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The Potential Role of Chemokines In Redirecting Progenitor Cell Migration Into The Lesioned Striatum

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Abstract

A number of studies have demonstrated directed migration of neural progenitor cells to sites of brain injury and disease. However, a detailed examination of when a cell is “born” in relation to injury induction and the migratory response of that cell has not previously been determined. This study therefore examined the temporal correlation between progenitor cell proliferation (“birth”) and neuroblast migratory response into the damaged striatum following quinolinic acid (QA) lesioning of the adult rat striatum. Retroviral labeling of subventricular zone (SVZ)-derived progenitor cells demonstrated that cell loss in the QA-lesioned striatum increased progenitor cell migration through the rostral migratory stream for up to 30 days. In addition, a population of dividing cells originating from the SVZ generated doublecortin positive neuroblasts that migrated into the damaged striatum in response to cell loss invoked by the QA lesion. The majority of doublecortin positive neuroblasts present in the damaged striatum were generated from progenitor cells dividing within two days prior to, or on the day of QA lesioning. In contrast, cells dividing two or more days following QA lesioning, migrated into the striatum and exhibited a glial phenotype. These results demonstrate that directed migration of SVZ-derived cells and neuroblast differentiation in response to QA lesioning of the striatum is acute and transient. We subsequently demonstrated a role for the chemokines MCP-1, MIP-1 α and GRO- α in directing adult SVZ-derived progenitor cell migration following striatal cell death. MCP-1, MIP-1 α and GRO- α were significantly upregulated in the striatum 2-3 days following QA-induced lesioning, correlating with maximum SVZ-derived progenitor cell recruitment into the lesioned striatum. We established that SVZ-derived progenitor cells express receptors for each chemokine, and demonstrated MCP-1, MIP-1 α and GRO- α to be potent chemoattractants for SVZ-derived progenitor cells *in vitro*. Immunofluorescence revealed MCP-1, MIP-1 α and GRO- α are predominantly expressed in the striatum by NG2-positive cells that appear to infiltrate from the bloodstream 6 hours following QA lesioning. These results indicate that upregulation of MCP-1, MIP-1 α , GRO- α following striatal cell death leads to chemoattraction of SVZ-derived progenitor cells into the damaged striatum and raises a potential role for blood-derived cells in directing the recruitment of SVZ progenitor cells following brain injury.

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Abbreviations

| | |
|------------------|---|
| AAV | Adeno-associated virus |
| ADAM | A disintegrin and metalloproteinase |
| AKT | V-akt murine thymoma viral oncogene homolog |
| ANOVA | Analysis of variance |
| AP | Anterior-posterior |
| BDNF | Brain-derived neurotrophic factor |
| BIII tubulin | Beta-III Tubulin |
| bp | Basepair |
| BK _{Ca} | Large-conductance calcium- and voltage-activated potassium channels |
| BrdU | Bromodeoxyuridine |
| BSA | Bovine serum albumin |
| CA1 | Cornu Ammonis field 1 |
| CA3 | Cornu Ammonis field 2 |
| Ca ⁺⁺ | Calcium |
| cAMP | Cyclic adenosine monophosphate |
| CBA | Chicken Beta Actin |
| CCR1 | CC-chemokine receptor 1 |
| CCR2 | CC-chemokine receptor 2 |
| CCR5 | CC-chemokine receptor 5 |
| CD11B | Cluster of differentiation molecule 11B |
| CD31 | Cluster of differentiation molecule 31 |
| CD68 | Cluster of differentiation molecule 68 |
| cdc42 | Cell division cycle 42 |
| cDNA | Complementary deoxyribonucleic acid |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CO ₂ | Carbon dioxide |
| CSF | Cerebrospinal fluid |
| CTG | Cell tracker green |
| CXCR1 | CXC-chemokine receptor 1 |
| CXCR2 | CXC-chemokine receptor 2 |
| CXCR3 | CXC-chemokine receptor 3 |
| CXCR4 | CXC-chemokine receptor 4 |
| DAB | Diaminobenzidine |
| DAPI | 4',6-diamidino-2-phenylindole |

| | |
|----------------|---|
| DCC | Deleted in colorectal carcinoma |
| Dcx | Doublecortin |
| DEPC | Diethylpyrocarbonate |
| Dil | 1,1'-dioctadecyl 3,3',3'-tetramethylindocarbocyanine perchlorate |
| DIV | Days <i>in vitro</i> |
| DMEM | Dulbecco's modified essential medium |
| DNA | Deoxyribonucleic acid |
| dNTP | Deoxyribonucleotide triphosphate |
| DTT | 1,4-dithiothreitol |
| DV | Dorsal-ventral |
| EDTA | Ethylenediaminetetraacetic acid |
| EGF | Epidermal growth factor |
| ELISA | Enzyme linked immunosorbent assay |
| eNOS | Endothelial nitric oxide synthase |
| ErbB4 | Erythroblastic leukemia viral oncogene homolog 4 |
| ERK1/2 | Extracellular signal-regulated kinase 1/2 |
| FAK | Focal adhesion kinase |
| FGF | Fibroblast growth factor |
| g | Gram |
| GABA | Gamma-aminobutyric acid |
| G-CSF | Granulocyte colony-stimulating factor |
| GDNF | Glial cell derived neurotrophic factor |
| GFAP | Glial fibrillary acidic protein |
| GFP | Green fluorescent protein |
| GFR α 1 | Glial cell derived neurotrophic factor family receptor alpha 1 |
| GM-CSF | Granulocyte/macrophage colony-stimulating factor |
| GP2-293 | HEK 293-based cell line that stably expresses the viral gag and pol genes |
| GPDH | Glyceraldehyde-3-phosphate dehydrogenase |
| GRO α | Growth regulated protein-alpha |
| HEK-293 | Human embryonic kidney 293 cells |
| HGF | Hepatocyte growth factor |
| IFN- γ | Interferon-gamma |
| IL-1 α | Interleukin-1 alpha |
| IL-1 β | Interleukin-1 beta |
| IL-2 | Interleukin-2 |
| IL-4 | Interleukin-4 |
| IL-5 | Interleukin-5 |

| | |
|----------------|--|
| IL-6 | Interleukin-6 |
| IL-9 | Interleukin-9 |
| IL-10 | Interleukin-10 |
| IL-12p70 | Interleukin-12 p70 |
| IL-13 | Interleukin-13 |
| IL-17 | Interleukin-17 |
| IL-18 | Interleukin-18 |
| IGF-1 | Insulin-like growth factor 1 |
| i.p. | Intraperitoneal |
| IP-10 | Interferon-inducible protein 10 |
| kb | Kilobase |
| kg | Kilogram |
| L | Litre |
| LPS | Lipopolysaccharide |
| M | Moles per litre |
| MCAO | Middle cerebral artery occlusion |
| MCP-1 | Monocyte chemoattractant protein-1 |
| MCP-2 | Monocyte chemoattractant protein-2 |
| μg | Microgram |
| mg | Milligram |
| MIA | Migration-inducing activity |
| MIP-1 α | Macrophage inflammatory protein-1 alpha |
| μL | Microlitre |
| mL | Millilitre |
| ML | Medial-lateral |
| mM | Millimoles per litre |
| MMP | Matrix metalloprotease |
| mOsm | Milliosmole |
| MPTP | 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine |
| mRNA | Messenger ribonucleic acid |
| NeuN | Neuronal nuclei |
| ng | Nanograms |
| NG2 | Chondroitin sulphate proteoglycan 4 |
| NMDA | N-methyl d-aspartate |
| OB | Olfactory bulb |
| OX42 | Integrin alpha-M |
| PB | Phosphate buffer |

| | |
|----------------|--|
| PBS | Phosphate buffered saline |
| PCNA | Proliferating Cell Nuclear Antigen |
| PCR | Polymerase chain reaction |
| PECAM-1 | Platelet endothelial cell adhesion molecule 1 |
| PI3K | Phosphoinositide 3-kinase |
| PKC | Protein kinase C |
| PKR1 | Prokineticin receptor 1 |
| PKR2 | Prokineticin receptor 2 |
| PSA-NCAM | Polysialylated neural cell adhesion molecule |
| Ptc | Patched |
| Pyk2 | Proline-rich tyrosine kinase 2 |
| QA | Quinolinic acid |
| RANTES | Regulated upon activation normal T cell express sequence |
| RMS | Rostral migratory stream |
| RNA | Ribonucleic acid |
| Robo | Roundabout |
| ROS | Reactive oxygen species |
| rpm | Revolutions per minute |
| RT-PCR | Reverse transcriptase polymerase chain reaction |
| RV | Retroviral vector |
| RV-GFP | Retroviral vector encoding green fluorescent protein |
| SCF | Stem cell factor |
| SDF-1 α | Stromal cell derived factor 1-alpha |
| Shh | Sonic hedgehog |
| SHP1/2 | Src homology 1/2 domain-containing tyrosine phosphatase |
| siRNA | Small Interfering ribonucleic acid |
| Smo | Smoothened |
| STAT | Signal Transducer and Activator of Transcription |
| SVZ | Subventricular zone |
| Syk | Spleen tyrosine kinase |
| TAE | Tris-acetate-EDTA buffer |
| TNF- α | Tumour necrosis factor alpha |
| TrkB | Tyrosine kinase B |
| UV | Ultraviolet |
| VEGF | Vascular endothelial growth factor |
| VEGFR2 | Vascular endothelial growth factor receptor 2 |
| VSV-G | Vesicular stomatitis virus G-protein |