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Editorial

Paclitaxel Delivery Systems; From A Stubborn Undruggable To an Efficient Chemotherapeutic In Clinic

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Excessive proliferation of cancer cells could be inhibited by disruption of microtubule network. Paclitaxel (PTX), a well-known chemotherapeutics, stabilizes microtubule networks and consequently interferes cell division. As other chemotherapeutics, pharmacodynamics of PTX seems to be promising. However, the pharmacokinetics of PTX is a bottleneck of PTX formulation development. Due to intrinsic hydrophobicity and instability in biological media, PTX is categorized as an undruggable molecule. Another complication in clinical administration of PTX is off-target effect and its side effects everywhere in the body. Furthermore, efflux-mediated drug resistance diminish tiny amount of PTX reached to the tumor cells. Drug Delivery Systems (DDS) are unique opportunity to transfer PTX formulations from test tubes to bed sides. This editorial focuses on the role of PTX DDSs on solubilization, tumor targeting and overcoming drug resistance.

PTX as other Taxanes suffers from low solubility in biological media. In commercial formulation of PTX, Cremophor EL is used as a co-solvent. Nevertheless, nephrotoxicity and hypersensitivity reactions limited Cremophor based formulations. Genexol-PM is a micellar based formulation which significantly increases the solubility by incorporation of PTX in hydrophobic core of micelle while hydrophilic shell interacts with biological media [1]. Recently an aromatic methacrylamide micelle is developed and evaluated [2]. In this study PTX content is stabilized within core of micelles via interactions with aromatic groups. In addition, biodistribution studies have proven the enhanced pharmacokinetics and tumor accumulation. In another study, PTX conjugated to chimeric peptides which spontaneously form self-assembled nanoparticles, improved the aqueous solubility and consequently tackled sub-optimal pharmacokinetics of PTX [3].

Off-target effect is another obstacle upon efficacy of PTX in clinic. Unwanted side effects exacerbate patient's condition and reduce compliance during chemotherapy period. DDSs could passively and actively deliver PTX payload to cancer cells. Enhanced permeability and retention effect (EPR) leads to accumulation of PTX drug delivery systems (PTX DDSs) to ravenous cancer cells due to anomalous-leaky vascular network of tumor tissue [4].It is also reported in literature that tumor priming with PTX DDSs modify tumor blood vessel pattern which leads to enhanced EPR effect [5]. So PTX DDSs could be both cause and effect of EPR phenomenon. Abrexane, albumin conjugated PTX, actively delivers cytotoxic payload to the target cancer cells [6]. Albumin conjugates demonstrated a promising therapeutic outcome while minimizing unwanted side effect. Decoration of DDSs with targeting moieties is another alternative for guiding PTX payload to its target. Targeting can be achieved in several levels; tissue targeting, cell targeting and sub cellular targeting. Our research groups have developed a hyaluronic acid coated micellar system which actively targets CD-44 markers over expressed on tumor tissue [7, 8]. The next level is targeting specific cell populations within tumor tissue. PLGA nanoparticles conjugated with anti CD-133 monoclonal antibodies target PTX to cancer stem cells [9]. Targeting specific cell population is not the end for adventure of DDSs, It is start of another challenge; sub cellular targeting. Functionalized liposomes with triphenylphosphonium (TPP) could be used for mitochondrial delivery [10].

Multidrug resistance (MDR) is another serious drawback in clinical efficacy of PTX. PTX is a suitable substrate for p-glycoprotein (P-gp) thus maintaining optimal intracellular levels of PTX is challenging. Co-administration of PTX along with efflux pump inhibitors using DDS platforms has attracted the attention of many scientists. However, serious drug interaction and unfavorable kinetics limited the administration of efflux pump inhibiters. So our research group focused on innovative efflux pump inhibitors such as Lapatinib (LPT, a tyrosin kinase inhibitor). LPT block HER-2 related signaling pathway while potentiating the effect of other chemotherapeutics via P-gp inhibition as well. PTX-LPT loaded micelles and PTX-LPT loaded liposome are two combined formulation which are developed for simultaneous delivery [11, 12]. Pluronic based delivery system is another alternative for conquering MDR cells and sensitizing them to PTX [13]. Pluronic destabilizes mitochondrial membrane which leads to ATP depletion and triggering intrinsic