Alpha-synuclein: Possible Link between Parkinson's Disease and Melanoma

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BACKGROUND

A positive association between PD and melanoma has been well established, but biologic explanation for this association is still lacking. The findings that α-synuclein is pathogenically related to PD and the fact that α-synuclein is robustly expressed in melanoma cell lines and in primary/ metastatic melanoma tissues suggest that α-synuclein could play a role in the link between PD and melanoma. We, therefore, explored the role of α-synuclein in ultraviolet B (UVB) light-induced injury in neuronal PC12 cells and in human melanoma cells.

METHODS

Stable inducible PC12 cells expressing α-synuclein were maintained at Dulbecco's modified Eagle's medium (DMEM) containing 10% horse serum, 5% fetal bovine serum (FBS), 75 μg/ml hygromycin B, and 100 μg/ml G418. The α-synuclein transgene was induced by doxycycline. SK-MEL-28 melanoma cells with high α-synuclein expression were maintained in Eagle's Minimum Essential medium (EMEM) containing 10% FBS. A375 melanoma cells without α-synuclein expression were maintained in DMEM containing 10% FBS. All cells were cultured at 37° C, 10% CO2. For UVB light irradiation, cells culture medium was replaced by PBS. After UVB exposure, the cultures were brought back to standard cell culture conditions and cultivated for specific time periods followed by MTT and immunoblotting assay to determine the viability and apoptosis of cells.

RESULTS

Alpha-synuclein was highly expressed in SK-MEL-28 melanoma cells as compared to that in PC12 neuronal cells and A375 melanoma cells (Fig. 1A). The transgene expression of α-synuclein in stable inducible PC12 cells could be induced when cells were treated with doxycycline for 48 h (Fig. 1A). The protein level of α-synuclein in SK-MEL-28 melanoma cells was decreased when cells were transfected with *SNCA* siRNA (Fig. 1B).

UVB light exposure caused loss of cell viability by 37% in A375 melanoma cells and by 19% in SK-MEL-28 melanoma cells. The cell viability was decreased by 30% in PC12 cells after UVB light exposure, which was further reduced by 46% in α-synuclein transgene overexpressed PC12 cells (PC12/Dox) (Fig. 2).

Additionally, UVB light exposure caused apoptosis in A375, SK-MEL-28 melanoma cells and in PC12 neuronal cells by showing increased protein levels of cleaved PARP (Fig. 3A). The increase of cleaved PARP protein level was lower in SK-MEL-28 cells as compared to than that in A375 cells (Fig. 3A). However, the apoptosis was enhanced when α-synuclein gene was suppressed in SK-MEL-28 melanoma cells (Fig. 3B). Additionally, increased transgene expressin of α-synuclein enhanced susceptibility of PC12 cells to UVB light-induced apoptosis (Fig 3B).

FIGURES

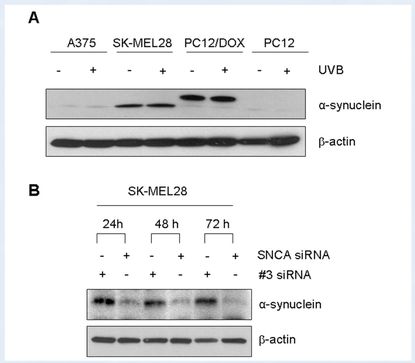

Figure 1

Fig. 1 Expression of α-synuclein in different cell lines. Total proteins were isolated from stable inducible PC12 cells expressing wild type α-synuclein with or without Dox treatment for 48 h, from A375 melanoma cells and from SK-MEL-28 melanoma cells and were subjected to immunoblotting assay. The protein level of α-synuclein was determined using anti-α-synuclein antibody. Dox = Doxycycline.

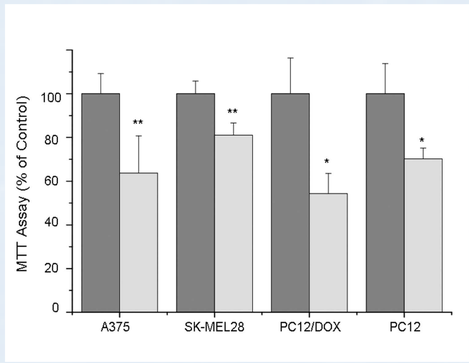

Figure 2

Fig.2 UVB light-induced loss of cell viability. A375 cells, SK-MEL-28 melanoma cells and stable inducible PC12 cells with or without Dox induction were exposed to UVB light at 450 MJ/cm2 and post cultured for 24 h. Cell viability was determined by MTT assay. *: $p < 0.05$; **: $p < 0.01$ as compared to its non-UVB control. Dox = Doxycycline.

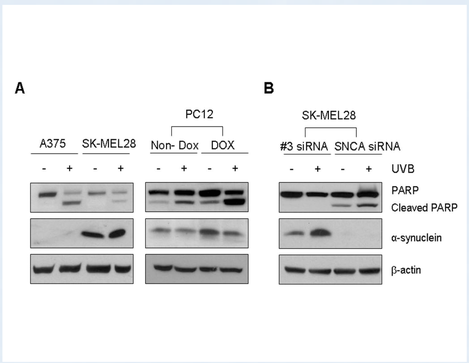

Figure 3

Fig.3 UVB light-induced apoptosis. A375 cells, SK-MEL-28 melanoma cells and stable inducible PC12 cells with or without Dox induction were exposed to UVB at 450 MJ/cm2 and post cultured for 24 h (A). Forty-eight hours after SK-MEL-28 melanoma cells were transfected with SNCA siRNA or #3 siRNA, cells were exposed to UVB at 450 MJ/cm2 and post cultured for 24 h (B). The apoptosis was determined by Western blot assay using anti-PARP antibody.

CONCLUSIONS

UVB light exposure caused loss of cell viability and increase of apoptosis. Melanoma cells with higher α-synuclein expression were more resistant to UVB light-induced injury; whereas, increased expression of α-synuclein enhanced PC12 cells to UVB light-induced injury, indicating that α-synuclein plays different roles in different types of cells. Further studies are required to explore possible mechanisms involved in α-synuclein-associated link between PD and melanoma.

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