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Cover Story

Targeted delivery nano/micro particles to inflamed intestinal mucosa in human

Patients with inflammatory bowel diseases (IBD), such as Crohn's disease or ulcerative colitis, require lifelong anti-inflammatory and immunosuppressive therapy. Treatment, in particular via the oral route, has been impeded by typical diarrhea and by strong systemic adverse effects of IBD drugs. The potential of particulate drug delivery systems to enhance IBD therapy was first recognized by Lamprecht et al. who studied the size dependent accumulation of polystyrene beads in a 2,4,6-trinitrobenzene sulfonic acid (TNBS) rat colitis model [1]. Orally applied nanoparticles of ~100 nm adhered significantly more to the inflamed than to non-inflamed areas of the intestinal mucosa. This effect was somewhat decreased with 1 μ m microparticles, and there was practically no effect by 10 μ m particles. It was thought that such accumulation of particles in the inflamed areas of the intestinal epithelium can be used as a novel targeting strategy, if particles of an appropriated size are employed. The particles were also made of poly(lactic-co-glycolic acid) (PLGA) for drug delivery.

The precise mechanism for the observed accumulation of particles at the inflamed mucosal areas still remains to be elucidated. The likely contributing factors, however, are thought to be mucoadhesion, uptake by invading immune cells and facilitated penetration into the widened intercellular junctions of an inflamed epithelium. The 100 nm PLGA nanoparticles preferentially adhered to the inflamed intestinal areas when applied by oral gavage. The targeting activity was weaker with 1 μ m microparticles, and no disease specificity was observed with 10 μ m particles. The PLGA nanoparticles loaded with rolipram, an anti-inflammatory drug, showed promising results in an acute rat colitis model. The PLGA nanoparticles led to a prolonged alleviation of inflammatory symptoms and also significantly reduced the adverse central nervous side effects as compared with the solution formulation [2]. These studies provided the first evidence that the targeting to the inflamed intestinal mucosa could indeed be used for prolonged and localized drug delivery, at least in such pre-clinical animal model.

In this issue, the paper by Schmidt et al. describes an in-depth study on possible translation of the particle-based targeted drug delivery in human IBD patients [3]. Accumulation of particles was monitored by confocal laser scanning endoscopy. It was found that

nanoparticles were not observed to accumulate in the inflamed areas. On the other hand, 2 μ m microparticles were found to adhere preferably to the inflamed tissue with a direct correlation between clinical disease score and targeting index. Using chamber studies revealed enhanced translocation of nanoparticles, and this resulted in no apparent visualization on the surface of the inflamed tissue. The significance of this study is that the effect of nanoparticles observed in small animal models was not observed in human patients, and microparticles showed the ability to target the inflamed tissues. The data indicates that the selection of the particle size has to be carefully made depending on specific applications. One important lesson from this study is that nanoparticles do not necessarily result in better drug delivery than microparticles in targeted delivery to the inflamed areas in the intestine. It is time to recognize that "nanoparticles" may not be a panacea for targeted drug delivery, and the drug delivery field in general needs to find alternative ways to achieve more efficient drug delivery in various routes of administration.

References

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