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| Sommario | Dopaminergic neurons (DA) are an anatomically and functionally heterogeneous group of cells involved in a wide range of neuronal network activities and behaviour. Among them, mesencephalic dopaminergic neurons (mDA) are the major source of dopamine in the brain. They present two main groups of projecting cells: the A9 neurons of the Substantia Nigra (SN) and the A10 cells of the Ventral Tegmental Area (VTA). A9 neurons form the nigrostriatal pathway and are involved in regulating voluntary movements and postural reflexes. Their selective degeneration leads to Parkinson’s disease (PD) and the loss of DA synapses in the striatum is believed to be primary cause for the disruption of the ability to control movements. A10 cells constitute the mesocorticolimbic pathway playing a fundamental role in reward and attention. Their abnormal function has been linked to schizophrenia, attention deficit and addiction while they are relatively spared in PD (Meyer-Lindenberg et al., 2002). The description of the repertory of genes of mDA neurons may provide crucial information on their physiology as well as on the mechanisms of cell-type specific dysfunction. Interestingly, in previous gene expression profiling experiments, mDA cells groups presented a limited number of differentially expressed genes (Chung |

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| | et al., 2005; Greene et al., 2005). By a combination of different gene expression platforms with Laser Capture Microdissection (LCM), it has been unveiled the existence of an alternative splice variant of Erythropoietin Receptor (EpoR) in A9 neurons. Moreover, the transcripts of hemoglobin alpha, adult chain 1 (Hba-a1) and hemoglobin beta, adult chain 1 (Hbb-b1) have been identified. The main goal of this study is the understanding of the role of Erythropoietin receptor (EpoR) and of alpha and -globin in dopaminergic neurons as well as in Parkinson's disease (PD). In blood Epo regulates erythrocyte differentiation and Hb production. Since Epo has been recently shown to protect dopaminergic neurons in neurochemical PD models and it is a very important pharmacological target, it has been analyzed by the RACE technique the expression of EpoR in spleen (as control) and in A9 mouse mesencephalic cells collected by Laser Capture Microdissection. 5'RACE analysis of DA neurons indicate the existence of an alternative transcription start site for the EpoR (referred to as DA-EpoR). EpoR expression was validated by PCR experiments and was restricted to A9 DA cells, which selectively degenerate in PD. The truncated cDNA corresponding to DA EpoR has been cloned from the A9 mesencephalic neurons, while the full-length WT EpoR has been cloned from the spleen. Both cDNAs have been expressed in HEK-T cells in order to unveil their function. DA EpoR may act as a decoy toward the WT EpoR. To unveil the role of and globin in the brain it has been investigated an animal model of -Thalassemia. I took advantage of a mouse model of -Thalassemia, in which -globin gene is deleted in heterozigosity. The goal is to study the status of global gene expression in A9 and A10 dopaminergic neurons in a thalassemic carrier genotype. This condition is present in 3 million individuals in Italy. No brain studies have been carried out so far both in mouse models and in post-mortem human brains. I bred -Thalassemic mice with TH-GFP mice where dopaminergic neurons are labelled. Then I took advantage of Laser Capture Microdissection to harvest A9 and A10 dopaminergic neurons from 12 months old wild type and heterozygous mice for -chain of Hb for four replicas. Liver and cerebellum cells were used as controls, since liver presents iron accumulation in old thalassemic carriers. Sample cells have been analyzed at the Affymetrix core facility. I identified among the genes differentially expressed Atg4, a major regulator of autophagy, and Hepcidin, the hormone controlling iron metabolism. Relevant target genes have been verified by qPCR. |
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