Identification of Tectorigenin as a natural pro-hypoxia compound: implications in modulation of cellular differentiation and senescence

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Background: Hypoxia, a suboptimal level of oxygen, evokes stress response in cells and activated hypoxia signaling has been largely established as a pro-metastasis and pro-angiogenic factor for tumor cells. On the other hand, age-related neurodegenerative disorders are characterized by hypoxic environment, accumulation of molecular garbage and induction of premature senescence. Several recent studies have reported anti-stress impact of the intermittent induction of hypoxia signaling in these cells. **Methods:** Screening of a phytochemical library using Hypoxia Responsive Element (HRE) driven luciferase as a reporter was carried out to identify hypoxia-modulating phytochemicals. Activation of HIF-1α (master regulator of hypoxia signaling) was validated by Western Blotting and immunostaining using specific antibodies. Short-term and long-term effect of the selected compounds on cell viability were determined by cell viability and colony forming assays, respectively. Furthermore, *in vitro* wound-scratch assays, protein aggregation models, and replicative senescence models were recruited to determine the effect of the selected compound on these phenotypes. **Results:** Tectorigenin (TEC) (iso-flavone obtained from leopard lily or *Iris domestica*) was selected as a pro-hypoxia factor. TEC treated cells showed significant activation HRE-driven luciferase reporter and upregulation of endogenous HIF-1α. On these lines, it was found that TEC resulted in de-aggregation of induced aggregation of protein reporters. cDNA microarray data revealed that TEC modulated the expression of genes involved in cell migration and differentiation. We used cellular senescence and astrocytic differentiation models and found lifespan extension of normal human fibroblasts and differentiation of rat-glioma cells, respectively. **Conclusions:** TEC could be defined as an anti-stress and anti-aging phytochemical that could be useful to manage hypoxia-driven ailments, involving protein aggregation and neurodegeneration. Further studies are warranted to support these claims and to dissect their molecular mechanism(s) of action.