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RANK/RANKL/OPG Biology

Foreword

The earliest report on the first molecule (osteoprotegerin - OPG, osteoclast inhibitory factor – OCIF) pertaining to the RANK/RANKL/OPG pathway appeared in the scientific literature nearly 7 years ago[1,2]. Since these initial reports, numerous articles have appeared in the scientific literature covering a wide range of topics related to this pathway. The exploration of the therapeutic potential of this pathway has progressed quite rapidly with the first human clinical trials to test the safety and potential efficacy of targeted RANKL antagonism initiated in 1998 employing an e.coli-derived form of osteoprotegrin[3] as the compound.

In this issue of the Journal of Musculoskeletal and Neuronal Interactions, there are six different articles relevant to aspects of RANK/RANKL/OPG biology. In the lead article, **Jack Martin** provides a historical backdrop to the initial discoveries starting with the Kolliker's anatomic description published in 1873[4]. Of particular interest in this manuscript is the description of how a number of labs using different methods and biological systems uncovered the molecules and their biologic activities. **Drs. Whyte and Mumm** provide an excellent review of the known heritable disorders of the RANK/RANKL/OPG pathway including a description of the history, clinical presentation, genetic basis, and treatment responses observed in these disorders[5]. The genetic basis of these heritable disorders was uncovered following the elucidation of the biological activity of the pathway members in genetically manipulated mice or other rodent models.

The next four articles delve into the translational discoveries that have taken place since the initial discoveries were made. These articles review potential clinical settings suggested by animal model data where RANKL antagonism could have an important therapeutic effect. In the review article by **Drs. Hofbauer, Kühne and Viereck**, the potential role of the RANKL pathway in a variety of osteoporoses and hyperparathyroidism is explored including a description of the various cellular and molecular mechanisms leading to the bone loss seen in these disorders[6]. The publications covered in this review encompass references where serum measurements of OPG and RANKL have been made in different clinical settings of osteoporosis. In the next review article, **Drs. Ritchlin, Schwarz, O'Keefe and Looney** focus on the role of the RANKL pathway in inflammatory arthritis and prosthetic joint loosening[7]. Of note is the summary of the extensive collection of articles that have documented the essential role of RANK signaling in the bone destruction seen in arthritis.

The final two articles are focused on the role of RANK/RANKL/OPG in cancer-related skeletal disease. In the first article, **Dr. Croucher** reviews the current understanding of the RANKL pathway mechanisms thought to play a role in a variety of oncologic settings[8]. The review goes into some detail about the skeletal disease associated with multiple myeloma, breast, and prostate cancers. Additionally, the available information from animal models pertaining to intra-skeletal tumor growth modulation in the presence of RANKL inhibition is reviewed. In the last article by **Drs. Clohisy and Mantyh**, a specific cancer-related morbidity (bone pain) and its modulation by RANKL inhibition is described[9]. In this review, the authors cover what is known about the role of the osteoclast in the development of pain in an experimental model, much of which has arisen from their own work. In their model system, RANKL inhibition using OPG has led to a more fundamental understanding of how tumor-driven osteoclastic bone destruction leads to spinal cord reorganization and that blockade of this process using OPG normalizes both the pain scores and the spinal cord reorganization.

There are some areas of evolving interest that were not covered in these articles but are of current interest. These topics would include the involvement of the RANKL pathway in the development of the mammary gland and immune system as well as the potential role that RANKL may play in the immune response[10-15]. While the reports included in this issue do not include one that summarizes human clinical trial data, the clinical development of therapeutic RANKL antagonists has been aggressively pursued by Amgen over the past several years[3,16,17]. Of note, an interim analysis of the safety and efficacy of the third generation RANKL antagonist (monoclonal antibody to RANKL) will be presented at the 2004 American Society of Bone and Mineral Research Meeting in Seattle later this year.

In summary, the past 7 years have ushered in a totally new era of understanding of bone resorption. This era was initiated by the discovery of the RANKL decoy antagonist (OPG, OCIF) and was then followed by an explosion of reports that have shown in numerous animal models and in early clinical trials that RANKL plays a central role in a wide variety of pathologic bone resorptive processes. Collectively, these data point to the promise that targeted RANKL therapy could bring to the many clinical settings where excessive bone loss leads directly to increased morbidity and mortality.

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