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Original contribution

Expression of autophagy-related markers at the surgical margin of oral squamous cell carcinoma correlates with poor prognosis and tumor recurrence☆,☆☆

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Summary Oral squamous cell carcinoma (OSCC) is the sixth most common cancer worldwide, and is associated with poor prognosis. Autophagy is a programmed cell survival mechanism involved in physiologic processes and various diseases including cancer. However, the relationship between autophagy and cancer is controversial. Several studies have claimed that the expression of autophagy-related proteins, namely microtubule-associated protein light chain3 (LC3) and p62/SQSTM1 (p62), is associated with poor prognosis in OSCC. In this study, we evaluated the expression of the autophagy-related markers LC3A/B and p62 by immunohistochemistry in 71 OSCC patient samples, especially focusing on surgical margins. Results were correlated with clinical characteristics. The expression of LC3A and LC3B was correlated with tumor recurrence and poor overall survival based on multivariate analysis, whereas the expression of p62 was correlated with only tumor recurrence and not prognosis. Thus, we suggest that the expression of autophagy-related markers at the surgical margins might be an indicator of local recurrence and poor prognosis in human OSCC. These results will aid in the development of new therapeutics and diagnostics for OSCC.

1. Introduction

Oral squamous cell carcinoma (OSCC), a type of head and neck cancer, is the sixth most common cancer worldwide and is associated with poor prognosis. More than 400 000 new cases are reported each year worldwide, and many cases have

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been reported in Asian countries [1]. Despite advances in treatment and diagnosis, mortality rates are increasing, and the 5-year survival rate for OSCC has been approximately 50% over the past few decades [2,3]. One reason for this is the lack of a significant marker for the early detection of this disease. For this reason, identifying new markers will significantly improve diagnosis and prognosis.

Autophagy is a physiologically regulated and highly conserved programmed cell survival mechanism in eukaryotes. It plays a critical role in the degradation and removal of damaged intercellular proteins and organelles. As a result, this process contributes to the recycling of cellular constituents and organelle turnover [4,5]. In addition, autophagy has also been identified in various pathological processes including myopathies [6], neurodegenerative disorders [7], tuberculosis [8], and cancer. Although the relationship between autophagy and carcinogenesis is debatable [9,10], various studies have reported that increases or decreases in autophagy-related proteins are associated with poor prognosis for OSCC [11-14]; in addition, some of those studies have also indicated that the expression of autophagy-related proteins in premalignant lesions is linked to poor prognosis.

In this study, we focused on the autophagy-related proteins light chain 3-A, B (LC3A, LC3B) and p62/SQSTM1(p62). LC3 is strongly associated with autophagosomal membranes and is necessary for the formation of the autophagosome [15-17]. p62 is an ubiquitin-associated protein involved in the induction of autophagy, clearance of protein aggregates, and inhibition of autophagy. Among these three proteins, we have performed previous studies on p62 and examined the relationship between the expression of p62 in tumors and various clinicopathological features, but no significant difference was observed (unpublished). In addition, regarding LC3A and LC3B, some reports indicate that the expression of these proteins in OSCC is related to poor prognosis [14,18]; we obtained similar results. In addition, expression of these three proteins was observed not only in the tumor but also at the surgical margin. To the best of our knowledge, there are no studies on the expression of these proteins in the normal mucosa near the surgical margin.

In this study, we aimed to investigate the expression of three autophagy-related proteins at the resection margin, and to clarify their relationship with carcinogenesis and prognosis.

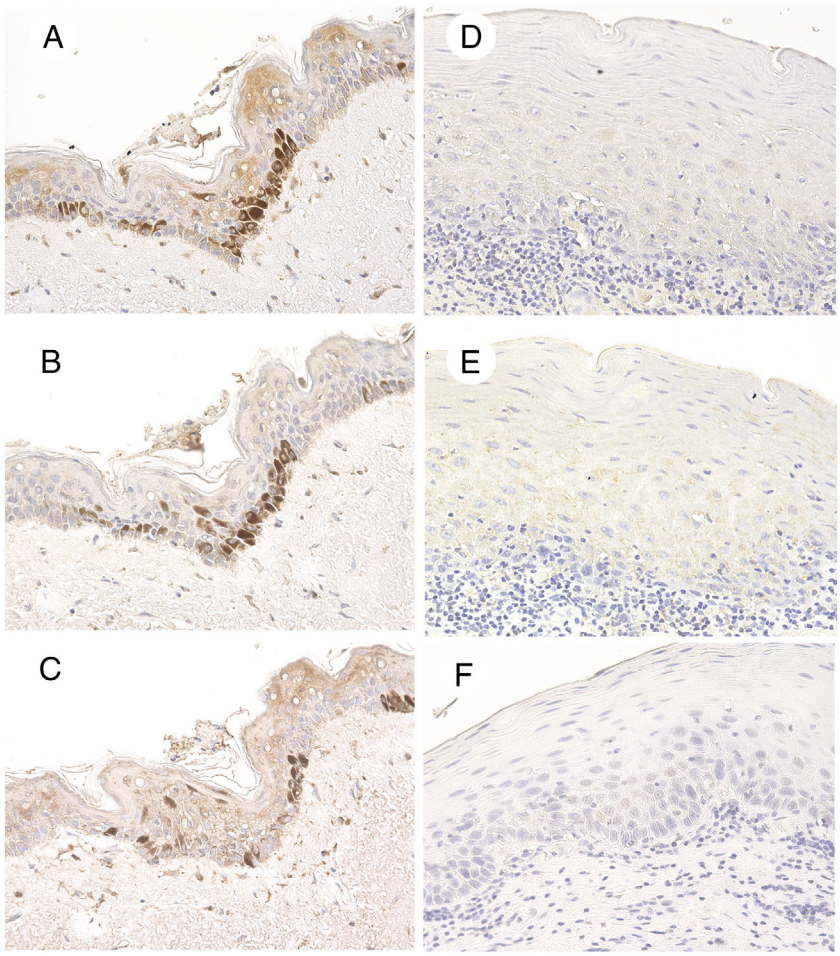

Fig. 1 The results of LC3A (A and D), LC3B (B and E) and p62 (C and F) immunohistochemical stains in surgical margin of OSCCs. Representative sections showing positive expressions (A-C) and negative expressions (D-F) of three proteins. The original magnification is × 400 in all figures.