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Review

Contrasting bone effects of temporary versus permanent IGFBP administration in rodents ☆

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Abstract

Transgenic animal technology has tremendously improved our current comprehension of IGFBP biology. The high potential of IGFBP transgenic mouse models is due to the fact that they mimic elevated serum IGFBP levels, which are diagnosed under the conditions of impaired growth or critical illness. In general, long term elevated levels of IGFBPs in transgenic mouse models almost exclusively resulted in inhibitory phenotypes e.g. of body or organ growth, indicating specific effects in different cell types. This holds especially for the distinct cellular populations present in the bone environment.

After establishing transgenic mouse lines modelling permanent increases of IGFBPs, a second question now poses challenge to current functional genome analysis: what is the function of temporary exposure of a certain cell type to isolated IGFBPs? This question is particularly important due to the fact that elevated IGFBP expression is often found in a conditional fashion and in line with the contradictory findings after long or short term IGFBP exposure in rodent models. In order to understand the potential roles of the conditional increases of IGFBP expression, e.g. during illness, and to further study the adaptive or even therapeutic potential of IGFBPs for certain applications like osteoporosis, it is imperative to take a closer look also to the acute effects of the IGFBPs.

Keywords: IGFBPs; Bone; Transgenic; Mice; Permanent; Temporary expression; Short term; Systemic application; Local administration

1. Introduction

The IGFBP family is composed of six different members (IGFBP-1 to IGFBP-6), with in part overlapping functions. Partial overlap of IGFBP functions has been deduced from the lack of massive phenotypes in knockout mouse models characterized by the lack of a single IGFBP. Not before three different IGFBPs were missing in a single knockout mouse model functional redundancy was abrogated to an extend providing also detection of stronger phenotypes [1]. On the other hand, mouse models characterized by constitutive expression of IGFBPs grossly assigned inhibitory functions of intact IGFBPs for different particularly growth related traits, which in distinct cases was realized with surprise. These inhibitory phenotypes were considered to be mainly related to the IGF-dependent effect. However, IGFBPs have not only IGF-dependent negative effects, which might be related to the inhibitory effects in vivo, but also IGF-independent effects in bone cells, which have been reviewed very recently [2]. Both IGF-dependent and -independent mechanisms contribute to cell type specific effects of IGFBPs, which were also reviewed recently [3,4]. Local expression of IGFBPs, IGF-dependent and -independent effects, posttranslational modifications and degradation by IGFBP-proteases concert an almost inextricable complexity of conditional effects [2,5]. Here, for the first time, an additional level of complexity is discussed and introduced since temporary exposure of IGFBPs in rodent models

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obviously had completely different effects from constitutive expression. This finding is particularly interesting in light of the observation that expression of IGFBPs is very often increased in critical illness [6] potentially as an acute first response, which might become chronic later on.

The present review summarizes results and conclusions from rodent models and describes insights from studies assessing IGFBP functions in constitutive versus temporary modes. Specific focus is set on the differential effects after different durations of exposure of IGFBPs in bone.

2. The effects of constitutive expression versus temporary exposure of IGFBPs on bone

Transgenic mouse models have been established, which overexpress each of the six IGFBP-family members in a single cell type or in different tissues [7]. Skeletal effects have received in depth investigations in these transgenic mouse models for IGFBP-1 to IGFBP-5 (Table 1). These mouse models, characterized by long term local or systemic transgene expression, have distinct and almost exclusively inhibitory effects in bone. In addition, the effects of IGFBP-2 to -5 alone or in combination with IGF-I or IGF-II have been studied after exogenous systemic or local administration (Table 2). In contrast to the transgenic approach, exogenous administration reveals short term effects of IGFBPs. As specified in detail below, constitutive IGFBP expression has a different outcome as that of temporarily restricted exposure to IGFBPs in bone and thus giving rise to contradictory hypotheses. By considering the duration of exposure, an improved view is to be established for the unbiased assessment of IGFBP-actions in bone.

2.1. IGFBP-1

Only the long term effects of IGFBP-1 have been studied to date, supporting the common concept of overall inhibitory effects after longer IGFBP exposure. Overexpression of human IGFBP-1 in hepatocytes from transgenic mice severely impaired body growth in 12-day-old mice [8]. IGFBP-1 produced in the liver had inhibitory effects on bone parameters of the skull and axial skeleton. Due to impaired mineralization in the skull, delayed suture closure was diagnosed. In addition, mineralization defects were present in appendicular and axial bones of transgenic mice. Negative effects of IGFBP-1 were also present in the form of reduced bone density at various sites of the skeletal system. IGFBP-1 transgenic mice characterized by early postnatal growth retardation were therefore discussed as a model for intrauterine growth retardation, which was also characterized by elevated expression of IGFBP-1, in humans. In a follow-up study [9], intrauterine growth retardation was in fact observed in homozygous IGFBP-1 transgenic mice at embryonic day 17.5. In homozygous mice, increased perinatal mortality was observed, which was probably due to decreased carbohydrate pools in the transgenic mice. Interestingly, maternal and fetal effects have been identified as causative for intrauterine growth retardation since heterozygous pups from homozygous mothers were lighter than those from heterozygous or non transgenic mothers.

2.2. IGFBP-2

The effects of chronic overexpression of IGFBP-2 on bone growth were studied in IGFBP-2 transgenic mice [10]. This study had been initiated since IGFBP-2 represents a consistent predictor of low bone density in humans and had been suggested as a negative regulator of bone growth and maintenance [11,12]. The bone mineral content was quantified by dual energy X-ray absorptiometry (DXA) and isolated parameters of bone growth (cortical and trabecular bone, cross sectional area and bone volume) were measured by peripheral quantitative computed tomography (pQCT). A clear dissection of IGFBP-2 effects could be found in mice chronically overexpressing IGFBP-2: although the femoral length was only reduced by 3%, femoral volume was reduced by 23%. Since bone mineral density was not decreased in IGFBP-2 transgenic mice, it was concluded that IGFBP-2 negatively affects bone size and mineral content, but not bone maintenance in adult mice. Notably, IGFBP-2 completely blocked effects of GH at cortical sites, suggesting locally antagonistic relations between GH and IGFBP-2. A potential clue for the role of IGFBP-2 during bone growth comes from a recent contribution in the field of functional genomics [13]. In that study, the four-point bending model was used to induce a single period of mechanical loading on the tibial shaft. In mechanosensitive osteocytes, but not in osteoblasts, bone marrow cells or chondrocytes from loaded endocortical tibial shafts increased IGFBP-2 mRNA expression was found and a role of IGFBP-2 for the lamellar bone formation process was suggested. Thus, the increase of IGFBP-2 under various conditions may also be interpreted as an adaptive response.

In fact, short term application of IGFBP-2 in combination with IGF-II clearly supported the idea of positive effects of IGFBP-2 on bone growth and thus differential effects depending on the exposure duration or mode of application. In order to investigate the effects of elevated IGFBP-2 on bone growth, IGF-II/IGFBP-2 was subcutaneously injected in a rat model of diffuse osteoporosis [14]. In this model, exogenous IGFBP-2 in combination with IGF-II could prevent the loss of BMD induced by neurectomy of the right hindlimb. Instead, an increase