MULTIPLE MYELOMA: CELLULAR MEDIATORS AND GENETIC LINKS OF THE DISEASE

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Multiple myeloma is a disorder in which plasma cells are produced in an uncontrolled and invasive fashion, arising from the bone marrow and often occurring at multiple sites.

Plasma cells develop from lymphocytes, a type of white blood cell found primarily in the bone marrow and lymph nodes. The marrow is located in spaces within the bones, especially within the sternum (breast bone), spine, ribs, skull, pelvic bones, and the long bone of the thigh. Bone marrow is a very active tissue that is responsible for producing the different cells that circulate in blood. These include red blood cells, platelets, and the many types of white blood cells.

Plasma cells are responsible for helping the body fight infection. They produce substances called antibodies (also called immunoglobulins). Antibodies circulate within the blood and recognize markers, called antigens, on the cells of invading organisms (like bacteria). These antibodies have a variety of functions, all of which ultimately serve the purpose of defending the body against invading organisms.

Multiple myeloma occurs when the plasma cells in the bone marrow begin reproducing uncontrollably. While normal bone marrow contains less than 5% plasma cells, in a patient with multiple myeloma the bone marrow contains over 10% plasma cells.

It tends to be a disease of the elderly average age if diagnosis being 68 years. During the last 10 years, there has been a surge in the cases of multiple myeloma occurring at younger ages, but the patients are usually over age 40. Men have a higher predisposition towards multiple myeloma, and African-Americans are twice as likely as Caucasians to develop the disease. Worldwide, the disease rates are about the same, with approximately four people in 100,000 developing multiple myeloma.

Bone pain is the predominant and most frequent symptom among patients with multiple myeloma.

About 70% of all patients will report bone pain as their first symptom. Bony pain is due to several different processes occurring in this diseased state. Plasma cells grow in number within the confines of the bone marrow, replacing normal marrow and putting pressure on the bone. Plasma cells also

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produce chemicals called osteoclast activating factors (OAF). OAF encourages special cells called osteoclasts to break down bone. This is a normal process in a healthy person, which is usually balanced by the building up of new bone by special cells called osteoblasts. In multiple myeloma, however, OAFs are produced in excess, upsetting the norms of bone remodelling. Bone is eaten away by these overly active osteoclasts at a rate much higher than the bone can be built up/rebuilt. This results in the bones becoming weak (causing osteoporosis) or brittle and may even break (causing pathologic fractures).

The antibodies that are excessively produced in multiple myeloma function abnormally. Furthermore, other types of counteracting antibodies are underproduced along with an increased destruction of circulating protective antibodies. This in turn leads to an increased risk of developing serious bacterial infections. The most common types include long infections (pneumonia) and kidney infections (pyelonephritis).

Over time a number of genetic links have been discovered which play a vital role in the pathogenesis of this disease.

IL-6

The role of IL-6 in MM bone disease has been contentious. Although correlations between IL-6 levels with tumour burden in MM has been shown through several studies (1,2), others have not been able to do so (3,4). DuVillard et al reported that IL-6 levels in myeloma correlated with tumour burden and Durie-Salmon staging of the disease, while the increase in IL-6 in monoclonal gammopathy of unknown significance (MGUS), a benign increase in immunoglobulin levels that is sometimes a precursor to MM, was related to inflammation (1).

TNF- α

Several studies have shown an increase in TNFα in patients with MM (5), but the role of TNFα in bone disease is unclear. Silvestris et al showed a dramatic increase in TNFα levels in plasma from myeloma patients with severe osteolytic lesions compared to myeloma patients without skeletal involvement or patients with MGUS (6).

T-LYMPHOCYTES AND IL-7

The role of immune cells in the bone destruction associated with multiple myeloma has only broken ground of late. Recently, Giuliani et al have proposed a role for T lymphocytes in mediating RANKL-induced osteoclastogenesis (7). Several studies have shown that by increasing the osteoclast stimulatory activity of T lymphocytes in estrogen deficiency, IL-7
can mediate bone destruction in post-menopausal osteoporosis. IL-7 treatment of mice for 20 days resulted in increased osteoclast activity and was associated with increased levels of B and T lymphocytes. In vitro, the IL-7 stimulation of osteoclast formation wasn’t direct, but required other cells in the bone marrow microenvironment to induce osteoclast production (8). It was clearly shown that although IL-7 increases both B and T cells in the bone marrow, B cells alone were not sufficient and that T cells were directly responsible for the increase in osteoclastogenesis. Athymic nude mice with normal levels of B220+ B cell precursors but lacking in T cells were not sensitive to IL-7 induced bone destruction, and reestablishment of these mice with T lymphocytes restored the effects of IL-7 on OCL formation (9).

**MIP-1α**

A study conducted that consisted of using a human myeloma cDNA expression library derived from marrow samples from MM patients had led to the identification of MIP-1α as a novel osteoclastogenic factor produced by myeloma cells (3). A recent publication also showed that higher levels of MIP-1α were present in 15/20 MM patients. In rabbits, this factor induced OCL formation and expression levels of MIP-1α produced by myeloma cells are directly linked with bone lesions in 16 out of 18 MM patients exhibiting elevated MIP-1α levels (10).

**DKK1 AND THE WNT SIGNALLING PATHWAY**

The WNT signalling pathway is substantial not only in the growth and development of osteoblasts but also in functioning seen in early lymphopoiesis (11). Prototypically, WNT binds to LRP5/6, another soluble mediator which then binds to the frizzled receptor. Signal transduction from the frizzled receptor leads to dephosphorylation plus stabilization of β-catenin. Now β-catenin then localizes to the nucleus in turn increasing the expression of target genes. Activation of the β-catenin pathway invariably can lead to the activation of OBL differentiation in cell lines in vitro (12).

**IL-7**

Estrogen deficiency due to ovariectomy resulted in loss of bone mass in a model of osteoporosis. There were increased levels of IL-7 in such mice. A study showed that IL-7 also blocked new bone formation after ovariectomy. In mouse calvarial osteoblast cultures, osteoblast activity was suppressed with both basal and BMP2-stimulated treatment (13).
IL-3

Distinguished as a potential osteoblast inhibitor in patients with MM, it has been demonstrated in both murine and human systems that IL-3 inhibited basal- and BMP-2–stimulated osteoblast formation in a dose-dependent manner without affecting cell growth. At concentrations comparable to those seen in bone marrow plasma from the diseased patients, IL-3 blocked differentiation of preosteoblasts to mature osteoblasts in vitro.(14)

CONCLUSION

As discussed above IL-3, IL-6, IL-7, TNF-α, DKK1, MIP-1α and T-lymphocytes are all critical cellular mediators of disease progression and pathogenesis in multiple myeloma. Therefore it would be worth while expanding this research area so as to aid in the better understanding of the involved pathways thereby helping us find a means to a cure or possibly a remission drug.

REFERENCES


