Cytokines as Mediators of Hypercalcemia of Malignancy

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Hypercalcemia of malignancy is due to the breakdown of the normal regulation of calcium homeostasis. It is caused by an abnormally large production of one or several cytokines and/or other regulatory factors by the tumor cells capable of influencing the effectors of calcium homeostasis. There is little doubt that calcium release from bone contributes greatly to the hypercalcemia seen with humoral hypercalcemia of malignancy. Bone resorption is also certainly the major contributing factor in the hypercalcemia observed with many hematologic diseases or local bone metastases. In this chapter I will focus on the role of cytokines in this type of tumor-increased bone resorption, although one should be fully aware that increased calcium reabsorption from the kidney or increased calcium absorption from the intestinal tract may contribute to a variable degree to the whole picture of hypercalcemia of malignancy.

Tumor-Induced Bone Resorption Is Osteoclast Mediated

Bone is constantly remodeled throughout life. Calcium release occurs during the resorption of bone by multinucleated osteoclasts through acidification of a tightly sealed space between the osteoclast surface and the bone surface. Although there is some in vitro evidence that tumor cells themselves may lyse bone by direct proteolytic effects (Eilon and Mundy 1978), the majority of bone loss seems to be mediated through an increase in osteoclastic bone resorption, as judged from the increased numbers of osteoclasts in histologic samples from patients with hypercalcemia of malignancy (Galasko 1976; Steward et al. 1982).

Which Are the Mediators of the Tumor-Induced Increases in Osteoclasts?

Increased osteoclastic activity as a result of the presence of a tumor implies that the tumor cells must secrete one or several agents capable of stimulating
osteoclast generation or function. These tumor products may be circulating systemically or be locally produced by tumor cells within the bone marrow in such quantities that local and systemic regulatory mechanisms of osteoclastic resorption and calcium homeostasis are being overwhelmed. As a consequence, hypercalcemia results.

Nearly all major classic hormones are capable of affecting the rate of osteoclast formation and activity. Among them are parathyroid hormone (PTH), 1,25-dihydroxyvitamin D₃, calcitonin, estrogens, glucocorticoids, and thyroid hormones (Mundy 1989). Indeed, we know many clinical syndromes where an unbalanced increase in the concentration of these classical hormones causes hypercalcemia, such as with PTH in primary hyperparathyroidism or with 1,25-dihydroxyvitamin D₃ in sarcoidosis. Nevertheless, with the exception of certain lymphomas, these hormones are only rarely produced by malignant tumors (Yoshimoto et al. 1989; Nussbaum et al. 1990) and they do not appear to be the predominant mediators of hypercalcemia of malignancy. Often their serum levels are rather downregulated in an attempt to counterbalance the increased bone resorption (Steward et al. 1980; Ralston et al. 1984).

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When therefore during the last 2 decades another class of hormone-like polypeptides appeared that seemed to be produced in abundant amounts by tumor cells and many of whose members had profound stimulatory effects on bone resorption in vitro, many researchers had the feeling that the mediators of hypercalcemia of malignancy had finally been found. These agents have been grouped together sometimes arbitrarily as lymphokines and growth factors, although the distinction between the different groups of these polypeptides has vanished with time. In the following text I will therefore rather use the global term “cytokine,” to summarize them. The list of peptide cytokines is ever increasing and today holds more than 50 different species and subspecies some of which may be grouped in larger families.

Just like the classic hormones, most cytokines are secreted in a regulated fashion from cells, bind to specific target receptors and use similar intracellular signal transmission pathways (Sporn and Roberts 1990). Many cytokines appear to have only a short range of action which restricts their effects to the tissue where they are produced. Nevertheless, as I will discuss below, there is more and more evidence that some cytokines may also have systemic effects if only produced in large enough amounts. The one major difference between the classic hormones and the various cytokines, however, appears to be the rather restricted expression of the classic hormones, whereas most cytokines are expressed in a large variety of tissues (Sporn and Roberts 1990).