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Glioblastoma E PIM Kinase

Lucia Lisi and Pierluigi Navarra*

Department of Pharmacology, Catholic University of the Sacred Heart, Italy

Short Communication

Glioblastoma (GBM) is a malignant astrocytic tumor (grade IV, according to the WHO classification) and the most aggressive and undifferentiated primitive brain tumor. GBM has a year-incidence of about 3/100.000 and prevalence of 1-9/100.000 [1]. Beside the surgical option, the gold standard of therapy consists of fractionated radiotherapy associated with temozolomide. Such treatment barely improves GBM patient's survival: in most cases, resistance to chemotherapy occurs and recurrence is common. After first-line treatment, GBM patients show a median survival of about 15 months, with only 10% of patients surviving at 5 years [2]. Hence, a need exists for the development of novel effective therapies; new agents should be able not only to easily cross the Blood-Brain Barrier (BBB), but also to target all cell types of tumor cell environment. The Proviral Integration sites for Moloney murine leukemia virus (PIM) family of serine/threonine-specific kinases consists of three members, PIM1, PIM2 and PIM3 [3]. Overexpression of PIM family members has been reported in various human hematological malignancies or solid tumors (e.g., prostate, pancreatic and gastro-intestinal cancers), and has been associated to advanced/metastatic cancer stages and poor patient survival [4]. Although PIM genes are up regulated in several malignancies and behave as oncogenes in many cellular and animal models, the correlation between PIM overexpression and clinical outcome varies depending on the PIM family member involved and type of cancer [5]. PIM subtypes are currently thought to as druggable targets to develop selective inhibitors for the treatment of various tumors. The number of small molecules generated by academia and pharmaceutical industry has steadily increased in the last years [6]. Early-phase clinical trials showed promising anti-cancer activity, but side effects -probably related to poor selectivity- proved problematic. Human GBM expresses higher levels of PIM1 compared to normal brain, and inhibition of PIM1 results in reduced GBM cell viability [7]. In addition, pharmacologic inhibition of PIM kinases impairs growth of patient-derived glioma sphere cells [8]. In this context, we analyzed 'The Cancer Genome Atlas' (TCGA) database, seeking for possible relationships between PIM gene expression and GBM overall survival. TCGA enlists 702 GMB cases, 690 out of 702 having data on PIM family gene expression. By dividing these cases in 2 subgroups based on PIMs expression levels, we found that survival is positively associated to lower PIM expression

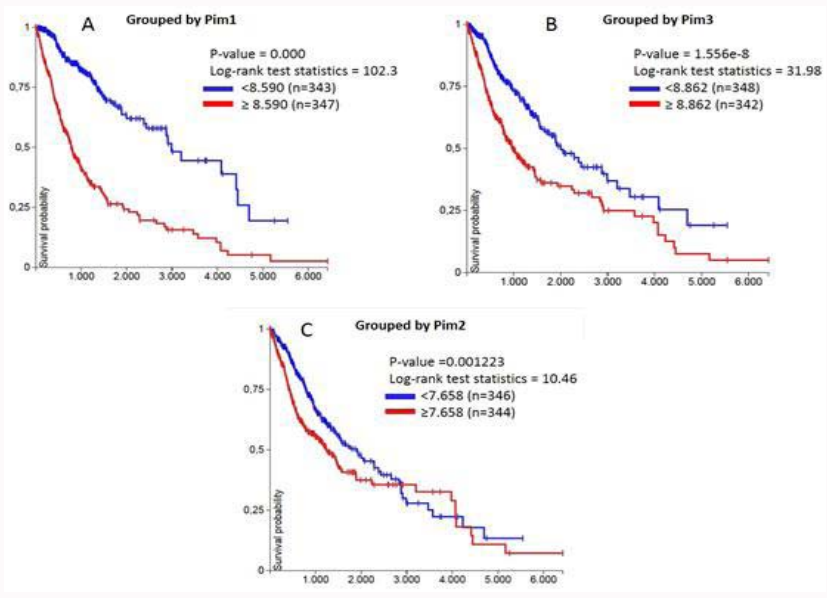

Figure 1: Analysis of PIM1 A) PIM3 B) and PIM2 C) gene expression and survival on TGCA data base.

Correspondence:
Lucia Lisi, Department of Pharmacology, Catholic University of the Sacred Heart L.go F Vito 1, 00168 Rome, Italy,
E-mail: lucia.lisi@unicatt.it

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levels (Figure 1). In particular, a strong positively correlation exists between survival and lower PIM1 expression (Figure 1A); to a lesser extent, a positive correlation also exists between survival and low PIM3 expression (Figure 1B), whereas a minimal correlation (although statistically significant) emerged between survival and PIM2 expression (Figure 1C). To date, no systematic studies of expression and functional characterization of PIM family in GBM microenvironment have been conducted. In conclusion, further studies on the role of PIM family in GBM pathology are desirable. In doing so, it will be useful to study PIM kinase both in GBM cells and tumor microenvironment. Thinking to drugs, based on the above data dual 1-3 inhibitors, possibly endowed with ease BBB crossing, should prove most useful.

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