Session 1

DUSRA meeting 19-05-2017

Jan Kammenga (WUR)

'From recognition to acknowledgement of individual aging'

The genetic background of the individual plays a decisive role in the context of gene mutations. Even when presenting the same mutation, the genetic variation can cause a completely different disease phenotype as well as variations in its degree of severity. Moreover, if gene editing is performed, the complete genome may make it behave dissimilarly between individuals, needing a good model to understand better these relations. When GWAS are performed also we have to be aware not to not fail into the diversity of the population (Kammenga-2017 PMID: 28390082), (Nature Biotechnology-2016 PMID: 27065010), (Neuron-2016 PMID: 27618673).

Questions:

- **We have performed studies in twin models, checking the genetic interactions in several diseases and we have not found such a significance in interaction, why do you think that this big significance it is so big in your models with *C.elegans* and not in our case?**
  This could be a matter of power and analyse it in high through ways. You may not see them at a single level but if you look at multiple interactions they may be there.
- **Genetic variation in C. Elegans is very conserved, how is this in humans?**
  We need to increase the sample size bringing them from different ethnics, countries, etc to have different genotypes and see what could happen if you KO a gene.
- **Did you check modifier genes in your experiment? Are there in the top of the GWAS?**
  The next step will be to do that.

Cor Calkhoven (UMCG)

'Reduced expression of C/EBPβ-LIP extends health- and lifespan in mice'

It is possible to reduce the progression of ageing with the C/ EBPB-LIP mutated gene in a mouse model. In these models LIP levels increase during ageing increasing the probabilities of developing cancer, etc. KI mice without LIP: reduced mTOR signalling at C/EBP β . Caloric restriction inhibits mTOR resulting in reduced C/EBP β; such female mice have increased lifespan; burn more fat.

Drugs were being validated in cell lines in order to see which ones reduce the most the LIP levels. Adefovir Dipivoxil: lowers lipid levels, enhances fatty acid β-oxidation (Calkhoven-2017 PMID: 28198412).

Questions:

- **Do you see differences in the constitution of the mice strains?**
  We have only checked so far in one mouse strain (expensive).
  Regarding their constitution they only have it reduced in body mass but not in lean mass.

- **What happens when you do caloric restriction in the mouse?**
  It doesn't appear to have a big effect in the mice.
- **How was the mitochondrial biogenesis of these reservoirs?**
  There is an increase in them.
- **Does the drug you tested have any liver or kidney problems in humans?**
  So far it has only been tested in cell lines and not in animals.

Peter de Keizer (Erasmus MC)
'Targeted Apoptosis of Senescent Cells against Chemotoxicity and Aging'

It is possible to therapeutically eliminate senescent cells in animal models increasing their life span in around 25% more. These cells can change from being senescent to present an apoptotic state. This is done playing with the FOX04 gene which is upregulated in senescent cells. This has been tested in mice (TTD mouse model) which normally present more senescent cells and when FOX04-DRI (D retro inverso) is added, it improves their condition while not showing signs of toxicity (de Keizer-2017 PMID: 28340339).

Questions:

- **Have you seen any tumorigenic effects?**
  So far no. Since they only eliminate senescent cells he thinks there shouldn't be any problem at all with that.
- **Can the drug be administered orally?**
  No, it has to be injected.
- **In which tissues did you get the senescence?**
  They have tested it showing positive results in hair and kidney and they are checking muscle and heart at the moment.
- **What is your definition of senescence?**
- **Have you tired any caloric restriction at the same time that your peptide is administered?**
  They think this will promote tissue regeneration when combined together.
- **Any thoughts about a response in humans?**
  Problem of heterogeneity in humans. Thus they will need to try with more strains of mice so far.
- **Do the peptides pass through the blood brain barrier?**
  Yes.
- **Have you ever checked their mental state, for example with dementia in your models? And how much do you think is it correlated with senescence?**
  This is complicated to test with mice.

Martin Denzel (Max Planck Institute)
'A sweet deal: the hexosamine pathway in protein homeostasis and ageing'

Message of the talk: As protein homeostasis is decreased upon aging: is it possible to increase or slow-down this reduction?
The hexosamine protein homeostasis pathway seems to improve life health span. Also Hgfat-1 gain of function seems to be effective against proteotoxicity and aggregates of proteins which are characteristics of some diseases. This Hgfat-1 gain of function is due to a loss of product inhibition and GFAT-1 in Hexosamine pathway (HP) with HP activation reducing polyQ aggregation (Denzel-2014 PMID: 24630720).

In summary: HP activation or GlcNac supplementation induce distinct protein quality control mechanism and may allow therapeutic intervention against age-related and proteotoxic diseases.

Questions:

- **Have there been any other mutations in the same pattern?** No

  Losing function is toxic; overexpression has similar effect
- **Unknown whether it affects multiple proteins, glutamine for example?**
  Measured some, and these did not change at steady-state; but maybe upon activation there is a change. HP modulates Tau activity.