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Molecular Mechanisms Underlying the Effect of Hypoxia on Stem Cell Growth and Differentiation

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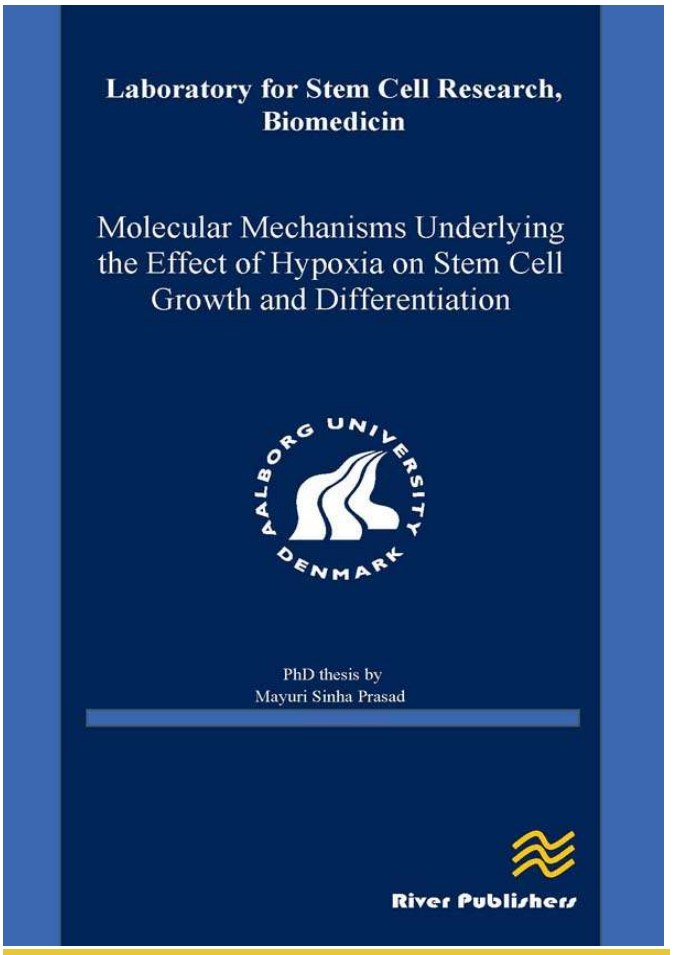
The potential use of stem cells in regenerative therapy is an exciting field of research, currently undergoing tremendous development in order to bring the applications from the laboratory benches to hospital bedsides. Both embryonic as well as adult stem cells have been shown to be beneficial in the treatment of various debilitating disease in clinical trials around the world. The main aim of this PhD dissertation is to gain a better understanding of the effect of low oxygen tension on the differentiation, proliferation and ion channel function of human embryonic stem cells (ESCs) and human adipose-derived stem cells (ASCs). For this purpose, the investigation was divided into 3 sub-studies.

The first study focused on identifying the oxygen tension at which the ESCs would attain optimal growth with minimal differentiation along with understanding the underlying molecular pathway responsible for the effect. The results from the investigation indicate that culturing ESCs at 5% oxygen tension can support long term undifferentiated propagation, without locking the cells in a permanent state of pluripotency. Additionally we found that Notch-hypoxia cross talk plays an important role in the maintenance of self-renewal. The understanding gained from the first study was then taken further by investigating the properties of human ESCs that were subjected to long term hypoxia to evaluate whether low oxygen tension brought about any change in the ESC characteristics like proliferation, expression of differentiation markers, karyotype, telomerase activity, differentiation capacity etc. This study established that the ESCs exposed to long term hypoxia maintained features associated with stable undifferentiated propagation and at the same time retained the capacity to differentiate into the 3 germ layers.

The aim of the last study was to investigate the difference in the ion channel expression of the embryonic and adipose-derived stem cell cultured in normoxic and 5% hypoxic conditions. The results from this study detected a small but significant change in the level of some ion channel gene expression in ESCs and further showed that hypoxic preconditioning influenced the electrophysiological profile of ASCs on a population level.

Innumerable steps are involved in the transformation of the undifferentiated stem cells into differentiated, functional cells. The understanding of molecular regulators that form a part of this process is absolutely crucial for the development of the regenerative therapy. This dissertation is a small part of the effort to unveil the molecular mechanisms underlying stem cells differentiation, proliferation and ion channel function.



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