DIFFERENTIAL CELLULAR MACROPHAGE RESPONSE TO ALUMINA CERAMIC AND ULTRA-HIGH-MOLECULAR-WEIGHT POLYETHYLENE PARTICLES

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Introduction: Implant wear producing particulate debris leading to osteolysis and subsequent loosening is a critical process that limits the longevity of total hip arthroplasty. We previously identified macrophage apoptosis in both in vivo pseudomembranes from failed THAs (1) and in vitro wear debris-induced macrophages (2). The recent explosion of interest in apoptosis lies in the fact that it is under positive and negative regulation through evolutionary conserved biochemical pathways that are dependent on the death stimulus and cell context. It may also be possible to modulate macrophage apoptosis in the treatment of periprosthetic osteolysis. The purpose of this study was to compare the macrophage response to identically sized particles of alumina ceramic and ultra-high-molecular-weight polyethylene in terms of TNF-α release and induction of apoptosis.

Materials and Methods: J774 mouse macrophages were cultured in RPMI containing 5% Fetal Bovine Serum - 100 U/ml Penicillin – 100 mg/ml Streptomycin, and incubated for 0-24 h in presence of alumina ceramic (Al2O3; Alcoa, Bauxite, AK, USA) and ultra-high-molecular-weight polyethylene (UHMWPE; Pfrizer, Rutherford, NJ, USA) particles of the same size (0.5 to 2 µm) and concentrations. TNF-α release was measured by ELISA (Genzyme, Cambridge, MA, USA); Poly(ADP-ribose)polymerase (PARP) expression was measured by Western blot using anti-PARP from Roche Diagnostics (Laval, Quebec, Canada); DNA fragmentation (DNA laddering) was analyzed on agarose gel containing ethidium bromide. PARP expression and DNA laddering were used as markers of apoptosis.

Results: Our results showed that Al2O3 particles induced TNF-α release after 4h incubation with concentrations reaching 483 and 800 pg/ml after 24h with 125 and 250 particles/macrophage respectively (control = 161 pg/ml). The same concentrations of UHMWPE particles induced a much larger and significant TNF-α release after 1h incubation with concentrations reaching 6250 pg/ml after 24h. TNF-α release was lower with 25 particles/macrophage reaching 343 pg/ml and 2750 pg/ml with Al2O3 and UHMWPE particles respectively. We also demonstrated that the proteolytic PARP fragment (85 kDa) was expressed after 1h incubation with 125 and 250 Al2O3 particles/macrophage. This fragment had lower expression and appeared after 8h incubation with fewer particles (25 particles/macrophage). PARP fragment expression was also lower with UHMWPE particles and appeared after 8h with 125 and 250 particles/macrophage. No PARP fragment expression was observed with 25 particles of UHMWPE per macrophage. Finally, DNA fragmentation (DNA laddering) was observed after 16h with 125 and 250 particles of Al2O3 per macrophage whereas no laddering was induced by 25 particles of Al2O3 per macrophage as well as with UHMWPE even after 24h incubation.

Discussion: Our results show that although both Al2O3 and UHMWPE particles induce TNF-α release, this stimulation was much greater (8-10 times higher) with UHMWPE than Al2O3. As well, the induction of apoptosis as measured by PARP cleavage and DNA laddering, is different for these two particles being faster and more efficient with Al2O3 than UHMWPE. We hypothesize that the ability of Al2O3 to induce macrophage apoptosis may explain the lower TNF-α release observed with these particles and explain the differences seen in osteolysis patterns of ceramic-ceramic vs. metal-polyethylene articulations (3).

In conclusion, there is an urgent need to better understand the mechanisms leading to osteolysis. Apoptosis may be a major internal mechanism to decrease macrophage activity. The identification of an apoptosis-related pathway in the macrophage response to ceramic particles provides crucial data for a rational approach in the treatment and/or prevention of periprosthetic osteolysis.