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Survey

Bone morphogenetic protein-2 and tumor growth: Diverse effects and possibilities for therapy

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ABSTRACT

Concern regarding safety with respect to the clinical use of human bone morphogenetic protein-2 (BMP-2) has become an increasingly controversial topic. The role of BMP-2 in carcinogenesis is of particular concern. Although there have been many studies of this topic, the results have been contradictory and confusing. We conducted a systematic review of articles that are relevant to the relationship or effect of BMP-2 on all types of tumors and a total of 97 articles were included. Studies reported in these articles were classified into three major types: "expression studies", "in vitro studies", and "in vivo studies". An obvious pattern was that those works that hypothesize an inhibitory effect for BMP-2 most often examined only the proliferative properties of the tumor cells. This subset of studies also contained an extraordinary number of contradictory findings which made drawing a reliable general conclusion impossible. In general, we support a pro-tumorigenesis role for BMP-2 based on the data from these in vitro cell studies and in vivo animal studies, however, more clinical studies should be carried out to help make a firm conclusion.

Contents

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1. Introduction

Currently, all clinical situations in which recombinant human bone morphogenetic protein-2 (rhBMP-2) is employed are orthopaedic in nature. As is evident from the name, “BMP-2”, this material induces a recapitulation of endochondral bone formation when appropriate undifferentiated cells are exposed to it. It should not be forgotten, however, that BMPs, including BMP-2, are found in many tissues and perform physiological functions that have nothing to do with bone formation or skeletal physiology whatsoever [1]. Thus, there are two very different but complementary clinical situations in which BMP-2 is central. First, obviously, BMP-2 is used in orthopaedic procedures such as spinal fusion as an agent that can enhance bone healing [2]. Because of the protean effects of BMPs in diverse tissues, systematic monitoring of treated patients for any type of unintended effect is prudent.

The U.S. Food and Drug Administration approved the clinical use of recombinant human BMP-2 applied to an absorbable collagen sponge (INFUSE, Medtronic, Memphis, TN) for use in anterior lumbar inter-body fusion and the treatment of acute open tibial fractures. Since that time, however, as much as 85% of the product sold has been in “off label” applications, such as posterolateral and cervical spine fusions. In addition, rhBMP-2 has been used at higher doses than those approved by the FDA. Safety issues pertaining to the use of rhBMP-2 have been of concern since the inception of its use. While many animal and clinical studies suggest a good safety profile [3], some studies have found reasons for concern with respect to uncontrolled bone formation [4], soft tissue inflammation [5], and carcinogenesis [6]. The effects of rhBMP-2 on carcinogenesis are of particular concern in light of a recent publication demonstrating a significant 6.75-fold increase in the incidence rate ration of new cancer two years after single level anterior spinal arthrodesis in patients treated