Canonical and non-canonical Wnt signaling in hematopoiesis and lymphocyte development

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Stellingen behorend bij het proefschrift getiteld:

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Farbod Famili

1- Loss of stemness in HSCs with high levels of Wnt signaling is not due to increased apoptosis. Instead, increased differentiation and diminished proliferation explains the deficiency in reconstitution capacity of the stem cells (**this thesis)**.

2- Although Ryk (member of tyrosine kinase receptors) plays crucial roles in neurogenesis (Schmitt AM, et.al. Nature 2006; 439: 31–37), its effect during hematopoiesis and lymphopoiesis is subtle, suggesting that the effect of this receptor is highly context and tissue dependent (**this thesis**).

3- Canonical Wnt signaling affects T cell development in a dosage dependent fashion. Although high and low levels of Wnt block T cell development at early stages, intermediate levels accelerate T lymphopoiesis. This effect has been shown previously at the level of cytoplasm by targeting β-catening (Luis TC, et.al. Cell Stem Cell 2011; 9: 345–356), and in **this thesis** with a different approach by targeting Wnt3a ligand at the cell surface level.

4- TCF-1 functions as a T-lineage fidelity factor (**this thesis**); similar to the role of Pax-5 in B- cell development (Mikkola I, *Science* 2002; 297(5578): 110-3).

5- The effects of transcription factors depend on combinatorial interaction with other factors and signaling pathways. These affect the binding of the essential factor to particular *cis*-regulatory elements, sometimes in an all-or-nothing fashion, and may change the net effect from activation to repression or vice versa (Rothenberg EV. *Annual review of immunology* 2014; 32: 283-321).

6- Non-canonical and Canonical Wnt signaling have distinct roles, in maintenance versus activation of HSCs, respectively. Non-canonical Wnt signaling maintains quiescent LT-HSCs through Fmi and Fz8 interaction in the niche. (Sugimura R. et.al, Cell 150, 351–365, 2012).

7- Wnt5a haploinsufficiency attenuates HSC ageing, whereas stem-cell-intrinsic reduction of Wnt5a expression results in functionally rejuvenated aged HSCs (Florian M.C et.al, Nature, 2013. 503(7476): p. 392-6.)

8- TCF-1 is induced by Notch signals in ETPs, and subsequently TCF-1 drives T-cell lineage specification. Among the genes induced by TCF-1 are components of the TCR, as well as T-cell essential transcription factors Gata3 and Bcl11b. (Weber, B.N., et al., Nature, 2011. 476(7358): p. 63-8.)

9- If you torture the data long enough it will confess. (Ronald Coase. Essays on Economics and Economists, 1994). A small difference in stem cell reconstitution of Ryk KO mice, encouraged us to perform a secondary transplantation, thereafter chapter 3 was formed.

10- Intelligence is the ability to adapt to changes. (Stephen Hawking, 1966). It is challenging to write a thesis while working in a different field.