Murine Avatars Permit Study of Glioblastoma Genesis and Progression

Paul Mintz PhD; Monica Cucciare; Denise Coley; Amber LaCrosse PhD; Richard A. Rovin MD; Amin B. Kassam MD; Chang-Hyuk Kwon PhD

Aurora Neuroscience Innovation Institute (ANII; A.K., R.R.); Neurosciences Research Program (M.C., D.C., A.L., C.-H.K.); Aurora Health Care Inc., 960 North 12th Street, Milwaukee, WI 53233, USA

CNS 2016 ANNUAL MEETING San Diego CALIFORNIA SEPTEMBER 24-28, 2016

Introduction

Murine glioblastoma patient derived xenografts (PDX) hold great promise in the development of personalized, treatments. Additionally, murine avatars present an unparalleled opportunity to understand the mechanisms of giloblastoma multiforme (GBM) migration, invasion, and resistance to treatment. The purpose of this preliminary study is to determine if murine GBM avatars demonstrate patterns of invasion and migration similar to the human counterpart.

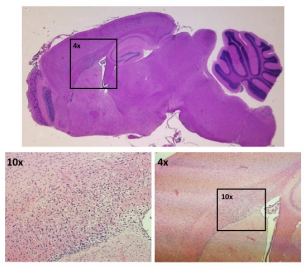
Methods

During surgery, GBM tissue abutting the subventricular zone (SVZ) is specifically collected using a non ablative suction/cutting device. Tissue is maintained in a closed loop system under continuous perfusion with chilled culture media. After processing into single cell suspension (Pollard et al., 2009), 1X10^5 cells were orthotopically injected into the left striatum of female athymic nude mice (6-10 weeks of age). Tumor-bearing mice were sacrificed when syptomatic; brains were processed for hematoxylin and eosin staining.

Results

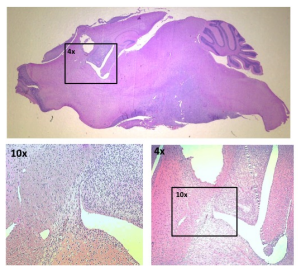
The PDXs recapitulated histological features of the origianl GBM. Distinct migration and invasion patterns were observed. The first GBM patient-derived cell line showed migration patterns away from the subventricular zone (SVZ) along the white matter tracts (figure 1). The second GBM patient-derived cell line also migrated along white matter tracts, but also formed distinct subpopulation of tumor cells ventral to the injection site (figure 2 and 3). GBM 1 was restricted to a dorsal migratory path, while GBM 2 migrated along multiple corridors. Table 1 shows the overall features of the patient-derived xenografts from the two GBM patient-derived cell lines.

Figure 1



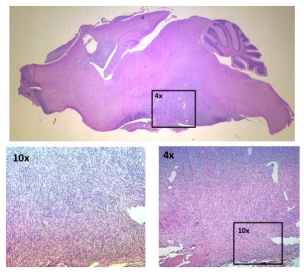
GBM patient-derived cell line 1 depicting anterior and dorsal tumor cell migration along the white matter tract. Patient cell line 1 shows a single preferred migratory pathway. Representative histological hematoxlyin and eosin staining.

Figure 2



GBM patient-derived cell line 2 depicting anterior and dorsal tumor cell migration from striatal injection site. Patient cell line 2 shows similar migration pathway as shown with patient cell line 1, suggesting that GBM patient-derived cell lines may have a common preferred migratory route.

Figure 3



GBM patient-derived cell line 2 depicting ventral and posterior tumor cell migration from striatal injection site. Patient cell line 2 shows a high degree of invasiveness, migrating both to the anterior/dorsal and ventral/posterior regions.

Table 1

Patient-derived cell line	Migration pattern of tumor cells from the striatum
Cell line one	
PDX-1	Anterior/dorsal to the SVZ and along the white matter tract
PDX-2	Anterior/dorsal to the SVZ and along the white matter tract
PDX-3	Anterior/dorsal to the SVZ forming a large tumor mass
PDX-4	Anterior/dorsal to the SVZ and along the white matter tract
PDX-5	Anterior/dorsal to the SVZ forming a large tumor mass
Cell line two	
PDX-1	Anterior/dorsal to the SVZ, and ventral/posterior forming a large tumor mass
PDX-2	Anterior/dorsal to the SVZ, and ventral/posterior to form two distinct subpopulations of tumor cells
PDX-3	Anterior/dorsal to the SVZ, and ventral/posterior forming a large tumor mass
PDX-4	Anterior/dorsal to the SVZ, and ventral/posterior forming a large tumor mass

Summary of orthotopic GBM patient-derived xenografts (PDX).

Conclusions

Preoperative identification of targets for tissue harvest combined with physiological tissue collection and processing yields GBM PDX models that are reflective of the typical features associated with GBM in regards to cell migration and invasion. We demonstrate that different GBMs have distinct patterns of invasion and migration. These preliminary findings indicate that the murine GBM avatar is a suitable model to study GBM migration and invasion.

References

Pollard et al (2009) Cell Stem Cell, 4, 568