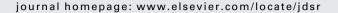


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### Review Article

# Cell cycle control factors and skeletal development

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#### **KEYWORDS**

Cell cycle; Transcription factor; Cdk; Cyclin; CKI Summary In the oral and maxillofacial region, conditions such as delayed bone healing after tooth extraction, bone fracture, trauma-induced bone or cartilage defects, and tumors or birth defects are common, and it is necessary to identify the molecular mechanisms that control skeletogenesis or the differentiation of cells, in order to establish new treatment strategies for these conditions. Multiple studies have been conducted to investigate the involvement of factors that may be crucial for skeletogenesis or the differentiation of cells, including transcription factors, growth factors and cell cycle factors. Several genetically engineered mouse models of cell cycle factors have been generated in research seeking to identify cell cycle factor(s) involved in the differentiation of cells, carcinogenesis, *etc.* Many groups have also reported the importance of cell cycle factors in the differentiation of osteoblasts, osteoclasts, chondrocytes and other cell types. Herein, we review the phenotypes of the genetically engineered mouse models of cell cycle factors with a particular focus on the size, body weight and skeletal abnormalities of the mice, and we discuss the potential of cell cycle factors as targets of clinical applications.

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### 1. Introduction

In the oral and maxillofacial region, conditions such as delayed bone healing after tooth extraction, bone fractures, tumors or birth defects and trauma-induced bone or cartilage defects are common, and it is necessary to elucidate the molecular mechanisms which control skeletogenesis and the differentiation of stem cells, osteoblasts, osteoclasts and chondrocytes to establish new treatment strategies for these conditions. Bone grafts are the current gold-standard strategy to repair irreversible skeletal damage or defects, but the use of bone grafts often entails problems with respect to the availability of bone graft material, difficulties with the donor site, and other factors. Thus, in order to establish new treatment strategies for such conditions, an important goal is to shed light on the molecular mechanisms that control skeletogenesis and the differentiation of cells.

Numerous studies have been performed in vitro and in vivo to investigate the involvement of factors that are thought to be crucial for skeletogenesis or the differentiation of cells; such factors include transcription factors, growth factors and cell cycle factors. In particular, cell cycle factors are thought to significantly influence the differentiation of cells, since withdrawal from the cell cycle or a temporal arrest in the G<sub>1</sub> phase of the cell cycle is thought to be a requirement for cell differentiation [1-3]. The proliferation of eukaryotic cells depends on their progression through the cell cycle. The cell cycle is controlled by many cell cycle control factors, namely cyclins, cyclin-dependent kinases (Cdks) and cyclin-dependent kinase inhibitors (CKIs). Cyclins and Cdks, which are positive regulators of the cell cycle, activate cell cycle factors that are essential for the start of the next cell cycle phase. In contrast, CKIs function as negative regulator of Cdks by direct binding to cyclins and Cdks [2,4]. In mammalian cells, the activities of the Cyclin Ddependent kinases Cdk4 and/or Cdk6 and those of the Cyclin E-dependent kinase Cdk2 are required to pass through the G<sub>1</sub> phase and the subsequent S-phase entry [5].

Retinoblastoma (Rb) protein is a member of a protein family that also includes p107 and p130. It is a key physiological substrate for Cdk4 and Cdk6, which binds and inactivates the E2F-DP transcription complexes essential for S-phase entry [6,7]. The phosphorylation of pRb by Cdk4/6 and additionally by Cdk2 reverses the growth-suppressive effects of pRb by releasing E2F-DP from inactivation and consequently promoting S-phase entry and progression. Cdk4 and Cdk6 have 71% amino acid identity and are structurally homologous. They share all three D-type cyclins, *i.e.*, CyclinD1, CyclinD2, and CyclinD3, as their catalytic partners to phosphorylate pRb *in vitro* [6]. As a result, Cdk4 and Cdk6 had been proposed to function redundantly in the  $G_1$  phase of the cell cycle.

In contrast to the D-type cyclins, Cyclin E is expressed periodically, binding to Cdk2 and inducing Cyclin E-dependent kinase activity to maximal levels at the  $G_1$ —S transition [8,9]. Once cells enter the S phase, Cyclin E is degraded, and subsequently Cdk2 forms complexes with Cyclin A. CKIs have been classified into two families: the INK4 family and the Cip/Kip family. Generally, the INK4 family (p16, p15, p18, and p19) inhibits only Cdk4 and Cdk6, whereas the Cip/Kip family (p21, p27, and p57) inhibits all the Cdks *in vitro* [2].

A schematic presentation of cell cycle regulation in the  $G_1$  phase is shown in Fig. 1. Because a temporal cell cycle arrest in the  $G_1$  phase or withdrawal from the cell cycle is regarded as a prerequisite for cell differentiation, herein we review the phenotypes of genetically engineered mouse models of the representative  $G_1$  cell cycle factors with a particular focus on the size, body weight and skeletal abnormality, and we discuss the potential of cell cycle factors as targets of clinical applications.

#### 2. Cdks

## 2.1. Cdk2

At birth, homozygous Cdk2-deficient mice did not differ in any obvious way from their control littermates. They

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