Abstract

The establishment of the nervous and the immune system represent some of the most complex mechanisms in development. Several molecules are involved in early differentiation and maturation processes by mediating adhesion and migration of cells. Following neuronal guidance processes, the establishment of functional neuronal connections, their maintenance and synaptic transmission are major objectives. The complexity of such processes is modulated by several mechanisms and increased by multiple functional properties of the involved molecules and their spatiotemporal distribution.

The present work comprises the characterization of two novel transmembrane EGF (epidermal growth factor)-like domains containing proteins. They were analysed to elucidate their possible involvement in the establishment of the nervous system. EGFL5 was identified as a protein containing five laminin (LE)-type EGF-like domains, whereas DNER contains EGF-like domains homologous to those of Notch-1 and its ligands Delta and Serrate/Jagged. As described for other signalling molecules, characteristic posttranslational modifications were found to be present in EGFL5 and DNER. Both proteins show a spatiotemporal expression pattern in neuronal tissues, which becomes more restricted during development. DNER is expressed in neuronal cells of the central (CNS) and peripheral nervous system (PNS), while EGFL5 was detected in neuronal cells of the CNS but also in associated glia cells of the CNS and PNS. EGFL5 mRNA was also found to be present in nonneuronal tissues, and this expression was confirmed at the protein level in skin and the gastrointestinal tract. EGFL5 and DNER were further detected in the immune system as being present on subpopulations of T-cells.

The functional role of DNER was elucidated by the analysis of DNER deficient mutant mice. According to these findings DNER seems to be involved in the establishment of action potentials in specific mechanosensitive fibers by possibly acting as a modulator of transduction channels contributing to the distribution of ions along the nerve fiber. DNER was further shown to be involved in the establishment and/or maintenance of the immune system as in DNER deficient mice a clear reduction in the amount and distribution of T-cells was observed.