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Short Communication

Liposome-loaded pingyangmycin: A new possible agent to treat hemangioma

Zhenghui Wang[1], Xiaoli Li[2]*, Baojun Wu[1], Dingwei Zhang[2], Min Xu[1], Xiaoyong Ren[1], Caiqin Wu[1] and Jingjing Li[1]

[1]Department of Otolaryngology-Head and Neck Surgery, The Second Hospital, Xi'an Jiaotong University, Xi'an 710004, China.
[2]Department of Dermatology, The Second Hospital, Xi'an Jiaotong University, Xi'an 710004, China.

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Infantile hemangioma is a tumor of the microvasculature composed predominantly of proliferating endothelial cells. Pingyangmycin (bleomycin A5), a water-soluble glycopeptide produced by *Streptomyces pingyangensisn*, has been used as a sclerosing agent for the treatment of hemangioma. However, its utility is limited by adverse side effects, including significant pain, swelling, pulmonary fibrosis and life-threatening dyspnea. Therefore, further improvement of the efficacy and safety of pingyangmycin sclerotherapy is essential. Here, we proposed to use liposomes as a carrier that can modify pharmacological properties of encapsulated drugs and thereby reduce tissue toxicity. Taking advantage of the finding that hemangioma-derived endothelial cells constitutively overexpress vascular endothelial growth factor receptor 2 (VEGFR2), an endothelial cell-targeting delivery system was designed by coupling liposomes with vascular endothelial growth factor (VEGF) ligand. Due to the interaction between VEGF and VEGFR2, the liposomal formulation of pingyangmycin would be delivered to desired endothelial compartments of hemangioma lesions. In conclusion, we believe that the VEGF-mediated targeting delivery of liposomal pingyangmycin would improve therapeutic efficacy, minimize the related complications, and represent a promising treatment option for hemangioma.

Key words: Pingyangmycin, sclerotherapy, hemangioma, endothelial growth factor (VEGF).

INTRODUCTION

Hemangiomas are the most common benign tumor of endothelial cell origin primarily affecting infants. It has been documented that approximately 5 to 10% of one-year-old children suffer from Hemangiomas (Drolet et al., 1999). Despite the prevalence of this tumor, its pathogenesis has not been completely understood. It has been proposed that hemangioma development may be associated with a clonal expansion of endothelial cells harboring somatic mutations. Boye et al. (2001) in a study showed that hemangiomas are composed of clonal endothelial cells that exhibit enhanced proliferation and migration compared with normal endothelial cells. Somatic mutations in genes regulating cell proliferation have been linked to the abnormal properties of hemangioma-derived endothelial cells. Hemangioma lesions are characterized by a growth phase and an involution phase. Typically, they are absent at birth, but appear around the second week of life, grow rapidly over the next 6 to 10 months, and then slowly regress over the next 7 to 10 years (Boye et al., 2001; Mulliken, 1993). Most hemangiomas will disappear without treatment, leaving minimal or no visible marks. However, a small proportion can cause severe complications such as disfigurement, ulceration and significant pain, which require immediate intervention.

Topical or systemic corticosteroids are the first-line treatment for proliferating hemangiomas, with the expectation of controlling tumor growth. By reviewing 25 consecutive patients with infantile hemangioma treated with oral prednisolone, Greene and Couto (2011) found that all tumors responded to therapy; 88.0% (n=22)

*Corresponding author. E-mail: anjala@163.com. Tel: +86-29-87679708. Fax: +86-29-87678421.

regressed and 12.0% (n=3) stabilized. A systematic review of 749 patients with head and neck hemangiomas revealed that >90% of the participants showed a good or excellent clinical response to intralesional steroid injections (Prasetyono and Djoenaedi, 2011). However, the steroid therapy is hindered by insidious adverse effects such as irritability, hypertension, neurodevelopmental impairment, decreased rate of growth and weight gain (Boon et al., 1999). There are now a number of alternative treatments, including the use of imiquimod cream, propranolol or interferon, surgical excision, embolization, compression, cryotherapy, laser therapy, and sclerotherapy (Mendiratta and Jabeen, 2010). Unfortunately, none of these approaches is totally satisfying.

PINGYANGMYCIN SCLEROTHERAPY

Percutaneous sclerotherapy as a minimally invasive treatment modality has been successfully used for low-flow vascular lesions (Blaise et al., 2011). Crawford et al. (2009) showed that ethanol sclerotherapy affords prompt pain relief in patients with symptomatic musculoskeletal hemangiomas. Sclerotherapy with monoethanolamine oleate has been reported to be effective in the treatment of hemangioma with late involution (Matsumoto et al., 2003). Various sclerosing agents have been developed for this procedure, including ethanol, polidocanol, monoethanolamine oleate, and OK-432. Pingyangmycin (bleomycin A5), a water-soluble glycopeptide produced by *Streptomyces pingyangensisn*, has a similar chemical structure to that of bleomycin and exhibits potent antitumor properties (Tai et al., 1998).

Recent studies have demonstrated that pingyangmycin sclerotherapy alone or combined with other drugs can provide benefits to patients with hemangiomas (Yang et al., 2009). Intralesional injection of pingyangmycin has been proposed as an effective alternative therapy for capillary, mixed and cavernous hemangiomas in oral and maxillofacial region. The mechanism for pingyangmycin sclerotherapy involves direct destruction of endothelial cells, induction of inflammatory responses, and formation of thrombus and fibrosis, leading to obstruction of the vessels. Being a mild sclerosing agent, pingyangmycin is not suitable for high-flow vascular anomalies, as it hardly remains within the lesions and flows away immediately after injection, thus resulting in poor sclerosing effects. Additionally, pingyangmycin injection may cause significant pain, swelling, pulmonary fibrosis, and life-threatening dyspnea. Therefore, further improvement of pingyangmycin sclerotherapy is essential.

Liposomal drug delivery system

Liposomes are polymeric nanoparticles that consist of phospholipid bilayers and generate an aqueous cavity in the inner phase, which have been widely used as drug delivery systems for many years (Garcia-Marco et al., 2009; Batist et al., 2009). Liposomal encapsulation of drugs exhibit stable pharmacokinetics, a better distribution in human bodies and reduce tissue toxicity, all of which are characteristics that improve therapeutic effectiveness. Most importantly, the targeted liposomal system (that is - liposomes conjugated with moieties such as antibodies and peptides that target particular types of cells) allows the delivery of drugs to the sites of interest. This strategy is often applied in anti-cancer studies.

Lee et al. (2007) developed a novel liposomal delivery system that could specially recognize tumor blood vessels and revealed that this system offered improved therapeutic effects over conventional anticancer drug therapy. Likewise, tumor-targeting liposomal complex was reported to enhance the therapeutic efficacy of GMC-5-193, an anticancer small-molecule quinazolinone analogue (Hwang et al., 2008). In light of these findings, we hypothesized that a liposomal formulation of pingyangmycin would increase therapeutic potentiality and minimize the related complications.

VEGF-mediated targeting delivery of liposomal pingyangmycin to endothelial cells

Endothelial cells represent an important therapeutic target in hemangioma. Cultured hemangioma-derived endothelial cells share a phenotype of constitutively active vascular endothelial growth factor receptor 2 (VEGFR2) signaling (Jinnin et al., 2008). This is attributable to decreased expression of vascular endothelial growth factor receptor 1 (VEGFR1), a receptor that is thought to negatively regulate VEGFR2 signaling by acting as a decoy receptor for vascular endothelial growth factor (VEGF) (Roberts et al., 2004). This constitutive activation of VEGFR2 signaling could partially explain the increased proliferation and migration of hemangioma-derived endothelial cells. Takahashi et al. (1994) reported that VEGF is elevated in proliferative phase hemangioma. Chang et al. (1999) also found that proliferative hemangioma specimens have a significantly high level of VEGF mRNA than involuted hemangioma specimens. These findings suggest that hemangioma-derived endothelial cells are characterized by an altered VEGF signaling, which provide a rationale for the development of an endothelial cell-targeting liposomal delivery system. This system involves the encapsulation of pingyangmycin in liposomes that are conjugated to VEGF. Taking advantage of the interaction between VEGF and VEGFR2, liposomal pingyangmycin would be delivered to desired endothelial compartments of hemangioma lesions. Indeed, VEGF-mediated drug delivery has been employed to target VEGFR2-overexpressing endothelial cells (Backer and Backer, 2001; Backer et al., 2005).

CONCLUSION

Summarily, we propose a novel approach for the treatment of hemangioma by selectively targeting endothelial cells using VEGF-coupled liposomal formulation of pingyangmycin. This therapy should hold the promise of high efficacy and low toxicity. Ongoing studies are conducted to test and confirm this hypothesis.

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