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Title

CELLS INVOLVED IN WEAR-MEDIATED OSTEOLYSIS

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Abstract:

Ultrahigh molecular weight polyethylene (UHMWPE) is extensively used to manufacture orthopedic total implant components. Wear debris of this polymer released at the periimplant region is responsible for osteolysis and implant failure. Cells around the implant where the metallic and polymeric components articulate, respond to these non-biodegradable particles (primarily UHMWPE) and release chemical mediators that eventually lead to aseptic loosening of the implant. In this short review we discuss the various cell lineages that respond to and are involved in the wear-mediated osteolytic process.

Keywords: UHMWPE, wear-debris, nanoparticles, cells, wear-mediated osteolysis.

Introduction:

Wear particles, primarily of UHMWPE (Figure 1) released at the articulating surfaces of total joints are responsible for subsequest bone loss and implant failure.

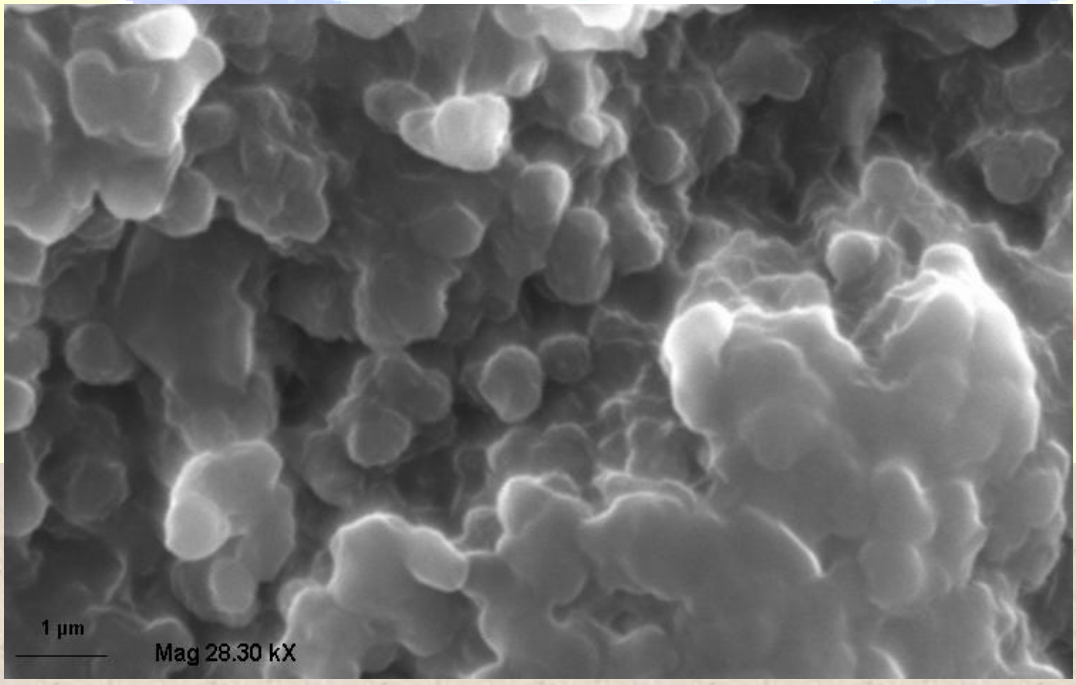

Figure 1: Scanning electron micrograph of UHMWPE particles.

Host immune response to wear particles at the periprosthetic region is a result of responses by a plethora of cell lineages that populate the area. The biological response to the wear particles is a function of their size, morphology and dose. Cells give a similar response to "non biodegradable" wear debris particles having similar size and morphology[1,2]. Periprosthetic osteolysis is synonymous with the formation of a granulomatous tissue at the interface of the bone and prosthesis and all cell types including fibroblasts, macrophages, osteoblasts and foreign-body giant cells present in this interfacial tissue contain wear debris from prosthetic components. New emerging scientific data have provided us a deeper insight of the pathophysiology of wear mediated osteolytic process and helped us in elucidating the functions and response of individual cell groups that participate in the whole process. Figure 2 is a schematic representation of the generation of wear particles subsequently leading to implant failure.

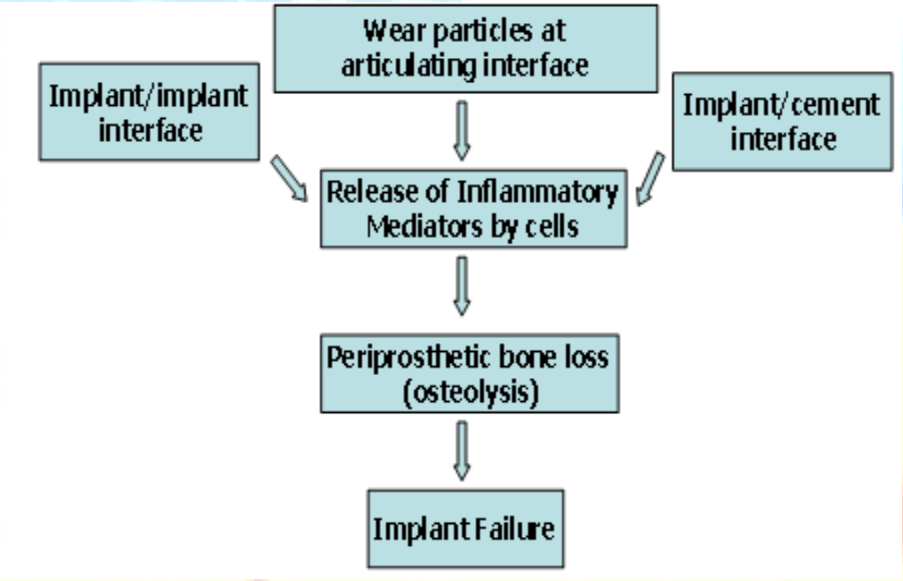

Figure 2: Schematic showing wear mediated osteolysis following release of wear-particles from orthopedic total joint components

There are various cell lineages involved in the osteolytic process

- Macrophage
- Osteoclasts (derived from monocyte/ macrophage haematopoietic cell lineage)

- Osteoblasts (derived from mesenchymal stem cells)
- Lymphocytes
- Fibroblasts

Macrophages:

Following opsonisation by plasma proteins, some of the wear particles are phagocytosed by macrophages, which are the primary cells that provide the first line of defense [3,4]. The non-biodegradable particles "frustrate" the cell's innate capacity of digesting the particles. This results in the activation of the macrophages which secrete MMP's, chemokines and cytokines[5]. The released factors increases vascular permeability, recruit other cell types like monocytes, activate innate and adaptive immunity, and support multinucleated osteoclast formation and activation – all of them leading ultimately to a shift in bone homeostasis towards resorption and bone loss. If the particle size is too large to be phagocytosed, multicellular foreign body giant cells are formed. The monocyte/macrophage cell line not only initiates osteoclast differentiation, it is also a precursor for the osteoclast lineage.

Osteoblast:

Osteoblasts are bone-lining cells derived from mesenchymal stem cells of the bone marrow stroma or periosteum[6]. They usually never act individually but in groups when they synthesize a number of substances, including bone matrix constituents, and participate in several pathways by regulating immune and non-immune factors (IL-6, IL-8, MCP-1, CXCL-12, COX-1, COX-2, PGE2, M-CSF, FGF-2, RANKL, OPG, Wnt)[7-9]. In osteoblastic lineage, progression includes osteoprogenitors, pre-osteoblasts, transitory osteoblasts, secondary osteoblasts, osteocytic osteoblasts and osteocytes. Osteoblasts are bone forming cells and along with osteoclasts help maintain bone homeostasis. Osteoblasts help initiate local inflammation by attracting monocytes, T lymphocytes and neutrophils. Wear particles alone or in conjunction with TNF-α and IL-1 stimulate osteoblasts to express MCP-1, IL-8 via the NF-kB pathway. Wear particles stimulate expression of membrane bound RANKL and M-CSF, thus participating in osteoclast recruitment

and activation. The same cytokines can also induce expression of OPG, IL-6 and Wnt in osteoblasts resulting in inhibition of Cathepsin K and tartrate resistant acid phosphatase expression by the JAK/STAT pathway.

Osteoblasts are also involved in the phagocytosis process resulting in the release of various cytokines. Osteoblasts also play a critical role in osteoclast activation. Furthermore activation of protein tyrosine kinases in particle challenged cells result in activation of NF-kB which upregulates other genes, including those of proinflammatory cytokines such as IL-1, IL-6, and TNF-∞[10-12]. PGE_2 and type-I collagen synthesis is also reduced resulting in decreased bone formation.

MG63 cells are an excellent and well established model for examining particle response in vitro[12-14]. Exposure of MG63 and primary human osteoblasts to UHMWPE particles induces their secretion of IL-6 and PGE_2 and reduces their production of collagen and alkaline phosphatase. These effects appear to depend on the maturational state of the osteoblast as well as the number, size, and chemical properties of the particles phagocytosed[15-18]. Although various studies have attempted to correlate levels of various mediators with the degree of osteolysis but there is no consistency among the studies. There are numerous studies describing MG63 cell response to UHMWPE particles based on their size. Studies performed in our lab showed that UHMWPE particles caused a dose-dependent increase in MG63 cell proliferation and a decrease in phenotypic expression. Both alkaline phosphatase specific activity and osteocalcin production were inhibited, whether the particles were isolated from human tissue or if they were purchased from a commercial vendor. Moreover, exposure to the particles resulted in a dose-dependent increase in PGE_2 production and a decrease in TGF-β production, which suggest that UHMWPE particles may be involved in decreased bone formation and increased bone resorption.

Osteoclast:

Osteoclasts are principal and exclusive bone resorptive cells and members of the monocyte/macrophage family. Osteoclast precursors arise principally in marrow as mononuclear macrophages. Following attachment to bone, osteoclast progenitor cells fuse with sister cells to form terminally differentiated polykaryons. Once progenitor cells differentiate into early

osteoclast precursors which express RANK on their surface, they bind RANKL and further differentiate towards osteoclasts. Osteoblasts, osteoclasts, their precursors and other present cells are engaged in cell-cell interactions *via* a variety of mechanisms including secretion of hormones and signalling molecules (BMP-2, Wnt, M-CSF, RANKL, IL-6 and IL-1β), and direct cell-cell contact (communicating gap junctions, RANKL:RANK)[19]. In addition, each BMU is influenced by the immune system through both soluble and membrane-bound cytokines, and growth factors. The most important pathway involved in osteoclast activation and maturation is mediated by receptor activator of nuclear factor-*k*B (RANK) and its ligand (RANKL). The endogenous inhibitory regulator osteoprotegerin (OPG) blocks osteoclast formation by binding to RANKL. The ratio of RANKL and OPG dictates local periprosthetic osteolysis. Binding of wear particles on osteoclast surface causes the induction of various MAP kinase pathways, regulating JAK/STAT cytokine response thus stimulating inflammatory and osteoclastogenic response[20].

Fibroblasts:

Fibroblasts are dominant cell type at the interface tissue membrane that play important role in the control of osteoclastogenesis after particle-induced resulting in secretion of chemokines including MCP-1, MCP-2, IL-8, matrix metalloproteinases, and cytokines such as TNF-α and RANKL and are thus important players in the wear mediated osteolytic process[21].

Lymphocytes:

Wear particles-activate macrophages which secrete MIP-1 and MCP-1 and these attract lymphocytes into the BMU[6]. T cells can influence BMU by expressing RANKL and TRAIL which stimulate osteoclast maturation. Although the RANKL/RANK/OPG pathway is a clear molecular link between the immune system and particle mediated osteolysis, the role of lymphocytes in osteolysis is not well understood.

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