



The potential of stem cells for the treatment of brain tumors and globoid cell leukodystrophy

Patrizia Tunicci*, Serena Pellegatta & Gaetano Finocchiaro

Istituto Nazionale Neurologico Besta, Unit of Neuro-Oncology and Gene Therapy, Milan, Italy

(* Author for correspondence)

Key words: neurodegenerative disorders, neurological diseases, stem cells

Abstract

Stem cells of different origin are under careful scrutiny as potential new tools for the treatment of several neurological diseases. The major focus of these researches have been neurodegenerative disorders, such as Huntington Chorea or Parkinson Disease (Shihabuddin et al., 1999). More recently attention has been devoted to their use for brain repair after stroke (Savitz et al., 2002). In this review we will focus on the potential of stem cell treatments for glioblastoma multiforme (Holland, 2000), the most aggressive primary brain tumor, and globoid cell leukodystrophy (Krabbe disease), a metabolic disorder of the white matter (Berger et al., 2001). These two diseases may offer a paradigm of what the stem cell approach may offer in term of treatment, alone or in combination with other therapeutic approaches. Two kinds of stem cells will be considered here: neural stem cells and hematopoietic stem cells, both obtained after birth. The review will focus on experimental models, with an eye on clinical perspectives.

Glioblastoma multiforme

Glioblastoma multiforme (GBM, grade IV astrocytoma) can be divided into two subtypes based on clinical characteristics: primary and secondary GBM (Maher et al., 2001). Primary GBM arises as a *de novo* process, in the absence of a pre-existing low-grade lesion, whereas secondary GBM develops progressively from low-grade astrocytoma, generally over a period of 5–10 yr. Genetic studies of GBMs indicate that there are distinct genetic pathways involved in the initiation and progression of these neoplasms.

The p53 tumor suppressor is a transcription factor that regulates cell-cycle progression and apoptosis in response to many external insults, such as DNA damage and oncogenic mutations (Vogelstein et al., 2000). p53 mutations are present in both low- and high-grade astrocytomas. These findings led to the hypothesis that these common mutations are involved in early phases of tumor formation.

Genetic analysis of astrocytomas indicates that RAS-mediated signalling is also involved in the initiation of astrocytoma development. The small GTP-

binding protein, RAS, is an important downstream effector of the growth-factor-RTK signalling pathway, and can activate at least three downstream cascades: RAF-MEK-MAPK (mitogen-activated protein kinase), phosphatidylinositol 3-kinase (PI3K)-AKT and CDC42-RAC-RHO. The growth-factor-RTK-RAS signalling cascade is one of the most frequently targeted genetic pathways in human cancers, possibly because activating mutations render cancer cells independent of exogenous growth factors. Elevated expression of growth factors and their cognate RTK receptors, including platelet-derived growth factor (PDGF) and platelet-derived growth-factor receptor (PDGFR), are found in every grade of astrocytoma. Furthermore, PDGF and PDGFR are often co-expressed in the same tumor cells, indicating that astrocytoma cells establish an autocrine stimulatory loop (Hermanson et al., 1992). These observations indicate that the PDGF/PDGFR-mediated signalling cascade could be involved in the initiation of astrocytoma development.

Genetic pathways that are specifically disrupted in high-grade but not low-grade astrocytoma are considered to be involved in tumor progression. To main-