

INVOLVEMENT OF GSK3 IN TGF β 1-INDUCED MITOCHONDRIAL DEFECTS

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We previously reported that TGF β 1 induces senescence-associated arrest of Mv1Lu cells in the presence of serum through persistent mitochondrial ROS generation via complex IV defects. In the present study, we investigated the molecular mechanism of how mitochondrial complex IV is damaged by TGF β 1. During the TGF β 1-induced senescent process, no significant changes of protein expression of complex IV subunits were observed. However, TGF β 1 immediately inactivated GSK3 within 15 min via phosphorylation on its negative regulatory site and this phosphorylation was continuously maintained. The early GSK3 phosphorylation (inactivation) was accompanied by AKT activation and ROS production. Interestingly, the conventional GSK3 inhibitor, SB415286, directly inhibited mitochondrial complex IV activity, concurrently generating ROS without change of respiratory protein expression. These results were further confirmed by knockdown of GSK3. Finally, we showed that GSK3 inhibition increased intracellular ROS level and induced senescent phenotypes. Our present results suggest that GSK3 inactivation may be the initial and important mediator of the TGF β 1-induced complex IV defects, resulting in senescence.

Key word :

GSK3, TGF β 1, Mitochondria and senescence