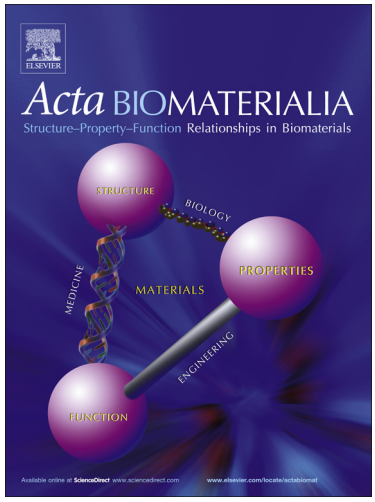


Full length article

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# Cobalt (II) ions and nanoparticles induce macrophage retention by ROS-mediated down-regulation of RhoA expression

Jing Xu[1], Junyao Yang[2], Agata Nyga[3,4], Mazdak Ehteramyan[5], Ana Moraga[5], Yuanhao Wu[1], Lingfang Zeng[5]*, Martin M Knight[1]*, Julia C Shelton[1]*

[1] Institute of Bioengineering, School of Engineering and Materials Science, Queen Mary University of London, London, UK.

[2] Department of Laboratory Medicine, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, China.

[3] Division of Surgery and Interventional Sciences, University College London, London NW3 2QG, United Kingdom

[4] Institute for Bioengineering of Catalonia, 08028 Barcelona

[5] Cardiovascular Division, Faculty of Life Science and Medicine, King's College London, London SE5 9NU, United Kingdom

*** Corresponding author:**

Lingfang Zeng: lingfang.zeng@kcl.ac.uk

Martin M Knight: m.m.knight@qmul.ac.uk

Julia C Shelton: j.shelton@qmul.ac.uk

**Abstract**

Histological assessments of synovial tissues from patients with failed CoCr alloy hip prostheses demonstrate extensive infiltration and accumulation of macrophages, often loaded with large quantities of particulate debris. The resulting adverse reaction to metal debris (ARMD) frequently leads to early joint revision. Inflammatory response starts with the recruitment of immune cells and requires the egress of macrophages from the inflamed site for resolution of the reaction. Metal ions ($Co^{2+}$ and $Cr^{3+}$) have been shown to stimulate the migration of T lymphocytes but their effects on macrophages motility are still poorly understood. To elucidate this, we studied *in vitro* and *in vivo* macrophage migration during exposure to cobalt and chromium ions and nanoparticles. We found that cobalt but not chromium significantly reduces macrophage motility. This involves increase in cell spreading, formation of intracellular podosome-type adhesion structures and enhanced cell adhesion to the extracellular matrix (ECM). The formation of podosomes was also associated with the production and activation of matrix metalloproteinase-9 (MMP9) and enhanced ECM degradation. We showed that these were driven by the down-regulation of RhoA signalling through the generation of reactive oxygen species (ROS). These novel findings reveal the key mechanisms driving the wear/corrosion metallic byproducts-induced inflammatory response at non-toxic concentrations.

**Keywords:** cobalt chromium; nanoparticles; wear debris; macrophage; ROS.