Do ginger-derived nanoparticles represent an attractive treatment strategy for inflammatory bowel diseases?

“...nanoparticles derived from edible ginger represent a natural drug delivery system with no toxicity and could be an attractive treatment strategy for inflammatory bowel diseases...”

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Inflammatory bowel disease treatment challenges

Inflammatory bowel disease (IBD) is a broad term that describes conditions with chronic, recurring immune responses and inflammation of the GI tract, which result in severe abdominal cramping and diarrhea. The two most common forms of IBD are ulcerative colitis (UC), in which inflammation affects the large intestine, and Crohn's disease (CD), in which the entire digestive tract is affected. IBD is most common in developed countries, affecting the quality of life of roughly 1.4 million people in North America and 2.2 million people in Europe [1]. Although the etiology of IBD is not fully understood, both genetic and environmental factors are known to increase contribute risk [2]. The development of colitis-associated cancer (CAC) in patients suffering from UC is one of the best-characterized clinical examples of an association between intestinal inflammation and carcinogenesis [3]. Colorectal cancer is in fact a major cause of morbidity and mortality in IBD patients.

The main goals of IBD treatment are to first reduce the symptoms during acute flares, and then to control chronic inflammation so as to avoid or delay new flares and decrease the long-term risk for colorectal cancer [4].

The current research into new therapeutic approaches to treat or prevent IBD can be divided into three categories: the development of inhibitors of inflammatory cytokines (e.g., anti-TNF- α antibodies) that induce T-lymphocyte apoptosis; the identification and targeting of anti-inflammatory cytokines that downregulate T-lymphocyte proliferation; and the synthesis of selective adhesion molecule (SAM) inhibitors that suppress the trafficking of T-lymphocytes into the gut epithelium. Indeed, anti-TNF- α agents are among the most potent drugs available for the treatment of IBD. These drugs, however, need to be administered systemically and their use is limited by serious side effects [5]. There is thus an unmet need for a carrier system capable of delivering drugs specifically, and exclusively, to the inflamed mucosa for a prolonged period of time. Such a delivery system could significantly increase the usefulness of the effective existing treatments by decreasing off-target side effects.

Nanoparticle drug delivery systems in IBD

Nanotechnology holds excitement and promise in all areas of science, and nanoparticles (NPs) have received global attention due to their extensive potential applications,

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especially in biomedical fields [6]. NPs have unique physico-chemical properties, with proper surface modification, NPs can exhibit specific kinetics and the ability to distinguish between diseased and healthy sites. NPs thus represent an ideal drug delivery system for use in the treatment of IBD [7]. Various carriers based on synthesized NPs (e.g., lipid, chitosan, polymer and silica NPs) have been designed to release the loaded drug at a specific pH value to resist digestive enzymes, and/or to require bacterial cleavage for activation. Several of these carriers are currently being investigated for clinical use [8]. We recently demonstrated that artificially synthesized NPs can deliver low doses of drugs, proteins, or siRNA to specific cell types and tissues, decreasing the systemic side effects of medications in IBD therapy [9]. However, two major challenges have been identified in the preparation and application of synthesized NPs: each constituent of a synthesized NP must be examined for potential *in vivo* toxicity before it can be used for clinical applications; and the production scale is limited [10]. NPs derived from natural 'safe' sources, such as edible ginger, may be cost effective and amenable to large-scale production, and thus may overcome these limitations of synthetic NPs.

Edible nanoparticles in IBD

Ginger, which is the 'root' or the rhizome of the plant, *Zingiber officinale*, has long been known for its health benefits. It has been used for thousands of years as a remedy for a range of health issues, including colds, nausea, arthritis, migraines and GI tract disorders [11,12]. Recently, we identified and characterized a unique population of NPs from edible ginger (so-called ginger-derived NPs [GDNPs]) by super-high-speed centrifugation and ultrasonic dispersion. Dynamic light scattering showed that GDNPs were approximately 230 nm in diameter and had a negative electrical potential. GDNPs comprise specific natural membrane lipids with a few membrane proteins, and contain miRNAs and different concentrations of 6-gingerol and 6-shogaol. Importantly, we found that 1000 g of ginger yielded ~50 mg of three different types of GDNPs (GDNPs 1, GDNPs 2 and GDNPs 3). This is a high production yield compared with that of synthesized NPs, supporting the potential for large-scale production of GDNPs.

The lipids of GDNPs are largely comprised of phosphatidic acid (PA; ~25–40%), digalactosyldiacylglycerol (DGDG; ~25–40%) and monogalactosyldiacylglycerol (MGDG; ~20–30%). Other lipids, such as phosphatidylglycerol, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol and phosphatidylserine, may also be found in GDNPs, albeit in lower quantities. The protein content of GDNPs is

predominantly comprised of cytosolic proteins, such as actin and proteolytic enzymes, plus a few membrane proteins, such as membrane channels/transporters. Intriguingly, we also found that GDNPs contain abundant unique microRNAs (15–27 nucleotides in length). MicroRNAs are a recently discovered class of non-coding RNAs that play key roles in regulating gene expression. They usually induce gene silencing by binding to sites within the 3'UTR of a target mRNA, thereby suppressing protein synthesis and/or initiating mRNA degradation [13]. Most of the microRNAs found within GDNPs were predicted to have multiple molecular targets, suggesting that these NPs might regulate the expression of genes. Other known bioactive constituents of ginger, such as 6-gingerol and 6-shogaol, were also found at relatively high concentrations. Together, these findings indicate that GDNPs can be considered to be naturally derived drug-containing NPs.

Ginger-derived nanoparticles in IBD

Unlike most IBD drugs, which must be administered systemically and are associated with serious side effects [14], GDNPs are delivered orally and have been tested in non-starved mice. Oral delivery offers several advantages over other therapeutic routes. Importantly, oral administration supports our primary goal of delivering GDNPs to the colon, which is the site of intestinal inflammation in UC. Once GDNPs reach the colon, they were taken up equally by intestinal epithelial cells and macrophages in mice with or without colitis. The dual cellular targeting of orally administered GDNPs is unlike the targeting previously reported for grape- and grapefruit-derived NPs, which primarily target intestinal macrophages and intestinal stem cells, respectively [15,16]. Oral administration of GDNPs to model mice reduced acute and chronic inflammation, decreased CAC and promoted healing of the intestinal mucosa, indicating that GDNPs could prevent chronic colitis and tumor development. GDNPs also reduced the expression levels of pro-inflammatory cytokines (TNF- α , IL-6 and IL-1 β) and increased the expression levels of anti-inflammatory cytokines (IL-10 and IL-22) in colitic mice, suggesting that these NPs block intestine-damaging factors and promote intestine-healing factors. An analysis of genes that were differentially expressed following oral administration of GDNPs identified some potential molecular targets that could explain how these NPs reduce acute colitis, chronic colitis and/or CAC.

Conclusion

This study presents proof-of-principle for a novel, natural nontoxic delivery system that can target inflamed

intestinal mucosa, block damaging factors and promote healing factors. This GDNP system can easily be developed for large-scale production and may represent an effective therapeutic strategy for preventing and treating IBD and CAC.

Future perspective

GDNPs are not just an attractive treatment strategy for IBD *per se*, but the lipids contained within them might be exploited as nontoxic ‘natural’ nanovectors, offering yet another alternate strategy for *in vivo* drug delivery in IBD. Ginger-derived lipid nanovectors have the potential to deliver chemotherapeutic agents, siRNA, microRNA, and even proteins to different types of cells. For example, we recently showed that ginger-derived lipid nanovectors can be loaded with a therapeutic agent (doxorubicin) as a novel drug delivery approach for colon cancer therapy [17]. These ‘natural’ nanovectors overcame the undesirable effects of synthetic liposomes, such as cells stress, inflammasome activation and apoptosis [10]. Thus, GDNPs and their

derived nanovectors offer multiple benefits (e.g., low toxicity, tissue-specific targeting, minimal hazardous effects on the environment and the potential for economical large-scale production) and could serve as next-generation therapeutic delivery systems for the treatment of IBD and other disorders.

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