shortened lifespans and restorative effects of telomerase restoration. However, the non-causal biomarker hypothesis suggests that telomere lengths utility as a predictor of health and fitness could instead reflect it acting as a non-causal biomarker of accumulated damage to other biological structures that themselves have causal deleterious effects on future performance.

#### <u>Calorie restriction theory of ageing</u>

Reduced generation of ROS, increased antioxidant capacity, increased heat shock protein concentration, and induction of autophagic processes, have all been reported with calorie restriction. A study conducted by Miller., et al., 2011 found the drug Rapamycin to extend the lifespan of mice. An increase in life expectancy at the time Rapamycin supplementation was initiated of 38% for female mice and 28% for male mice, was reported. Rapamycin is an inhibitor of the kinase enzyme, target of rapamycin (TOR). TOR signalling has been linked to the ageing process. TOR is the first protein that has been shown to modulate lifespan in each of the four model organisms most commonly used to study ageing; yeast, worms, files, and mice. TOR promotes translation of messenger RNA into protein by the ribosome, and inhibits a pathway that degrades cellular products in lysosomal vesicles (autophagy). TOR signalling mediates dietary restriction, a reduction in nutrient availability without malnutrition. Dietary restriction has been shown to increase lifespan in species. ranging from years to rodents. TOR activity is reduced by dietary restriction n d genetic studies in invertebrate models have linked the inhibition of IOR to increased longevity by dietary restriction. A recent study in yeart a dwed that TOR inhibition increases the amounts of a nutritional reprise transcriptional activator Gon4, and demonstrated that this is required for full lifespare to nsion from dietary restriction. Autopahgy nult winduced for lifesnan to be extended by dietary restriction in celevans. Rapamycin nay by functioning as a dietary mimetic, a small n de the that provides the belief of dietary restriction without requiring a reduction n food intake. Life dietary restriction, TOR inhibition also confers protection in invertebrate and rodent models against age-associated disorders, including; cardiovascular dysfunction, diet-induced obesity, and cancer. Rapamycin analogues are used clinically to treat certain forms of cancer.

## Senescence theory of ageing

Cellular senescence, first discovered by Hayflick 1961, is defined as irreversible cell cycle arrest driven by a variety of mechanisms, including telomere shortening, genotoxic stress, mitogens, or inflammatory cytokines, that culminate in the activation of the p53 tumour suppressor and/or the cyclin-dependent kinase inhibitor p16. The hayflick limit is the limit on cell replication imposed by the shortening of telomeres with each division. Senescence functions as a tumour suppression mechanism. Senescence is controlled by two pathways; telomere p53 and p16 pRB axis. Faragher and Burton 2015, described the variety of other phenotypic characteristics that can associate with irreversible cell cycle exit in senescent fibroblasts, including; a pro-inflammatory secretory response, the up-regulation of immune ligands, altered responses to apoptotic stimuli, and promiscuous gene expression (stochastic activation of genes as a result of chromatin remodeling). Many features associated

the synaptic cleft and synaptic transmission as part of the tripartite synapse, control CNS metabolism, and maintain blood brain integrity. Astrocytes undergo a functional decline with age. Astrocytes can; clera and degrade amyloid, secrete inflammatory mediators and respond to injury.

### Bhat., et al., 2012

The Abeta peptide has deleterious effects on synaptic cleft plasticity. This study found that treatment with either Abeta conditioned media or Abeta 1-42 peptide induced senescence associated beta-galactosidase activity and increased expression of the p16ink4a senescence biomarker, these results show that Abeta 1-42 peptide leads to astrocyte senescence. Senescent astrocytes display characteristics of senescence associated with secretory phenotype, such as increased secretion of proinflammatory cytokines, such as IL-6. IL-6 is a mediator of chronic inflammation associated with ageing and age-related disorders. The study also found an increase in p16ink4a- positive astrocytes from fetal to non-AD adults and from non-AD adults to AD adults. This suggests that senescent astrocytes do accumulate with normal ageing, and increase further in the setting of AD. p38MAPK is a mediator of the senescnce arrest in response to diverse stimuli and regulates the SASP. increased p38 MAPK signalling has been associated with cognitive decline associated with AD pathophysiology. p38 MAPK is activated in senescent astrocytes.

### Oligodendrocytes

co.u closely associated Oligodendrocytes are the principal neuroglial cell type 2 with neurons. Oligodendrocytes function in many emation of axons and thus increase nerve impulse conduction. Orgedendrocytes are found predominantly in the white matter area of the trace white matter if from in the deeper tissues of the brain (subcortical)

Microglial

Microglia belong to macrophage lineage and are the first and main form of active immune defense in the immune privileged CNS. When severe brain injury occurs, microglia cells change their morphology, migrate to the lesion sites and proliferate. Proliferated microglial cells phagocytose dying cells and other debris and/or release cytokines to maintain the microenvironment homeostasis and support injured neurons, and thus are beneficial for the neuronal survival. However, when over activated in severe injury or neurodegenerative diseases microglia have neurotoxic roles. Microglial cells play a role in brain development. Microglia can differentiate into a proinflammatory or neuroprotective form. In absence of injury microglia are in quiescent state.

## Xiao-Guang Luo., et al., 2010

Microglial alterations play crucial roles in increased inflammation in the CNS during ageing due to increased production of proinflammatory cytokines.microglial alterations can lead to neurodegeneration. The inflammatory state of microglia in the aged brain primes them to be over responsive to small stimuli, eventually activation of microglia in the aged brain becomes uncontrolled. Uncontrolled microglia response ultrastructure and TER indicated that uropathogenic E.coli infection promotes a paracellular permeability defect associated with the failure of umbrella cell tight junction formation and umbrella cell sloughing. In addition, bacterial interaction with the urothelium promoted secretion of cytokines from the urinary bladder with bioactivity capable of modulating epithelial barrier function including TNF-alpha, IL-6 and IL15. dysregulated IL-15 secretion results in dysregulated tight junction formation.

# - <u>Smith., et al., 2015</u>

Tight junctions are multicomponent structures, with claudin proteins defining paracellular permeability. Claudin 3 is responsible for the exceptional tightness of human urothelium, being localised to the terminal tight junctions= if superficial cells. In this study normal human urothelial cells maintained as non-immortalized cell lines were retrovirally-transduced to over-express or silence claudin 3 expression. Stable sublines induced to stratify or differentiate were assessed for tight junction formation by immunohistochemistry and transepithelial electrical resistance (TER). expression of claudin 3, ZO-1, and 2OHalpha were examined in native urothelium in immunohistochemistry. Claudin 3 expression was associated with differentiation and development of a tight barrier and, along with ZO-1 and ZO-1alpha+, was localised to the apical tight junction in native urothelium. Knockdown of claudin 3 inhibited formation of a tight barrier in three independent cell lines, however, overexpression of claudin 3 was not sufficient to induce tight barrier development in the absence of differentiation. A differentiation-dependent induction of the ZO-1alphan is form was found to coincide with barrier formation. Whereas claudin 30 perceptession did not induce the switch to c-=expression of ZO-1alpha-ZG tapha+, claudin 3 knockdowns decreased localisation of ZO-1 to the tig, t U offer and resulted in compromised barrier function. Urethral cytodific rentiation is accompanied by induction of claudin 3 which is essential for the development of a terrin al tight junction. A coordinated switch to ZC-relpta+ isotype was observed, indicating that ZO-1alpha+ is involved in the st Dch rat assembly on bfu fictor of the urothelial terminal tight junction. propathogenic E.coli con decrease ZO-1 and claudin 3 overexpression, resulting in a leaky urothelium, and release of ammonia into the systemic circulation, which can then cross the BBB and cause neurological dysfunction.

## Pharmabiotic approaches to treat hyperammonemia

- Liu., et al., 2018

The gut contains large numbers of microorganisms. The intestinal bacteria play an important role in human health, such as by supplying essential nutrients, synthesising vitamin k, aiding in the digestion of cellulose, and promoting angiogenesis and enteric nerve function. A significant alteration in the types and amounts of microorganism affect the ammonia production and function of the intestinal immune system since ammonia can move through the intestinal lumen and body fluid, the removal of intestinal ammonia by gut microbial species such as lactobacillus species could reduce blood ammonia levels. Probiotics are intended to affect the hosts health beneficially. The most common probiotic strains are lactic acid bacteria, including lactobacilli, lactococcus lactis, streptococcus and bifidobacteria. Probiotics reduce the total amount of ammonia in the portal blood because probiotics inhibit bacterial urease activity due to the production of lactic acid. Probiotics also decrease intestinal permeability, and bacterial urease secretion, increase ammonia excretion. Probiotics