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Review

A meta-analysis of microarray-based gene expression studies of olfactory bulb-derived olfactory ensheathing cells

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ABSTRACT

Genome wide transcriptional profiling and large scale proteomics have emerged as two powerful methods to dissect the molecular properties of specific neural tissues or cell types on a global scale. Several genome-wide transcriptional profiling and proteomics studies have been published on cultured olfactory ensheathing cells (OEC). In this article we present a meta-analysis of all five published and publicly available micro-array gene expression datasets of cultured early-passage-OB-OEC with other cell types (Schwann cells, late-passage-OB-OEC, mucosa-OEC, an OEC cell line, and acutely dissected OEC). The aim of this meta-analysis is to identify genes and molecular pathways that are found in multiple instead of one isolated study. 454 Genes were detected in at least three out of five microarray datasets. In this "Top-list", genes involved in the biological processes "growth of neurites", "blood vessel development", "migration of cells" and "immune response" were strongly overrepresented. By applying network analysis tools, molecular networks were constructed and Hub-genes were indentified that may function as key genes in the above mentioned interrelated processes. We also identified 7 genes (ENTPD2, MATN2, CTSC, PTHLH, GLRX1, COL27A1 and ID2) with uniformly higher or lower expression in early-passage-OB-OEC in all five microarray comparisons. These genes have diverse but intriguing roles in neuroprotection, neurite extension and/or tissue repair. Our meta-analysis provides novel insights into the molecular basis of OB-OEC-mediated neural repair and can serve as a repository for investigators interested in the molecular biology of OEC. This article is part of a Special Issue entitled: Understanding olfactory ensheathing glia and their prospect for nervous system repair.

Contents

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[2] All full gene names are given in Table 2.

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Introduction

Olfactory ensheathing cells (OEC) are the resident glia cells of the primary olfactory nerve. These cells enwrap the axons of the primary olfactory neurons and form a permissive cellular pathway for growing axons of new adult-born primary olfactory neurons. After transplantation in the spinal cord OEC appear to promote a wide range of processes that are beneficial for repair (Fairless and Barnett, 2005; Franssen et al., 2007; kay-Sima and Chuahb, 2000; Raisman and Li, 2007; Ramon-Cueto and Avila, 1998; Richter and Roskams, 2008; Santos-Benito and Ramon-Cueto, 2003; Wewetzer et al., 2011; Lindsay et al., 2010; Ruitenberg et al., 2006). OEC promote axon regeneration after transplantation in a lesion of the spinal cord and although they do not form myelin in their natural habitat, they have been reported to myelinate axons after transplantation (Franklin et al., 1996; Imaizumi et al., 1998; Li et al., 1998; Dombrowski et al., 2006). They have protective effects on tissue around a spinal cord lesion, promote angiogenesis, modulate the immune response and appear to have phagocytic properties (Harris et al., 2009; Kocsis et al., 2009; Leung et al., 2008; Ramer et al., 2004; Ruitenberg et al., 2003; Toft et al., 2007). Overall, OEC appear to adapt quickly to foreign cellular environments where they can play a positive role in the wound healing and the regenerative response (Cui et al., 2003; Plant et al., 2011).

When OEC, acutely dissected from the olfactory bulb (OB-OEC), are cultured they secrete neuroprotective proteins, including neurotrophic factors of the neurotrophin, glial cell line-derived growth factor and fibroblast growth factor families (Boruch et al., 2001; Chuah and Teague, 1999; Fairless and Barnett, 2005; Lipson et al., 2003; Ramon-Cueto and Avila, 1998; Roskams et al., 1996; Woodhall et al., 2001) and they produce cell adhesion and extracellular matrix proteins (Au et al., 2007; Doucette, 1996; Fairless and Barnett, 2005; Pastrana et al., 2006; Richter and Roskams, 2008; Santos-Silva et al., 2007; Vincent et al., 2005a; Vukovic et al., 2009b, 2009a). Together with Schwann cells (SC), OEC are the most pro-regenerative cells in the nervous system, warranting research efforts to advance understanding of the molecular signals that are deployed by OEC to stimulate axon regeneration and neural tissue repair.

Genome wide transcriptional profiling and large scale proteomics have emerged over the last 10 to 15 years as two powerful methods to dissect and understand the molecular properties of specific neural tissues or cell types on a more global scale (Cahoy et al., 2008; Geschwind and Konopka, 2009; Nelson et al., 2006). Four microarray (Franssen et al., 2008; Guerout et al., 2010; Pastrana et al., 2006; Vincent et al., 2005a) and four proteomics studies (Au et al., 2007; Boyd et al., 2006; Jahed et al., 2007; Liu et al., 2010b) have been conducted to investigate the molecular properties of OEC and are shown in more detail in Table 1. Results of a fifth microarray study have been discussed in a review but the study has not been published (Ruitenberg et al., 2006). Overall, these studies consistently demonstrate that OEC are a rich source of growth factors, chemokines, serine protease inhibitors (serpins), matrix metalloproteinases, complement factors and a myriad of other extracellular and matricellular proteins from a variety of gene families.

A superficial comparison of the results of these microarray studies does also highlight inter-study differences in the genes that are expressed in OB-OEC. These apparent differences are most likely due to the origin of OEC, purification methods, possible contamination with other cell types (Kawaja et al., 2009) and culture conditions but also to false positive and false negative findings that are inherently associated with large gene expression datasets. Meta-analyses of microarray datasets, however, do reveal the overlap between microarray studies (De et al., 2009; Greco et al., 2008) and by combining information from multiple existing microarray studies the reliability and specificity of the results can be improved (Ramasamy et al., 2008). This will greatly enhance the confidence in the observations and therefore help investigators to focus on those molecular properties of OB-OEC that have been uncovered in multiple independent experiments instead of one isolated study.

In this article we present a meta-analysis of the publicly available microarray data sets that compare gene expression in early-passage-OB-OEC with either acutely dissected OB-OEC, cultured OEC that were derived from the olfactory mucosa, an OEC cell line, OB-OEC after extended culturing and finally, cultured SC. The aim of this endeavor was to identify gene expression signatures that distinguish OB-OEC from two other pro-regenerative cell types (mucosa-OEC and SC) and from late-passage-OB-OEC that exhibit diminished regenerative properties and from an OEC cell line. To this end, we employed a three-pronged approach: i) identification of those genes that were reproducibly detected in multiple datasets (generating a Top-list of genes), ii) identification of the biological processes and molecular networks that are associated with the Top-list and iii) identification of those genes (Hub-genes) that are likely to play a central role in the repair-promoting properties of OB-OEC by studying their connection(s) with other Top-list genes.

The gene expression data sets used in our meta-analysis were downloaded from the GEO database hosted by the National Center for Biotechnology Information (NCBI). The combined data set yielded a "Top-list", with 7 genes that were detected in five out of five comparisons, more than 60 genes detected in four out of five comparisons and almost 400 genes that were detected in three out of five comparisons. These genes were subjected to Ingenuity Pathway Analysis (IPA) to identify overrepresented biological processes, molecular relationship networks and Hub-genes with a putative central role in the repair promoting properties of OB-OEC.

Our meta-analysis provides a window on the transcriptional profile of early-passage-OB-OEC. It identifies individual genes of interest,