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The melatonin-MT1 receptor axis modulates tumor growth in *PTEN*-mutated gliomas

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ABSTRACT

More than 40% of glioma patients have tumors that harbor *PTEN* (phosphatase and tensin homologue deleted on chromosome ten) mutations; this disease is associated with poor therapeutic resistance and outcome. Such mutations are linked to increased cell survival and growth, decreased apoptosis, and drug resistance; thus, new therapeutic strategies focusing on inhibiting glioma tumorigenesis and progression are urgently needed. Melatonin, an indolamine produced and secreted predominantly by the pineal gland, mediates a variety of physiological functions and possesses antioxidant and antitumor properties. Here, we analyzed the relationship between PTEN and the inhibitory effect of melatonin in primary human glioma cells and cultured glioma cell lines. The results showed that melatonin can inhibit glioma cell growth both in culture and *in vivo*. This inhibition was associated with PTEN levels, which significantly correlated with the expression level of MT1 in patients. In fact, c-fos-mediated MT1 was shown to be a key modulator of the effect of melatonin on gliomas that harbor wild type *PTEN*. Taken together, these data suggest that melatonin-MT1 receptor complexes represent a potential target for the treatment of glioma.

1. Introduction

Glioma is the most common malignancy of the central nervous system, and has a high recurrence rate and poor prognosis [1–3]. This is because of the rapid and uncontrolled proliferation and high invasiveness of glioma cells [4–6]. Therefore, new therapeutic strategies focusing on inhibiting glioma tumorigenesis and progression are urgently needed.

Melatonin is an endogenously produced hormone secreted by the pineal gland and the retina [7,8]. Within the body, the highest concentration of melatonin is in the brain [9,10]. As reported, melatonin plays an important role in regulating various physiological processes such as circadian rhythms, body temperature, seasonal reproduction, and inflammatory responses [11,12]. Most importantly, the potential benefits of melatonin have been evaluated based on their inhibitory effects on many cancer types such as breast, colon, and gastric [13–15]. However, the inhibitory effect of melatonin on glioma cell proliferation is somewhat controversial. In 2006, Martín et al. reported that melatonin suppresses glioma cell proliferation both *in vitro* and *in vivo*, and this was related to its inhibitory effect on key intracellular effectors such as PKC and NF-kB [16]. However, other studies indicated that melatonin did not induce glioma cell death and affect viability [17,18]. These differences in results could be attributed to different cellular genetic backgrounds, which might affect melatonin inhibitory responses in glioma patients.

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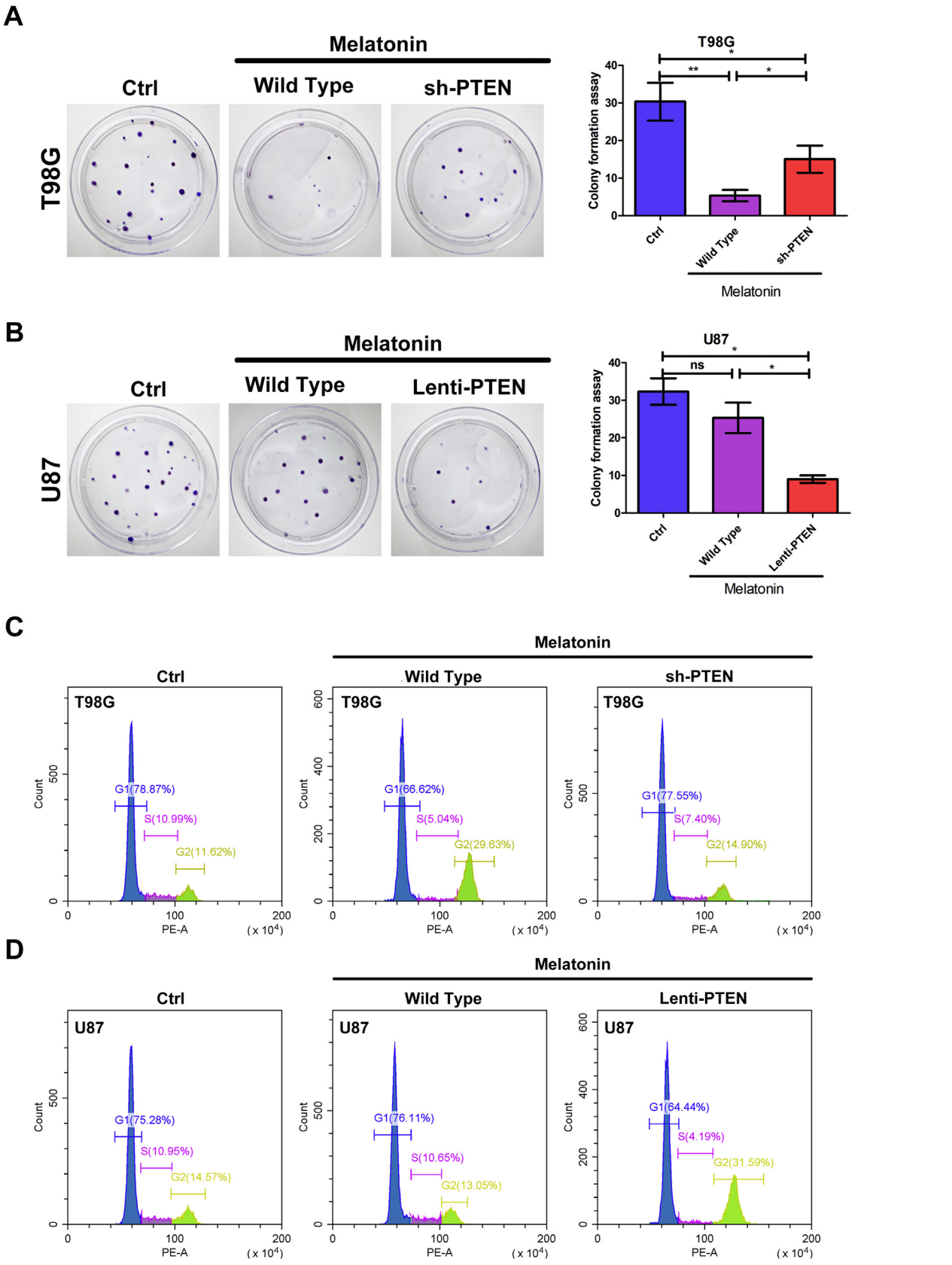

Fig. 1. Melatonin inhibited cell growth and induced G2/M arrest in PTEN-expressing glioma cells. (A) Clonal expansion analysis of PTEN^{WT} and sh-PTEN T98G cells with or without 48-hour melatonin (1 mM) treatment. (B) Clonal expansion analysis of PTEN-deficient and Lenti-PTEN U87 cells with or without 48-hour melatonin (1 mM) treatment. Data for each system are from at least three independent experiments. Data are shown as mean ± s.e.m. *$P < 0.05$; **$P < 0.01$; ns, not significant. (C) Cell cycle analysis of PTEN^{WT} and sh-PTEN T98G cells with or without 48-hour melatonin (1 mM) treatment. (D) Cell cycle analysis of PTEN-deficient and Lenti-PTEN U87 cells with or without 48-hour melatonin (1 mM) treatment.