Patterning and Specification of Dopamine- and Oxytocin-Producing Neurons in the Vertebrate Brain

Department of
Molecular Cell Biology

Gil Levkowitz

Janna Blechman
Liat Amir-Zilberstein
Yossy Machluf
Niva Russek-Blum
Natalia Borodovsky
Amos Gutnick
Shani Frenkel

☎ 972 8 934 6077
FAX 972 8 934 4125
@ gil.levkowitz@weizmann.ac.il
www.weizmann.ac.il/mcb/GLevkowitz/index.html

Our lab's research goal is to understand how distinct neuronal populations are formed within the diencephalon, which is a major part of the vertebrate forebrain. We focus mainly on dopaminergic (DA) and oxytocinegic (OT) neurons of the zebrafish as a paradigm for the development of two prominent diencephalic cell types.

During embryonic development DA and OT neurons are generated next to each other at approximately the same time, and each of these neuronal clusters reaches a fixed cell number. It is therefore apparent that the generation and maintenance of DA and OT neurons must be tightly coordinated for proper brain functioning, as well as for the organism's fitness.

Within the context of adult physiology, concurrent activation of oxytocin and dopamine receptors results in inter-neuronal communication between the DA and OT systems, modulating social behavior, pair bonding, sexual behavior and arousal, lactation and anxiety/stress responses.

Despite their great importance, the mechanisms controlling diencephalic cell fate decisions and anatomical configurations are not well understood. This is mainly due to lack of early molecular markers of diencephalic progenitors, difficulties in tracking the migration and specification of neural progenitors, and limited knowledge of the progenitor specification signals. To overcome these hurdles, we chose to study diencephalic neural specification in the zebrafish, danio rerio, a vertebrate organism readily amenable to genetic manipulations. Zebrafish embryos are optically transparent, allowing detailed *in vivo* analyses of the developing diencephalic neurons and their circuits.

Our current work addresses the following questions:

1) What is the origin of DA and OT neurons in the neural plate?
2) What is the nature and hierarchy of signals that dictate different diencephalic fates?
3) What is the "transcriptional code" underlying DA and OT specification?
4) How is coordinated development of multiple diencephalic cell types achieved in this relatively narrow anatomical region?
5) Which developmental cues regulate the nearly fixed number of diencephalic neuronal types, and how?

To answer these critical questions we set out to identify the genetic requirements for cell fate decisions involved in diencephalic DA and OT cell types, and to characterize a set of marker genes that can be used to distinguish the progenitor populations destined toward these neuronal fates. Taking advantage of the optical transparency of zebrafish embryos, we track individual cells in the developing brain using real-time imaging of labeled neuronal populations. By utilizing these and other approaches, we hope to gain a better understanding of early cell fate decisions, proliferation and migration of diencephalic progenitors.

This fundamental information could greatly contribute to our understanding of the selective vulnerability of diencephalic neurons in the context of various neurological conditions, including deficits in energy balance, motor defects, neuro-endocrine and psychiatric disorders.

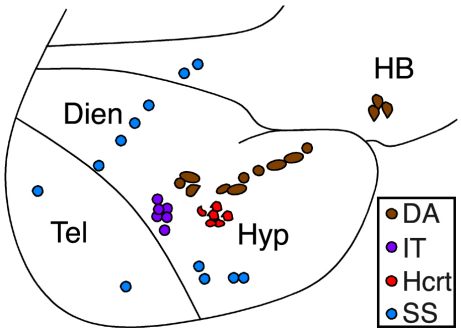

Fig 1. *Neuronal cell types in the zebrafish diencephalon*
Schematic representation of neuronal cell types of the zebrafish hypothalamus (part of the diencephalon) as they appear in the brains of 2 days-old zebrafish embryos. DA, dopamine; Dien, diencephalon HB, hindbrain; Hcrt, hypocretin Hyp, hypothalamus; IT, isotocin (oxytocin-like); SS, somatostatin; Tel, telencephalon.

Selected publications

Levkowitz, G., Zeller, J., Sirotkin, H.I., French, D., Schilbach, S., Hashimoto, H., Hibi, M., Talbot, W.S., and Rosenthal, A. (2003) Zinc finger protein too few controls the development of monoaminergic neurons. Nat. Neurosci., 6(1), 28-33.

Blechman, J., Borodovsky, N., Eisenberg, M., Nabel-Rosen, H., Grimm, J., and Levkowitz, G. (2007) Specification of hypothalamic neurons by dual regulation of the homeodomain protein Orthopedia. Development, 134(24), 4417-4426.

Acknowledgements

Our study is supported by the Israel Science Foundation, National Institute for Psychobiology in Israel, the German Israeli Foundation and the Minna James Heineman Foundation.

G.L. is an incumbent of the Tauro Career Development Chair in Biomedical Research.

INTERNAL support

The Dekker Foundation