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Indian gold treating cancer in the age of nano

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Curcumin, a diphenolic compound that gives the spice turmeric its characteristic yellow color, has an extensive history of use as a natural remedy in Ayurvedic and ancient Chinese medicine.[1-3] Indeed, modern science has now confirmed that curcumin possesses diverse pharmacologic activities, including anticancer efficacy, when used as a single agent and/or in combination with conventional radiochemotherapy protocols. Accumulating circumstantial evidence suggests that curcumin's anticancer effects occur through interaction with multiple molecular targets and signaling pathways,[3] although experimental evidence for a direct interaction between curcumin and most of these targets has not yet been established. Evidence from preclinical and phase I/II clinical trials have demonstrated that curcumin is relatively safe even at relatively high doses.[1]

The major remaining roadblock to the clinical usefulness of curcumin is poor bioavailability due to solubility limitations, intestinal metabolism and rapid clearance on first pass through the liver.[1,3] This problem of limited bioavailability is not novel among cancer therapeutics.[4,5] A range of strategies has been suggested to improve drug efficacy, including active targeting through peptide conjugation, PEGylation and perhaps most notably, encapsulation.[4,6] Encapsulation of therapeutics provides routes to improved biodistribution and bioavailability through solubilization of poorly-soluble drugs and protection of the cargo from destructive elements in vivo. Many vehicles have been developed for encapsulation and delivery of therapeutics, including solid nanoparticles, micelles, lipid and polymer vesicles (polymersomes) and nanohydrogels.[7-11] The type of cargo to be delivered (i.e., small molecule vs. protein or hydrophilic vs. hydrophobic) determines which vehicle is most ideal.

Since curcumin is a drug candidate limited by both poor water solubility and rapid biological degradation, a carrier that can solvate and protect hydrophobic materials is required. Numerous such nano materials have been developed ranging from liposomal formulations to solid nanoparticles to nanogels.[12] In the work presented by Lim and coworkers, a cross-linked, micelle-forming polymer that encapsulates curcumin in its hydrophobic core (NanoCurc) is utilized.[13,14] The copolymer of N-isopropylacrylamide (NiPAAm), N-vinyl-2-pyrrolidone and poly(ethylene glycol) acrylate spontaneously forms micelles when synthesized in water. The hydrophobic NiPAAm forms the core of the micelle while the pyrrolidone and PEG stabilize the emulsion in aqueous media. The use of a co-organic solvent allows for quantitative loading of the curcumin into the nanoparticle, minimizing drug loss during formulation. Additionally, this system provides a route to protect the curcumin from serum proteins by burying it in the center of the micelle while the PEG shell provides stealth character to the formulation.

While encapsulating curcumin and other neutraceuticals is seen as a way to increase plasma and tissue concentrations of curcumin, the choice of nanomaterial used in these formulations must be amenable to eventual release of the compound at the target tissue. Earlier work in a mouse model of pancreatic cancer demonstrated inhibition of tumor growth when Nanocurc was administered parentally.[15] However, with neurological cancers

the blood brain barrier represents another potential barrier to Nanocurc's therapeutic effectiveness. While the paper by Lim et al. examines Nanocurc's effects in cultured glioma and medulloblastoma cell lines, it does not directly address the ability of Nanocurc to pass through the blood brain barrier.[13] However, a recent report evaluating the therapeutic potential of Nanocurc in an animal model of Alzheimer's disease (from some of the same authors) did demonstrate significant accumulation of curcumin in brain tissues when administered via I.P. injection,[16] suggesting that Nanocurc could be useful in treating neurological cancers.

As pointed out by Lim et al.[13] understanding the molecular targets responsible for the Nanocurc's actions is crucial to successfully implementing its use in the clinical setting. So what are the molecular targets that account for the enhanced sensitivity of glioma and medulloblastoma cell lines? The authors demonstrate that Nanocurc, much like free curcumin, affects multiple, diverse target molecules.[1-3] Of particular interest is their demonstration that CD133, a prognostic marker of cancer stem cells, is downregulated by Nanocurc treatment in a dose and time dependent fashion.[13] These data suggest that curcumin might decrease clonogenic potential by selectively targeting cancer stem cells. Alternately these effects could be from downregulation of CD133 protein levels. These two hypotheses will need to be tested more closely, and it will need to be determined by an in vivo model, whether Nanocurc's ability to target cancer stem cells will limit growth of tumor xenografts.

Lim et al. also observed significant downregulation of IGF-1 receptor on microarray analysis following Nanocurc treatment.[13] These results were confirmed by western blot analysis. Deregulation of IGF receptor signaling was previously reported to occur in breast cancer cells following curcumin treatment.[17,18] While it is interesting that this pathway is downregulated by curcumin in diverse subtypes of cancer, there is no direct evidence provided to suggest that IGF receptor signaling mediates the response of glioma and meduloblastoma cells to curcumin. Indeed, if understanding the pathways affected by curcumin is key to its eventual clinical use, then identifying targets that are directly modified by curcumin is absolutely essential. The direct interaction between curcumin and biological macromolecules occurs via nucleophillic addition across one of the two unsaturated carbonyl bonds in the "alkene linker" portion of the curcumin molecule (Michael addition). Proteins with substrate accessible reduced cysteine and selonocyteine residues are therefore likely direct targets.[19] For example, curcumin has been shown to modify the penultimate selenocysteine residue in TxnRd1 by mass spectrophotometric analysis of proteolytic fragments.[19] Moreover covalent binding of curcumin to the selenocysteine residue in TxnRd1 is sufficient to convert the activity of this key redox modulator from anti- to pro-oxidant.[20,21] In addition to demonstrating a direct interaction between curcumin and a potential molecular target, molecular biology techniques must then be applied to validate whether the target has any role in the observed response. By knocking down protein expression in squamous cell carcinoma cell lines, we demonstrated that sensitivity of these cells to curcumin depended on elevated expression of TxnRd1.[22] Similar rigorous validation should be performed with all putative molecular targets of curcumin.

Ultimately, proof of the potential usefulness of Nanocurc in treating brain cancers awaits in vivo studies in preclinical rodent models and subsequently in human clinical trials. Curcumin itself has shown potential as a radiation and chemosensitizer;[23] it is highly likely that Nanocurc's usefulness in treating brain cancer will be as an adjuvant to current standard of care radio-chemotherapy protocols.[24] Therefore as the evaluation of Nanocurc and other similar formulations moves forward it is essential to consider combined modality studies as part of these studies.

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