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Chemokines in Glioma Progression

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1. Introduction

Gliomas represent a formidable challenge in terms of pathophysiologic and clinical behaviour.

The frequently used term "glioma" applies to neoplasms derived from components of neuroglia: astrocytes, oligodendrocytes and ependima cells with the corrisponding tumors, astrocytomas, oligodendrogliomas and ependymomas (Louis et al 2007, Graham et al 2006). They represent the most common primary intra-axial brain tumor (40% of intracranial tumors with an estimated incidence of 12.000 new cases /year in the U.S.). Importantly, when discussing gliomas, the terms benign and malign have little meaning; the WHO classification provides a grading system to subdivide gliomas. Grading is based on cellularity, presence of giant cells, anaplasia, mitotic activity, microvascular proliferation with or without endothelial proliferation, necrosis and pseudopalisading. Astrocytomas and oligodendrogliomas are usually defined as grade II (III in the anaplastic form) while glioblastomas are grade IV. So a simpler classification describes these tumors as being of low or high grade.

From a clinical point of view the grading system has an inverse correlation to patient survival and it is important in taking decisions as to the therapeutic strategies.

With the exception of one or two entities (e.g. pilocytic astrocytoma-grade I), a low grade glioma will continue to acquire genetic mutations and eventually will transform into a high grade neoplasm. This process is defined dedifferentiation and represents the major cause of morbidity with low-grade astrocytomas. Genetic markers that correlate with a higher degree of malignant degeneration include loss of heterozygosity at chromosomes 10 & 17, alteration in tumor suppressor genes 9p, 13q, 19q & 22q, changes in epidermal growth factor receptor (EGRF) and platelet derived growth factor (PDGF) and mutation of the p53 suppressor gene. To underline the importance of this behaviour, the gliomas that developed in the adult are frequently defined as "diffuse" because of their ability to profoundly infiltrate the brain parenchyma (Louis et al 2007).

Glioblastomas (the most malignant form of glial tumors) are characterized by extensive dissemination of tumor cells within the brain that are hallmarked histologically by the presence of vascular endothelial proliferation and wide areas of necrosis often presenting hemorrhagic components. Besides invasion, enhanced proliferation, angiogenesis and

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All authors contributed equally to the chapter.

resistance to apoptosis are all involved in the progression and maintenance of this malignancy.

As mentioned above gliomas still represent a formidable clinical challenge. In spite of optimal and multidisciplinary treatment (in high grade forms, surgery followed by chemotherapy and radiotherapy) the prognosis of patients affected with gliomas is poor and it becomes dramatic in patients with glioblastomas. As a matter of fact patients with glioblastomas survive less than 1 year and prognosis has not consistently changed over the last two decades. Again, the reason of this defeat can be found in the rapidly expanding nature of these tumors and their capability of invading the normal brain by active cell migration.

Inflammatory cells are a key component of the tumor microenvironment (Mantovani et al 2008; Hanahan and Weinberg 2011). Chemokines play an important role in orchestrating leukocytes recruitment in tumors including gliomas. Moreover, these molecules affect various aspects of tumor cell function (Balkwill et al 2004, Mantovani et al 2006-2008, Lazennec and Richmond 2010). Here we will review available information on the expression and role of chemokines in gliomas.

2. The chemokine universe

Chemokines are a large family of small chemoattractant cytochines. They comprise approximately 50 ligands and 20 receptors in humans. The number and position of conserved cysteine residues divide this family of related molecules into two major (CXC and CC) and two minor (C and CX3C) chemokine classes (Mantovani et al 2006, Charo and Ransohoff 2006).

Chemokine receptors are G-protein coupled, seven transmembrane receptors. Based on the chemokine class they bind, the receptors have been named CXCR1-7 (bind to CXC chemokines); CCR1 through CCR10 (bound to CC chemokines), XCR1 (bound to the C chemokine, lymphotactin/XCL1) and CX3CR1 (bound to the CX3C chemokine, fractalkine/CXCL1) (Zlotnik 2006). Another classification is between homeostic and inflammatory molecules according to the chemokine constitutive (e.g. SDF1/CXCL12) or inflammatory-induced (e.g. CCL2) production, respectively Importantly, if this classification is useful it can be criticized because it does not take into account chemokines classified as inflammatory that are locally but constitutively expressed by tumor cells or in a tissue specific manner (e.g. CX3CL1 in brain).

The most important targets of chemokines are leukocytes. Their ability to orchestrate leucocyte trafficking under basal and inflammatory conditions is generally named as chemotaxis, but chemokine control is also exerted on cell adhesion, proliferation, survival and gene transcription (Campbell and Butcher 2000).

Moreover, chemokine action is not only limited to white cells but it extends to many other cell populations. In particular, chemokine and chemokine receptors are widely expressed into the central nervous system both by neurons and glial cells. The chemokine network in the central nervous system is involved in several brain processes such as cell migration, regulation of neuronal survival, neurotransmission and cell-cell communication (Ambrosini and Aloisi 2004). For this reason chemokine and chemokine receptors can be considered the third major transmitter system in the brain (Adler et al 2005). Interestingly, the chemokine universe seems to be altered in neurodegenerative disorders such as Alzheimer like dementia, multiple sclerosis and brain tumors (Ransohoff et al 2009, Sciumè et al 2010-2011, Marchesi et al 2010, Trettel et al 2010).

3. Chemokines in gliomas

3.1 Glioma cell expression of chemokine and chemokine receptors

The migratory ability of gliomas has been investigated by electron microscopy and it was shown that neoplastic cells easily adjust their shape and size to slip through the narrow brain spaces, a process that requires Cl channels (Mc Coy and Sontheimer 2007).

It is now established that migrating malignant cells exploit chemokine receptors to invade surrounding tissues thus leading to distant metastasis (Balkwill 2004, Zlotnik 2006, Mantovani et al 2010).

The expression of chemokines and chemokine receptors is considered to play a role in tumor cell proliferation, invasion, migration and ability to metastasize. This expression can be activated or amplified by both stromal cells and tumor cells themselves (Mantovani et al 2010).

Moreover the immune cell infiltration in the neoplastic area largely depends on the chemokine expression.

Since 1990 the production of chemokines by cell lines of glioma has been described (IL-8/CXCL8; MCP1/CCL2 etc). In particular, CCL2 was described to be expressed in low and high grade glioma cells both "in vitro" and "in vivo" (Jiang et al 1990, Kasahara et al 1991, Nitta et al 1992, Kuratsu et al 1993). In 1997 Desbaillets and colleagues demonstrated high levels of expression of CXCL8 and its receptors CXCR1 and CXCR2 within the necrotic areas surrounding brain tumor cells. Significantly, the presence of these two receptors was described in endothelial cells of new blood vessels, suggesting they may be implicated in neoangiogenesis.

At the early 2000s an important role of the CXCR4/CXCL12 axis has been identified for the regulation of different aspects of glioma tumor progression. High levels of this complex expression were demonstrated in areas nearby tumor necrosis (Rempel et al 2000). CXCR4 as well as CXCL8 were also demonstrated to be expressed both in glioma cells lines and primary glioblastomas. Interestingly, CXCL8 and CXCL12 "in vivo" secretion can also arise from other cellular populations such as endothelial cells and macrophage/microglial cells, and these populations are implied in gliomagenesis (Hong et al 2009). The expression of CXCL10, CXCL8 and CCL2 is increased by CXCL12-induced CXCR4 stimulation in gliomas thus creating a sort of amplification loop which influence tumor growth, angiogenesis and immune cells infiltration.

The increased expression of IP10/CXCL10 and of CCL3L1 and their receptors found in glioma cells compared to "normal" astrocytes lead to hypothesize an autocrine role for these axes in glioma control (Maru et al 2008). The high expression of CX3CL1 (or fractalkine) in the brain has suggested that also CX3CL1/CX3CR1 axis may play a role in malignancies of the central nervous system (Locatelli et al 2010, Marchesi et al 2010, Sciumè et al 2010). Indeed, neurons and astrocytes are major producers of the ligand and microglia express the receptor CX3CR1 expression has been detected both in glial cells and in neurons. Experimental evidence established that this axis play a major role in the neuron/microglia cross-talk and in neuroprotection under conditions of inflammation (Cardona et al 2006, Gunther et al 2005, Miller et al 2008).

Using a murine model a positive in situ hybridization for CX3CR1 corresponding with the localisation of CD11b-positive microglia was described (Liu et al 2008). As for human glioblastomas CX3CR1 immunopositivity was found in neoplastic cells (Ludwig et al 2005, Locatelli et al 2010).

Moreover, Sciumè and colleagues in 2010 described that glioblastomas cells express both the membrane-bound and the secreted form of CX3CL1 and its receptor CX3CR1. Marked expression of CX3CR1 was similar across low and high grade tumor though it was highest in glioblastomas. The presence of receptor expression in low grade tumor suggests that its upregulation is an early event during malignant transformation. In a recent paper (Erreni et al 2010) CX3CR1 was similarly detected in low and high grade tumors while the uppermost score of CX3CL1 were found in grades II and IV. Accordingly, the expression of fractlakine was inversely correlated to the patient survival.

Notably, constitutive expression of CX3CL1 in CX3CR1 positive glioblastomas negatively regulates tumor cell invasiveness by promoting their aggregation (Sciumè et al 2010). CX3CL1 is induced by TNF α and TNF β in neurons (Chen et al 2002, Sciumè et al 2010). These mediators are frequently present in tumors including gliomas and may be involved in the modulation of CX3CL1/CX3CR1 axis in neoplastic conditions (Mantovani et al 2008, Balkwill et al 2009).

In 2005 Ludwig and colleagues demonstrated that another membrane-bound chemokine, CXCL16 is upregulated in human glioma being this chemokine expression low in normal brain and substantially limited to brain endothelial cells.

Expression of chemokines and their receptors is modulated by factors produced by gliomas or by the tumor microenvironment. Examples are CXCL8, CXCL12 anCXCR4 which are up regulated in hypoxic conditions or upon stimulation with VEGF, an angiogenetic growth factor expressed in glioma tissues (Desbaillets et al 1997, Zagzag et al 2008).

3.2 Chemokines in glioma invasion

The peculiar adhesive function of fractalkine in the nervous system suggests that this chemokine/receptor complex plays a role in the neurotropism of cancer cells to peripheral nerves. This is a distinct and largely underestimated way of metastasis compared to blood and lymphatic routes; many human carcinomas such as bladder, prostate and pancreas take advantage of this route (Marchesi et al 2010).

The invasive process of glioma cells requires the detachment of invading cells from the primary mass of the tumor, attachment to extracellular matrix components and degradation of this matrix. At this point tumor cell migration into brain structures can take place. CX3CL1 would have a negative role in this process, as suggested by the increase in glioma cell invasion properties by the blockade induced by CX3CR1-CX3CL1 axis. Moreover, the reduced CX3CR1 expression consequent to TGF-beta 1 activation can favour glioma invasiveness (Sciumè et al 2010).

Another axis which is acquiring an increasing consideration in this complex process is the CXCL12/CXCR4 axis. This axis has been linked to glioma progression both "in vitro" and "in vivo" (Zhou et al 2002, Zhang et al 2005, Ehtesham et al 2006, Bajetto et al 2006) because of its ability to activate metalloproteinases, including the membrane type-2-MMP. Accordingly, invasive human glioma cell overexpress CXCR4 while noninvasive glioma cell do not. These data were confirmed "in vivo" in neoplastic cells from a rat C6 glioma cell line (Ehtesham et al 2006).

Co-expression of CXCL12 and its receptors is mainly localized to the pseudopalisade zones that surround necrotic foci (Rempel et al 2000). These regions are believed to represent tumor cells which are leaving necrotic regions because of their low or absent oxygen levels. In hypoxic condition, tumor cells release an angiogentic growth factor (VEGF) which

promotes the over-expression of CXCL12 and consequently tumor invasion outside the hypoxic area (Zagzag et al 2008).

Promotion of glioma cell invasion is also mediated by Gro-alpha/CXCL1 that is expressed by oligodendroglioma and anaplastic astrocytomas (Zhou et al 2005). Interestingly CXCL1 overexpression conferred increased tumorigenicity to U251 cells following implantation into the brain of nude mice (Zhou et al 2005).

3.3 Chemokine role in glioma proliferation

In addition to CXCL12, also CXCL8, CXCL10 and CCL3L1 have been described to promote glioma cell proliferation in vitro (Kouno et al 2004, Maru et al 2008). Notably, a correlation between CXCL8 expression levels in cells surrounding necrotic areas and histologic grade in glioma has been demonstrated (Desbaillets et al 1997).

Chemokines also contribute to create a proangiogenic microenvironment by promoting attraction of endothelial cells and leukocytes to the tumor. The chemokine receptor panel of human microvascular endothelial cells includes CXCR2, CXCR3B, CXCR4 and CX3CR1 (Bernardini et al 2003).

As mentioned above, CXCR4 is expressed by both tumor cells and vascular endothelial cells in different grades of gliomas; this is associated with CXCL12 production in the tumor microenvironment, which is capable to modulate migration, proliferation and survival of endothelial and tumor cells (Salmaggi et 2004). It was demonstrated that CXCR4 is expressed by both tumor cells and vascular endothelial cells in all grades of gliomas. The administration of AMD-3100, a CXCR4 antagonist, inhibits the growth of glioblastoma xenografts in mouses, demonstrating the dependence of tumor cells proliferation on CXCR4 (Rubin et al 2003).

3.4 Chemokine network and leukocyte infiltration

Besides its direct effects on tumor growth, the network of chemokines implicated in human astrcytomas can influence the degree and phenotype of immune cell infiltration. However, it is well accepted that glioma cells can be recognized by both innate and adaptive immunity (Mantovani et al 2008, Friese et al 2004, Dunn et al 2007). T-cell infiltration has been described to be present in neuroephitelial tumors, on the contrary NK cells are poorly included in the glioma lymphocyte infiltrate (Vaquero et al 1989).

To date, data regarding the specificity and function of tumor –infiltrating lynphocytes such as the involvement of the chemokine network in the recruitment of these cells or tumor infiltrating microglia/macrophages are lacking. Glia derived CCL2 might be implicated in the process leading to the abundant tumor infiltration by macrophages/microglia and T cells (Jordan et al 2008). CCL2 expression by glioma cells would be advantageous for tumor progression thanks to the attraction of T regulatory cells that suppress lymphocyte anti tumor effector functions and of microglia cells with reduce anti-tumor functions. Another effect would be the secretion of metalloproteinases. The corresponding receptors were the CCR2 on microglia and CCR4 on T regulatory cells (Hussain et al 2006). The role of the CX3CL1/CX3CR1 chemokine/receptor pair in microglial and lymphocyte infiltration remains to be defined.(Liu et al 2008, Rodero et al 2008)

3.5 Concluding remarks

Available information strongly suggest that chemokines play an important role in gliomas. In particular, evidence suggests that they are orchestrators of leukocyte recruitment in the

glioma microenvironment. Moreover, glioma cells express a defined repertoire of chemokine receptors including CXCR4/CXCL12, CX3CL1/CX3CR1 axis.

On the basis of available information and extrapolation from other tumors, chemokine receptors expressed on gliomas may have a broad impact on biological and clinical behaviour of the tumor, affecting different functions including invasion, cell survival and proliferation.

Despite increasing evidence on this complexity, further investigations of this network will allow a better understanding of tumor specificities, biological behaviour and therapeutic failures.

These data and considerations raise the possibility of targeting components of the chemokine system to complement available therapeutic strategies against gliomas.
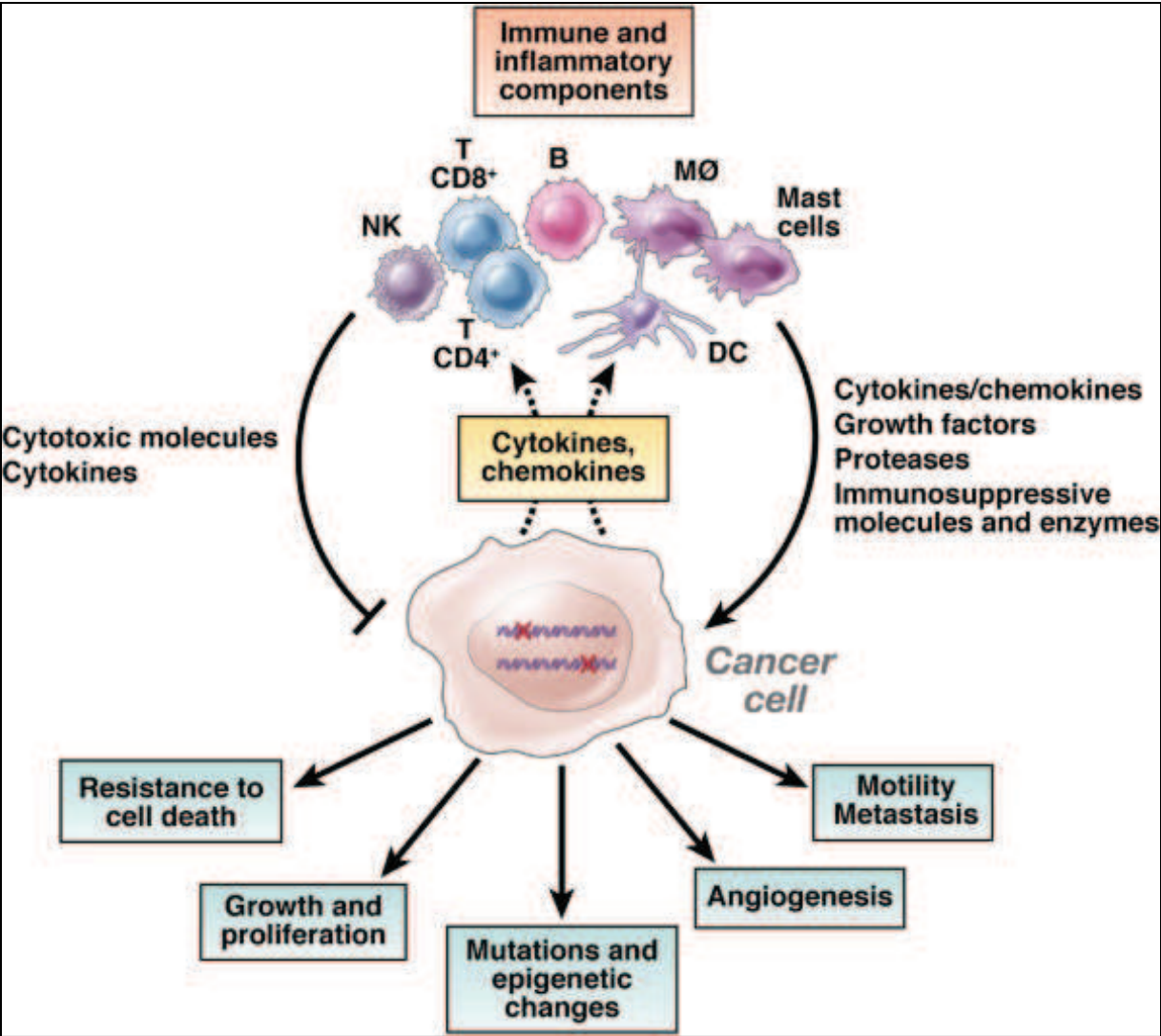
Fig. 1. Inflammatory mediators in gliomas. Innate and adaptive immune cells together with inflammatory molecules and cancer cells are part of an inflammatory microenvironment which may have an impact on biological and clinical behaviour of gliomas.

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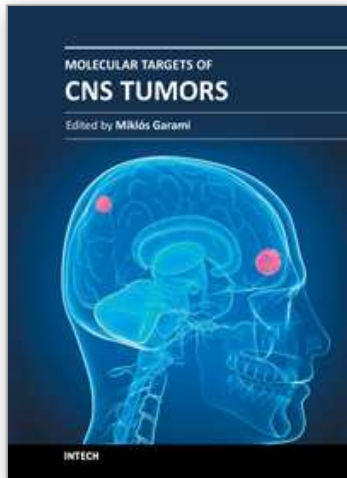
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