Relationship between Glutaminase 1 and Stump Classification in Rotator Cuff Tears

Tatsuo Kato, Yutaka Mifune, Atsuyuki Inui, Hanako Nishimoto, Shintaro Mukohara,
Takahiro Furukawa, Shuya Tanaka, Masaya Kusunose, Yutaka Ehara, Shunsaku Takigami, Ryosuke Kuroda
Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan
E-mail: t.kato.ort@gmail.com

Disclosures: Tatsuo Kato (N), Yutaka Mifune (N), Atsuyuki Inui (N), Hanako Nishimoto (N), Shintaro Mukohara (N), Takahiro Furukawa (N), Shuya Tanaka (N), Masaya Kusunose (N), Yutaka Ehara (N), Shunsaku Takigami (N), Ryosuke Kuroda (N)

INTRODUCTION:

Glutaminase1 (GLS1), which degrades glutamate into glutamine and ammonia, is required for the survival of human senescent cells, and GLS1 inhibitors are expected to contribute to the improvement of various pathological conditions associated with aging [1]. Rotator cuff tears (RCT) increase with age, and recently the Stump classification has been proposed to evaluate the fragility of the torn rotator cuff site, with Type 3 being the most fragile and a high risk of re-tear after rotator cuff repair surgery [2]. This study aimed to evaluate the relationship between GLS1 and the Stump classification.

MATERIALS AND METHODS:

Twelve patients who underwent surgical treatment for RCT were included: Stump Type1 (n=6) and Type3 (n=6). The cases of reoperations, traumatic tears and RA were excluded. Tissue was harvested during arthroscopic rotator cuff repair, and rotator cuff-derived cells were isolated and cultured. Tissue evaluation involved quantitative assessment of mRNA expression of GLS1 using real-time PCR (qPCR) and immunostaining. Rotator cuff-derived cells were isolated and cultured, divided into four groups (Stump Type1 and Type3 with or without GLS1 inhibitor treatment), and evaluated for cell viability using the WST assay and mRNA expressions of aging markers (GLS1 and p16) and inflammation marker (IL-6) using qPCR at 48 hours after treatment.

RESULTS:

Type3 showed significantly higher mRNA expression of GLS1 and positive immunostaining compared to Type1 (Fig.1). The histoscore (H-score) was significantly higher in Type 3 (Fig.1). Type3 cells exhibited significantly lower cell viability than Type1, and GLS1 inhibitor (G-I) increased cell viability specifically in Type3 (Fig.2). Additionally, GLS1 inhibitor significantly reduced the mRNA expression of GLS1, p16, and IL-6 in Type3 (Fig.3). However, Type1 did not show significant changes in cell viability or mRNA expression with GLS1 inhibitor (G-I) treatment (Fig.3).

DISCUSSION:

In Stump Type 3 RCT, the rotator cuff is considered to be highly fragile and degenerated. Our study revealed elevated expression of GLS1 in Type3, suggesting GLS1 may play a role in the pathogenesis of Stump Type3 RCT. Additionally, GLS1 inhibitors showed potential in enhancing cell viability and reducing aging and inflammation markers specifically in Type3 rotator cuff-derived cells, indicating their possible anti-aging and anti-inflammatory effects. Preoperative administration of GLS1 inhibitor might improve the fragility of the torn rotator cuff site.

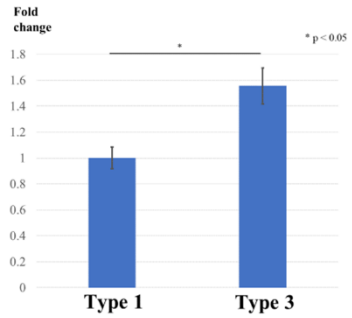
SIGNIFICANCE:

GLS1 expression was elevated in Stump Type3 RCT compared to Type1. GLS1 inhibitor improved cell viability and reduced aging and inflammation markers in Type3 rotator cuff-derived cells.

REFERENCE:

[1] Johmura Y et al. Senolysis by glutaminolysis inhibition ameliorates various age-associated disorders. Science 2021 Jan 15;371(6526):265-270.
[2] Ishitani E et al. Tendon stump type on magnetic resonance imaging is a predictive factor for retear after arthroscopic rotator cuff repair. J Shoulder Elbow Surg 2019, 28(9):1647–1653.

Fig.1 (a) mRNA expression of GLS1.



(b) GLS1 immunostaining

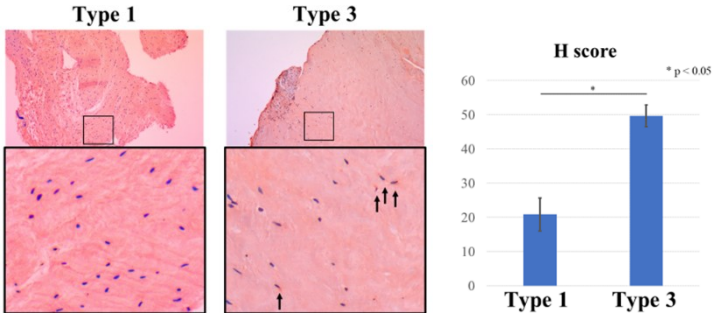


Fig.2 cell viability

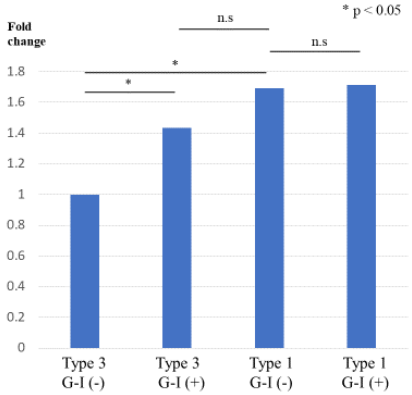
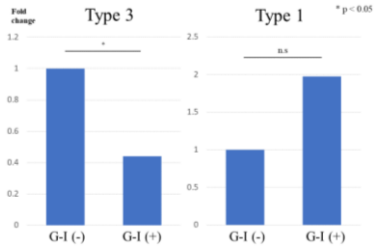
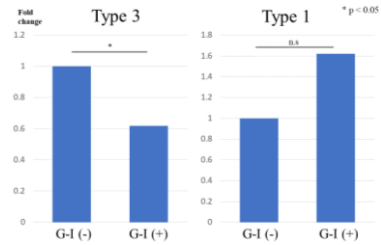


Fig.3 mRNA expressions

(a) GLS1



(b) p16



(c) IL-6