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Gö6983 attenuates titanium particle-induced osteolysis and RANKL mediated osteoclastogenesis through the suppression of NFκB/JNK/p38 pathways

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ABSTRACT

Osteoclast activation by wear particles has caused major difficulties for surgeons. Wear particles are the main causes of aseptic prosthetic loosening. Gö6983, a protein kinase C inhibitor, inhibits five subtypes of protein kinase C family members. Here, we found that Gö6983 had an obviously inhibitory effect on wear-particles-induced osteolysis *in vivo*. *In vitro*, Gö6983 inhibited RANKL-stimulated osteoclast formation and function by inhibiting the RANKL-stimulated nuclear factor-κB/JNK/p38 signaling pathway. We also observed that Go6983 had no effect on the differentiation of osteoblasts and osteoblast-associated genes expression. According to our data, Gö6983 has potential therapeutic effects for aseptic prosthetic loosening caused by osteoclast activation.

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1. Introduction

Total joint arthroplasty (TJA) improves the lives of most patients [1,2]. As the number of patients receiving this treatment has increased, the number of patients with failed arthroplasty has also increased. Aseptic loosening caused by long-term use of artificial joints is the main cause of TJA failure. Currently, joint aseptic loosening depends on surgical renovation and no drug treatments for aseptic loosening are available in the clinic. An increasing number of studies has examined wear-particle-induced aseptic loosening of the prostheses to develop a specific drug to overcome bone dissolution by inhibiting or blocking the progress of wear-particle-induced osteolysis [3]. The major factor in the failure of arthroplasty is osteolysis around the artificial joint, and the main cause of bone dissolution in the arthrosis is the production of wear particles [4,5].

Titanium (Ti) particles released from the artificial femoral head play a key role in the initiation and development of osteolysis [6,7]. Titanium particles elicit inflammatory cytokine secretion, including interleukin-1, interleukin-6, and tumor necrosis factor-α [7–9]. Furthermore, osteoblasts (OBs) and osteoclasts (OCs) are related to periprosthetic osteolysis; OBs express two stimulating factors, including nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF), and then induce differentiation of bone marrow macrophages (BMMs) into osteoclasts [10]. Osteolysis is activated by mobilization of RANK, RANKL, and M-CSF [11,12] The interaction of RANKL with RANK stimulates the signaling pathways of osteoclast activation, including the nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways.

PKC is linked to osteoclasts, including their differentiation, survival, and apoptosis [13–15]. The PKC family comprises three groups (classical PKCs, novel PKCs, and atypical PKCs) [16–18].

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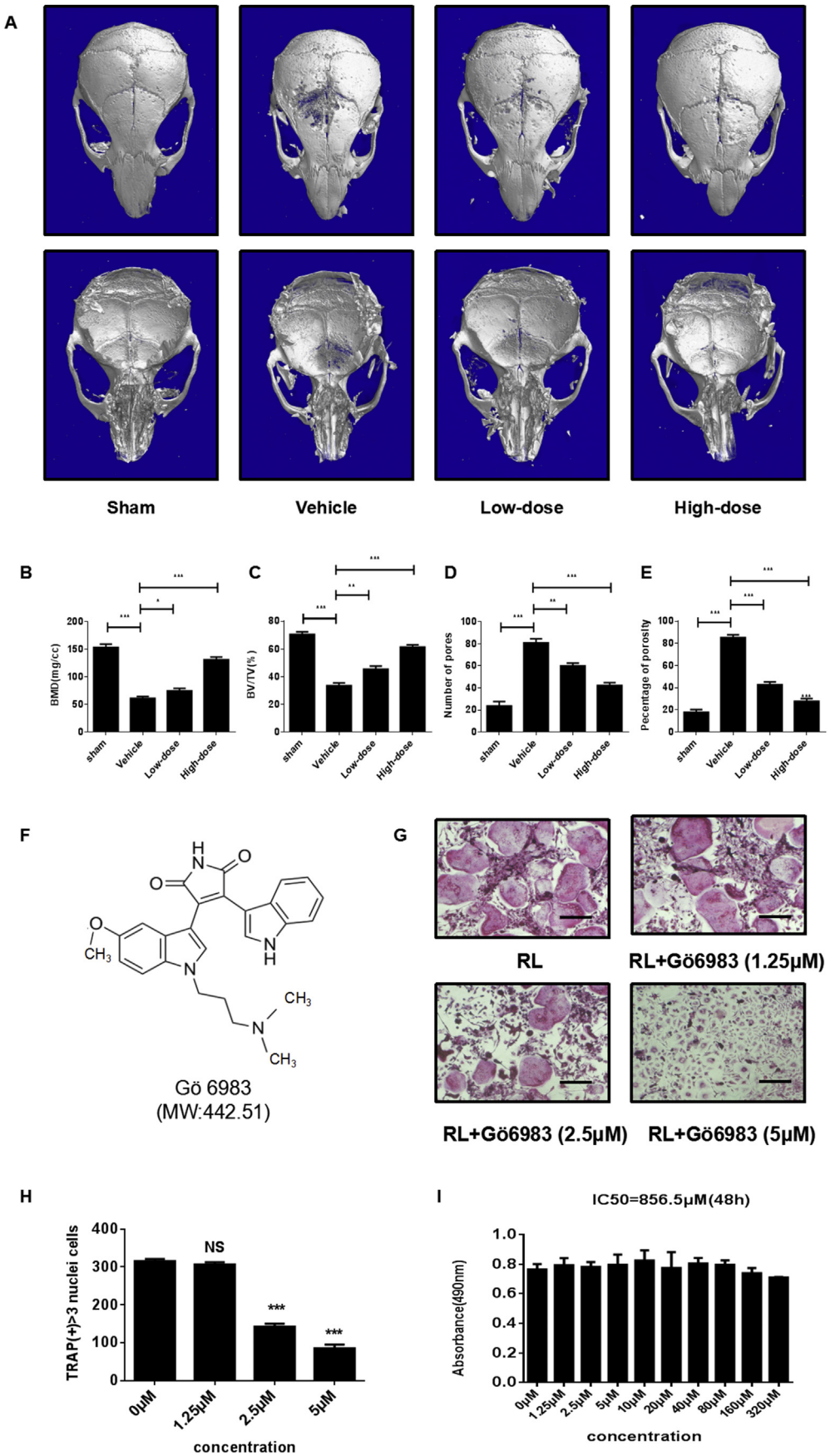

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