In Vivo both limit the longevity of THA. We previously identified macrophage apoptosis in the pathway leading to apoptosis contributes to our understanding of the mechanism leading to periprosthetic osteolysis and to a more rational strategy for the treatment and/or prevention of osteolysis.

**Relevance to Musculoskeletal Conditions**

Osteolysis and subsequent loosening are critical processes that limit the longevity of THA. We previously identified macrophage apoptosis in both in vivo osteolytic PM from failed THAs and in vitro wear debris-induced macrophages. These latter findings, combined with the recent demonstration that osteoclasts may also be involved in the induction of apoptosis contributes to our understanding of the mechanism leading to periprosthetic osteolysis and to a more rational strategy for the treatment and/or prevention of osteolysis.

**Introduction**

Osteolysis is a complex disease, the etiology of which remains to be fully understood. The identification of apoptosis in pseudomembranes (PMs) of aseptically loose Total Hip Arthroplasty (THA) may offer specific target points for therapeutic modulation of osteolysis. The identification of a specific pathway leading to apoptosis contributes to our understanding of the mechanism leading to periprosthetic osteolysis and to a more rational strategy for the treatment and/or prevention of osteolysis.

**Materials and Methods**

The study consisted of 30 specimens of PM harvested at the time of revision THA surgery in 25 patients. The mean patient age was 59 years (range, 28-82 years) and the duration of implantation was 11 years (range, 1-21 years). Control tissues were obtained from 6 cases of hardware removal (range, 28-82 years) and the duration of implantation was 11 years (range, 1-21 years). Control tissues were obtained from 6 cases of hardware removal (range, 28-82 years) and the duration of implantation was 11 years (range, 1-21 years). Control tissues were obtained from 6 cases of hardware removal (range, 28-82 years) and the duration of implantation was 11 years (range, 1-21 years). Control tissues were obtained from 6 cases of hardware removal (range, 28-82 years) and the duration of implantation was 11 years (range, 1-21 years).

**Results**

Our results (Fig. 1) showed that both the native (113 kDa) PARP and the proteolytic fragment (85 kDa) are present in osteolytic PM whereas control membranes expressed only the 113 kDa native form. We also demonstrated that caspase-3 is over-expressed in PMs compared to control tissues. The presence of PARP fragment was demonstrated in 96% of analyzed specimens while the over-expression of caspase-3 (CPP32) was visualized in 93% of our samples. PARP cleavage and caspase-3 over-expression were observed with the same incidence on both the acetabular and femoral sides of the prostheses. While we were able to detect the recombinant protein of p53, the presence of p53 was not detected in PM or in control specimens.

**Discussion**

The ICE-like protease caspase-3 (CPP32), one of the key enzymes implicated in the induction of apoptosis, is known to inactivate PARP by cleaving it. PARP is a nuclear enzyme responsible for DNA repair and its proteolytic cleavage is closely associated with apoptosis. The protein p53 is a transcriptional factor activated in DNA damage-induced apoptosis. In order to situate that part of the CPP32/PARP pathway that we have identified in this study, we propose the sequence of events shown in Fig. 2. Particulate debris is the exogenous cytotoxin that may be responsible for direct DNA damage, but more likely acts as an indirect role through the induction of TNF-α release. TNF-α is in fact one of the first cytokines to have been implicated in the induction of apoptosis. It is the indirect route via TNF-α that we feel the specific CPP32/PARP pathway is implicated in wear debris-induced apoptosis.

Finally, apoptosis may be a major internal mechanism to decrease macrophage and osteoclast number and activity. Our results suggest that activation of specific proteases of the caspase-3 pathway, independent of p53, are implicated in the induction of apoptosis and imply that osteolysis can be specifically targeted by therapeutic induction of apoptosis. The implication that the new generation of potent anti-osteoclastic drugs (bisphosphonates) act by the induction of apoptosis contributes to a more rational clinical strategy for the treatment and/or prevention of periprosthetic osteolysis.

**References**


**Figure 1:** PARP, caspase-3 (CPP32), and p53 protein expression in PMs of aseptically loose total hip arthroplasty.

**Figure 2:** Schematic representation of particle-induced apoptosis in PMs of aseptically loose total hip arthroplasty.

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