Title: Investigating the contribution of hypoxia-inducible factor to cobalt-induced pseudotumour formation

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For a hip replacement to be successful, the material it is made of must have certain characteristics. It must be able to provide a near frictionless surface, be durable, and not cause irritation or inflammation. A metal alloy of chromium and cobalt was introduced as an alternative to polyethylene and ceramic, but these joints have their own problems. In some patients with metal hip replacements, wearing of the metal has resulted in the release of metal particles into the tissues, and in more extreme cases patients have developed pseudotumour growths of soft tissue around their hip. The pseudotumours have the appearance of a tumour and can grow quite large but are not cancerous and will not spread.

It is currently not known what causes these growths and this study aimed to explore the mechanism of pseudotumour formation. Cobalt is a major component of the metal toxicity associated with metal implant failure and is also known to act as a hypoxia mimetic, generating the expression of proteins that are known to promote tumour formation in cancerous cells. In particular, Co^{2+} stimulates the activity of the transcription factor hypoxia-inducible factor (HIF)-1 by poisoning the hydroxylase enzymes that regulate its activity. In human cancer, up regulation of HIF-1 results in gene transcription of proteins associated with glycolysis, angiogenesis, vascular function, and cell survival pathways. Previous studies have shown that this assists abnormal proliferation and survival of cells. It is hypothesized that the pseudotumour tissue, especially that contaminated by the heavy metals, will have high concentrations of HIF-1 and its downstream proteins. This would strongly indicate that HIF-1 is a major contributor pseudotumour growth.

The aim of this project was to determine whether HIF-1 is activated in pseudotumours. We have obtained two pseudotumour tissue samples from patients undergoing hip prosthesis repair. These samples have been investigated using immunohistochemistry on tissue sections, allowing for specific detection of the HIF-1alpha protein subunit and also for the expression of proteins that are regulated by HIF-1 and that control tumour growth. The immunohistochemistry shows the presence of these proteins in relevant regions of the tissue and can be correlated with the morphology staining and localization of the contaminating cobalt, which can also be seen microscopically. The tissues have also been extracted under liquid nitrogen and analysis of these preparations allowed for the detection and quantification of HIF-1 and its downstream proteins.

This was a novel exploratory project that has investigated whether there is a link between tissue hypoxia and the development of pseudotumours. This is novel and relevant both to the study of Co^{2+} toxicity and to the understanding of tumour biology.