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Editorial

Combination Therapy by Using Natural Anti-Cancer Drugs for Effective Delivery

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Drug resistance by tumors has been a subject of extensive study. There are some mechanisms have been identified through which tumors develop this resistance. The tumor microenvironment, such as the high interstitial fluid pressure makes it unfavorable for the easy cellular internalization of drugs. Tumors host a collection of mutations and intracellular changes that affect the activity of cytotoxic agents including changes in cell cycle progression or increased repair of damaged DNA. The most generally reported mechanism is the increased energy-dependent efflux of hydrophobic drugs from the cell by ATP-binding cassette (ABC) transporter transmembrane proteins such as MDR-1 or P-glycoprotein (P-gp). The overexpression of MDR-1 in cancers has been associated with poor prognosis in various tumor types including myeloid leukemia, breast cancer, ovarian carcinoma, osteosarcoma, and lung cancer. The nuclear factor kappa-B (NF-κB) is (a signaling pathway) involved in a variety of cellular processes. It is known that more than 500 genes are controlled in some form by NF-κB. NF-κB upregulation in cancer has been shown to play an antiapoptotic role and is ascribed to the development of drug resistance. NF-κB does indeed induce the expression of the gene MDR-1. Curcumin, extracted from the *Curcuma longa*, downregulates the NF-κB and Akt pathways and much evidence validates its use as a strong chemosensitizer to improve the therapeutic potential of various chemotherapeutic agents, such as Paclitaxel, Mitoxantrone etc. In spite of the usefulness of curcumin, its use in the cancer treatment has been limited by its hydrophobicity and instability in serum. Many drug delivery systems are being soughted to address these limitations. A lipid-based polymeric micellar system to deliver such poorly soluble drugs because of their ease in preparation and the various advantages attributed to them has been recognized. A transferrin (TF)-targeted mixed micellar formulation, comprised of PEG-PE and vitamin E/folic acid/vitamin C, co-loaded with curcumin and Paclitaxel might be useful. The cytotoxicity of these micelles has been investigated against SK-OV-3 and SK-OV-3TR human ovarian adenocarcinoma cells *in vitro*. TF is an 80 kDa glycoprotein ligand for the transferrin receptor (TFR) overexpressed on SK-OV-3 cells. The TF ligand has gained popularity as a top choice targeting moiety since it is overexpressed in a variety of cancer cells and has a great potential for in the targeted delivery to tumor cells. The transport of iron predominantly occurs through the TFR. The larger iron demand mediated by fast growth and division is the key factor attributed to the overexpression of TF on cancer cells. This effect of TF, combined with curcumin and other natural anti-cancer drugs have significant advantages at reversing MDR gene. Significant improvement in antitumor efficacy *in vivo* due to the heterogeneous nature of cancer is still an affair of confront. Therefore, co-loading curcumin and Paclitaxel into a TF-targeted mixed micellar formulation of suitable polymer/vitamin E and their simultaneous delivery in one targeted micellar drug delivery system, may be an effective system. Combination therapies aimed at reducing the plasticity of tumor cells, synchronizing the cell cycle or otherwise maintaining sensitized tumor cell states, or targeting epigenetic dysregulation hold further promise for the prevention of drug resistance. It is highly advantageous to use the minimum amount of a potent toxic drug, such as paclitaxel in ng/ml together with a natural and safe anticancer drug like curcumin, artemisinin to reduce the systemic toxicity. A drug delivery cargo engineered by functionalizing reduced graphene oxide with an amphiphilic polymer, like PF-127 (P) by hydrophobic assembly might be more effective and useful. The combined treatment showed more synergistic effect for overcoming drug resistance compared with chemotherapy effect alone for effective cancer treatment.

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