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Genes modulating cancer, ageing and neurodegeneration derived from studying Down syndrome

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Down Syndrome (DS) (caused by trisomy 21 (T21)) is an accelerated ageing condition on cellular and organism level. Paradoxically, people with DS have a much lower incidence and mortality from a range of solid tumours. They have an approximately 50-100 fold higher overall incidence of leukaemias in childhood than normal children, including all types of acute myeloid leukaemia (AML) and B-cell acute lymphoblastic leukaemia (ALL). Children with DS are prone to suffer a relapse and have a higher risk of death from therapy-related side effects. Paradoxically though, individuals with DS have a substantially reduced incidence of second malignancies following radiation therapy, even at a juvenile age, despite DS haematopoietic cells in vivo showing a significantly increased "passenger" mutation rate per year of age, even in the short age-span (1-16 years, Kendall-tau non-parametric rank coefficient=0.45, p=0.023). We also detected that T21 causes a significantly increased number of DNA double strand breaks (γH2AX foci) in undifferentiated proliferating hiPSCs, post-mitotic neurons derived from hiPSCs, as well as in a transchromosomic mouse model of DS. Experiments aimed at identifying the chromosome 21 genes whose trisomic overdose is responsible for accelerated ageing and neurodegeneration using iPSC and other cellular models are on-going and will be presented. Using isogenic T21-iPSC-derived cerebral organoids, we also identified a novel mechanism that delays the onset of Alzheimer's disease, despite the triplication of the myloid precursor protein (APP) gene in T21.

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