Layered double hydroxide nanoparticle-based anti-restenotic drug delivery system

Zi Gu[a], Barbara E. Rolfe[b], Anita C. Thomas[c], Julie H. Campbell[b], Max Lu[a], and Zhi Ping Xu[a,*]

[a]ARC Centre of Excellence for Functional Nanomaterials, Australian Institute of Bioengineering and Nanotechnology, The University of Queensland, Brisbane, QLD 4072, Australia
[b]Centre for Research in Vascular Biology, Australian Institute of Bioengineering and Nanotechnology, The University of Queensland, Brisbane, QLD 4072, Australia
[c]Bristol Heart Institute, University of Bristol, Bristol, BS2 8HW, United Kingdom

z.gu@uq.edu.au; gordonxu@uq.edu.au

Abstract

The biological and medical applications of layered double hydroxide (LDH) nanoparticles have attracted wide interest. LDHs consist of brucite-like layers and the exchangeable anions-containing gallery space. The present abstract reported that an anti-restenotic drug, low molecular weight heparin (LMWH), was intercalated into LDH interlayers which enhanced the biological and therapeutical effects of LMWH *in vitro* and *in vivo*. Results from powder X-ray diffraction and transmission electron microscopy demonstrated successful intercalation of LMWH into LDH interlayers by observation of enlarged LDH interlayers [1]. LMWH-LDH presented a hexagonal plate-like shape with ~90 nm in size [1]. Under physiological conditions, the intercalated LMWH was released from LDH in a sustained manner, resulting from the diffusion of LMWH from LDH and the dissolution of LDH layers [1]. The biological examination on cultured rat smooth muscle cells (SMCs) demonstrated the low cytotoxicity of LDH nanocarriers [2]. Comparison of the effects of unconjugated LMWH and LMWH-LDH conjugates showed the enhanced inhibitive effects of LMWH on SMC proliferation and migration (Figure 1A) [2]. The cellular uptake of LMWH by SMCs was also increased (more than 10 times) by conjugation to LDH nanoparticles [2,3]. After internalization by SMCs, LMWH-LDH was found to undergo the endocytic pathway (Figure 1A), and (unlike unconjugated LMWH) escape from endosomal compartment, thus avoiding biodegradation of LMWH [3]. Compared with unconjugated LMWH, LMWH-LDH enhanced suppression of mitogen-activated protein kinas signal transduction, probably due to the sustained release and improved cellular uptake of LMWH-LDH; the enhanced suppression of MAPK signal transduction is associated with enhanced inhibition of SMC proliferation and migration [3]. To target deliver LMWH-LDHs to the site of arterial injury, LMWH-LDH was conjugated with a targeting moiety (an antibody to XLF) and examined in a rat model (Figure 2A) [4]. Our preliminary results showed that targeted delivery of LMWH-LDH with anti-XLF effectively limited restenosis and thrombus formation (Figure 2B), which suggested the potential of this technique for clinical application [4].

References

[1] Gu Z, Thomas AC, Xu ZP, Campbell JH, Lu GQ, Chemistry of Materials, **20** (2008) 3715-3722.
[2] Gu Z, Rolfe BE, Xu ZP, Thomas AC, Campbell JH, Lu GQM, Biomaterials, **31** (2010) 5455-5462.
[3] Gu Z, Rolfe BE, Thomas AC, Campbell JH, Lu GQ, Xu ZP, Biomaterials Biomaterials, **32** (2011) 7234-7240.
[4] Gu Z, Rolfe BE, Xu ZP, Campbell JH, Lu GQ, Thomas AC, Advanced Healthcare Materials, **1** (2012) 669-673.

Figures

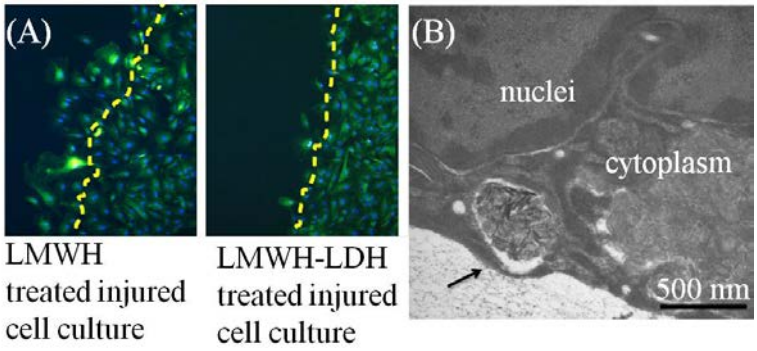

Figure 1. (A) LDH carrier enhanced the inhibitory effect of LMWH on rat vascular smooth muscle cell migration. (B) LMWH-LDH nanoparticles internalized by the endosomal compartment (indicated by the arrow).

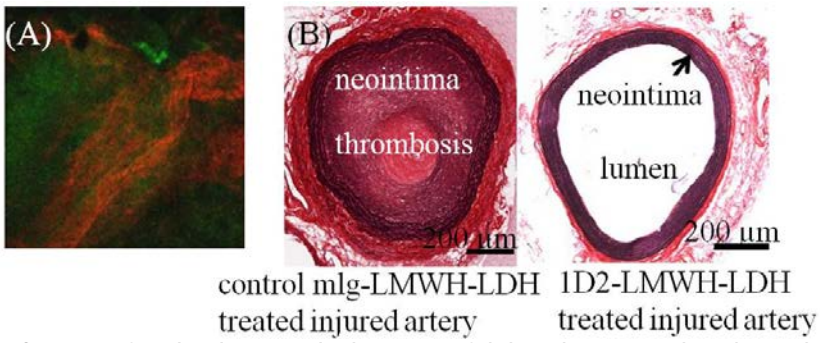

Figure 2. (A) *En face* confocal microscopic images of injured rat arteries (green) treated with red fluorescence labeled antibody-LMWH-LDH. (B) Typical cross-sections of injured artery showing antibody-LMWH-LDH reduced neointimal formation and thrombosis.