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-1α and GRO-α in directing adult SVZ-derived progenitor cell migration following striatal cell death. MCP-1, MIP-1α 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-1α and GRO-α to be potent chemoattractants for SVZ-derived progenitor cells *in vitro*. Immunofluorescence revealed MCP-1, MIP-1α 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-1α, 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
DiI	1,1'-dioctadecyl 3,3,3',3'-tetramethylindocarbocyanine perchlorate
DIV	Days *in vitro*
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
GFRα1	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
GROα	Growth regulated protein-alpha
HEK-293	Human embryonic kidney 293 cells
HGF	Hepatocyte growth factor
IFN-γ	Interferon-gamma
IL-1α	Interleukin-1 alpha
IL-1β	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-1α	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-1α	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