Response

Role of TRAIL in osteoclastogenesis

In their letter, Labrinidis and colleagues raise the important issue of what (if any) might be the role of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) in osteoclastogenesis. In previous studies, we[1,2] and 2 other independent groups of investigators[3-5] have shown that histidine-tagged (His-tag) recombinant TRAIL negatively regulates osteoclastogenesis by inhibiting preosteoclast differentiation and by inducing apoptosis of mature osteoclasts. On the other hand, Labrinidis et al were unable to confirm these previous findings when exposing osteoclastic cultures to the version of Apo2L/TRAIL that is currently being used in phase 1b clinical trials. Although Labrinidis et al emphasize the differences between the recombinant TRAIL preparations used in their and previous studies,[1-5] the possibility that the antiosteoclastic activity of TRAIL merely reflects an aspecific toxic effect of recombinant His-tag TRAIL is ruled out by 2 major considerations: (1) different groups of investigators have clearly documented the ability of recombinant His-TRAIL to induce in vitro prosurvival and even proliferative responses in a cell-type specific manner[6]; and (2) Roux's group has recently demonstrated that native TRAIL, produced and released in vitro by end-stage osteoclasts, promotes osteoclastic apoptosis through autocrine/paracrine mechanism.[4] Thus, besides blocking receptor-activator of NF-κB ligand (RANKL)–mediated osteoclastogenesis, osteoprotegerin (OPG) seems also able to protect mature osteoclasts from apoptosis mediated by native TRAIL endogenously produced by osteoclasts.[4] These findings corroborate the hypothesis that the relative concentrations of RANKL, OPG, and TRAIL at the local bone marrow level are critical for determining the fate of osteoclasts.[6,7] The net effect of TRAIL on osteoclastic differentiation and survival likely depends on the network of prosurvival and proapoptotic signals operating at a given time in the bone marrow microenvironment. In this respect, it should be considered that the antiosteoclastic activity of TRAIL reported by our and other groups[1-5] was observed in culture conditions in which purified populations of preosteoclasts were induced to differentiate along the osteoclastic lineage by adding recombinant macrophage–colony stimulating factor (M-CSF) plus RANKL to the culture medium. On the other hand, Labrinidis et al have cultured peripheral blood mononuclear cells (used as a source of preosteoclasts) in the presence also of vitamin D3 and dexamethasone, which are known to potently promote osteclastic survival and differentiation.[8] Thus, in our view, the novel contribution of the findings of Labrinidis et al with respect to previous data[1-5] relies on the demonstration that the presence in culture of vitamin D3 and dexamethasone abrogates the antidifferentiative and proapoptotic activities of TRAIL. However, this does not exclude a role of TRAIL in osteoclastogenesis, as suspected by Labrinidis et al, but rather suggests a level of molecular control on the antiosteoclastic activity of TRAIL. To verify our interpretation about the findings of Labrinidis et al, it will be important to analyze whether vitamin D3 and dexamethasone induce changes in the surface expression level of "death receptors" TRAIL-R1 and TRAIL-R2 and/or act at the level of intracellular critical determinants.

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To the editor:

Imatinib mesylate for platelet-derived growth factor receptor-beta–positive Erdheim-Chester histiocytosis

Erdheim-Chester disease (ECD) is a non-Langerhans form of $CD68^+$ $CD1a^-$ histiocytosis.[1-4] Interferon α (IFNα) is effective in ECD.[3,5] Efficacy is however depending on the site of involvement. Central nervous system (CNS) and cardiovascular involvement do not respond to IFNα and have a poor prognosis.[5]

Two patients suffering from Langerhans cell histiocytosis (LCH) and Rosai-Dorfman disease histiocytosis (RDD) were dramatically improved with imatinib mesylate (IM), a tyrosine kinase inhibitor, which selectively inhibits bcr-abl, KIT and platelet-derived growth factor (PDGF).[6,7] IM, initially given at 100 mg/d and raised to 400 mg/d after 1 month dramatically improved LCH cerebral infiltration,[6] and, for the multisystemic RDD patient,[7] the manifestations almost completely resolved under 600 mg/d within 6 weeks. Rationale for the use of IM was the