Analysis of immunoexpression of common cancer stem cell markers in ameloblastoma

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Abstract. Recent studies have established that, in benign tumors, a large number of cancer stem cells are present, which have great implications in tumor development. However, in ameloblastoma, a highly aggressive, locally invasive tumor with a high recurrence rate, whether or not cancer stem-like cells are present remains undetermined. Therefore, in this study we analyzed the protein expression of three candidate stem cell markers in ameloblastoma. Immunohistochemical staining for cancer stem cell (CSC) markers (CD133, CD44 and ABCG2) and for the proliferation marker Ki-67 was performed using 23 ameloblastoma cases. In all 23 samples, CD133, CD44 and ABCG2 were expressed. Nine (39.13%) cases showed high expression and 14 cases (60.87%) showed low expression for CD133. Twelve of the 23 cases (52.17%) showed high expression and 11 cases (47.83%) showed low expression for both CD44 and ABCG2, respectively. Ki-67 was mainly expressed in peripheral ameloblast-like cells, suggesting that these cells have a higher degree of differentiation and, therefore, are less likely to contain cancer stem-like cells. On the other hand, cells positive for CSC markers situated at the close proximity to peripheral cells were devoid of Ki-67 and may have the potential to be cancer stem-like cells. After analyzing the correlation between expression of three CSC markers with clinicopathological factors and Ki-67 expression, only CD44 expression was correlated with tumor recurrence (P=0.0391). In conclusion, this study showed various expression patterns of different types of cancer stem cell markers and the presence of candidate CSC-like cells in ameloblastoma, which are possibly involved in cell proliferation, tumor progression and recurrence.

Introduction

Ameloblastoma is the most frequently encountered benign, locally invasive tumor and the second most common odontogenic tumor (1). It may arise from rests of dental lamina, from a developing enamel organ or from basal cells of the oral mucosa. Ameloblastomas tend to infiltrate between intact cancellous bones at the periphery of the lesion before bone resorption becomes radiographically evident. As a result, the actual margin of the tumor often extends beyond its apparent radiographic or clinical margin. Attempts to remove the tumor often leave small islands of tumor, which later result in recurrence in 50-90% of cases (2). This has raised questions regarding the tumor cell populations that are responsible for tumor growth and recurrence.

In the past few years, it has been hypothesized that tumors are most likely initiated in normal stem cells or their immediate descendants, and then are perpetuated by a minority of these cells, known as cancer stem cells (CSCs) or tumor-initiating cells (TICs) (3). According to the American Association for Cancer Research (AACR), ‘a cell within a tumor that possesses the capacity to self-renew and to cause heterogeneous lineages of cancer cells that comprise the tumor is known as a cancer stem cell’. This observation implies that within a given tumor, there exists a small population of cells with the capacity to behave like stem cells (4). The difficulty in eradicating tumors may be due to the fact that conventional treatments target the bulk of the tumor cells leaving unaffected the CSCs, which like their normal counterparts, maintain tumor tissue. According to this hypothesis, identifying and exterminating CSCs may be an effective treatment modality (5).

Recently, several CD markers have been identified as solid CSC markers. CD133, also known as PROM1 or prominin, is a stem cell surface antigen that has been recently identified as a potential CSC marker in brain, colon, hepatocellular and prostate cancer (6-10). CD44, also known as homing cell adhesion molecule, is a cell surface glycoprotein expressed on lymphocytes, monocytes and granulocytes, which has been identified as a stem cell marker for breast, prostate, pancreatic and head and neck cancer (6,11-13). The ABCG2 transporter is a member of the ATP binding cassette transporter family (14) responsible for the side population phenotype in various

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