT besides inducing repair mechanisms rather favors anti-tumor immune responses than tumor immune escape reactions. Therefore combining PDT and immunotherapy seems to be an attractive direction for the establishment of novel multimodal tumor therapies.

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