

Original

Role of Heparanase in the Release of Heparan Sulphate Binding Growth Factors in Odontogenic Tumors

Phuu Pwint Han^{1,2}, Hitoshi Nagatsuka², Ryo Tamamura², Naoki Katase², Lefevre Mathieu Bernard², Hailong Hu², Shin Takagi³, Nobuhisa Ishida³, Keisuke Nakano⁴, Toshiyuki Kawakami⁴ and Mehmet Gunduz²

¹*Orofacial Pain and Oral Medicine Center, Division of Diagnostic Sciences, School of Dentistry, University of Southern California, Los Angeles, USA.*

²*Department of Oral Pathology and Medicine, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan.*

³*Department of Oral Surgery I, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan.*

⁴*Hard tissue Pathological Unit, Matsumoto Dental University Graduate of Oral Medicine, Shiojiiri, 399-0781 Japan*

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Abstract: Immunolocalization of heparan sulphate(HS) and heparanase was evaluated in benign and malignant odontogenic tumors in order to know whether these molecules have potential roles in odontogenic tumorigenesis. Archival formalin-fixed, paraffin-embedded tissues of 6 human tooth germs, 7 adenomatoid odontogenic tumors, 10 ameloblastic fibromas, 20 ameloblastomas and 4 ameloblastic carcinomas were subjected to immunohistochemical staining using antibodies to HS, heparanase and BMP-4. HS was ubiquitously localized in tooth germ but heparanase and BMP-4 were observed in limited areas only. In benign epithelial tumors such as ameloblastoma and adenomatoid odontogenic tumor, these molecules were localized in neoplastic epithelium but in ameloblastic fibroma, positive reactions were observed in both epithelial and mesenchymal cells. Stromal localization of HS and BMP-4 accompanied by intense immunoexpression of epithelial heparanase was observed in ameloblastic carcinoma, and this may represent the malignant progression of ameloblastoma to ameloblastic carcinoma. Stronger intensity and more diffuse localization of heparanase in odontogenic tumors compare to that of human tooth germ was the most significant finding. Taken together, the results inferred that heparanase may be responsible for the growth and progression of odontogenic tumors by modulating the availability and function of HS binding growth factors and the derangement in immunoexpression and localization of HS and heparanase molecules may have important roles in progression of malignant odontogenic tumors.

Key words: Heparanase, Heparan sulphate, BMP-4, Odontogenic tumors, Tooth germ, Immunohistochemistry

Introduction

Heparan sulphate proteoglycans (HSPG) constitute a group of ubiquitous extracellular matrix macromolecules and are composed of a core protein and covalently linked heparan sulphate (HS) sugar chains¹. Although HSPG play critical functions in cell-cell and cell-matrix interactions through the core proteins, their HS chains confer most of the biological functions^{1,2}. The negatively charged HS chains can bind and sequester numerous heparin/HS binding molecules ranging from growth factors, cytokines and cell adhesion molecules thereby protecting these tethered molecules from proteolytic cleavage. HS chains also take part in the important cellular events conferred by these tethered molecules

and have influence on various developmental and pathological processes^{2,3}.

Heparanase is a mammalian endo- α -glucuronidase enzyme capable of selectively degrading HS chains at specific intrachain sites. Although there are several distinct HS degrading endoglycosidases, cloning of a single gene and subsequent biochemical characterization suggests that mammalian cells primarily express a single dominant heparanase⁴. The degraded HS chains are biologically active causing the release of HS bound molecules⁵ in large quantities for respective functions⁵. Furthermore, HSPG are integral components of extracellular matrix (ECM) and basement membrane (BM) and the cleavage of HS chains by heparanase can cause profound decrease in ECM and BM integrity. These were exemplified in the increased expression of heparanase in a number of human malignancies which correlated with disease progression and metastasis^{4,5}. Apart

Corresponding to Dr. Phuu Pwint Han, Department of Oral Pathology and Medicine, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata Cho, Okayama 700-8525, Japan. Tel: 81-(86)-235-6652, Fax: 81-(86)-235-6654, Email: phuupwinthan@gmail.com