With a population growing older by each generation, age-related diseases are also steadily increasing. One of the most common age-related diseases among people around 70 years of age is ischemic stroke, an acute neurodegenerative disease. During an ischemic stroke, the blood flow to a part of the brain is blocked, often by an embolus from the heart reaching a blood vessel in the brain. Neurons in the affected part then start to die due to lack of glucose and oxygen. The symptoms following the stroke can vary, but there is usually a mix between impairments of motor and cognitive functions. Currently, the only treatments available are administration of thrombolytics or thrombectomy, but they can only be applied to a minority of patients shortly after the stroke. It is known, though, that there is a regenerative function working in the brain that tries to repair the stroke-induced damage. If this capacity could be strengthened to promote the recovery, then perhaps there would be a possibility of an additional option to treat ischemic stroke and support functional recovery.

At the Laboratory of Stem Cells and Restorative Neurology, Zaal Kokaia and his research group focus on using stem cells to help the stroke-lesioned brain to repair and recover, to enhance the regenerative properties of the brain and make the regeneration faster and more efficient. By better understanding the brain’s regenerative mechanisms, and looking into the use of stem cells to repair the brain damage, Zaal is hoping to provide a new treatment to combat ischemic stroke lesions. To help in their investigations, rat and mouse models of ischemic stroke have been used to generate an injury similar to the one observed in humans. Once the damage has been induced, it is possible to study the effects of stem cells transplanted to the site, or monitor the brain’s own regenerative capacity and try to understand which parameters can affect it.

Recently, Zaal’s group investigated the importance of monocyte-derived macrophages (MDMs) recruited from the blood stream to the ischemic damage in the brain. Apparently, MDMs improve the long-term recovery following stroke through a dual-purpose function. In the early stages after the ischemic stroke, the MDMs promote a pro-inflammatory environment and clear the site of the lesion from damaged neurons. In the later stage, the MDMs shift to an anti-inflammatory phenotype which promotes regeneration and long-term spontaneous recovery. When the CCR2 receptor on the MDMs was blocked, the MDMs were not recruited to the site of injury and the spontaneous long-term recovery of somatosensory and motor functions was impaired. This finding provided strong evidence that endogenous MDMs can improve functional recovery. In a follow-up study, Zaal’s group showed that when monocytes were isolated from the bone marrow and activated towards an anti-inflammatory phenotype, prior to injection into stroke-injured brain, recovery was enhanced. Apparently, the MDMs play an important role in the regenerative process after an ischemic stroke, and the idea is currently to initiate clinical investigations of the role of MDMs.

In parallel with the research on MDMs, Zaal’s group is looking into the possibility of replacing the neurons lost in the brain after an ischemic stroke. Here, they use long-term neuroepithelial stem (lt-NES) cells generated from human skin-derived induced pluripotent stem (iPS) cells. The lt-NES cells are multipotent neural progenitor cells capable of differentiating into neurons. Since these cells are generated from human fibroblasts, they can be produced from the patient’s own skin cells. This strategy eliminates the need to use immunosuppressive treatment to prevent graft rejection in a clinical setting. In their previous studies, lt-NES cells were administered to rats with stroke-induced brain lesions through intracerebral transplantation. Once at the site of the lesion, the lt-NES cells released transcription and trophic factors, which enhanced the plasticity and survival of remaining
neurons at the lesion site. Later on, the lt-NES cells differentiated to neurons, which integrated into the host’s neural network.

Whether or not these neurons actually functionally integrate and act in a similar fashion as the host neurons is only one piece of the puzzle. For the lt-NES cell-based therapy to be clinically viable, pre-clinical data must be in alignment and the biological processes involved in the regenerative capacity of the brain have to be better understood. Zaal stresses the fact that no clinical case of ischemic stroke is similar to another and that the challenge in the coming years will be to provide a more tailored therapy to suit groups of patients with similar lesions and conditions. To reach this level of therapy one must better understand which specific types of cells were lost due to the stroke, and how to best guide the regeneration of these types of cells with stem cell therapy.

Having adopted a translational research approach to his research early on, Zaal is hoping that by his close connection to the clinic, it will be easier to guide the research to what is most beneficial for the patients. Thus, in one collaborative effort with clinicians, greater impairments were observed in patients with stroke lesions in the cortex compared to what was found in those with pure basal ganglia lesions. In the light of those results, Zaal’s group put a strong effort looking into which cell types were lost after an ischemic stroke in the cortex (and should be replaced), and using animal models which could mimic the clinical setting. Zaal believes strongly in this translational approach for pre-clinical research, and is hoping that in the future he and his group together with clinicians will be able to apply stem cell-based therapy in stroke patients.

- Joakim Hising

References:
