sunitinib doses (10 and 100 µM) after 72-hours generated the greatest response, whilst a moderate reduction in VEGF cytokine levels occurred after 48 hours. The human glioblastoma U87 cell line expresses upregulated VEGF levels (Ke et al., 2000, Mesti et al., 2014). The addition of exogenous VEGF to glioblastoma cells consequently resulted in increased phosphorylation of major intracellular signaling pathways, including PI3K/Akt and MAPK pathways, known to propagate glioma cell proliferation and tumor progression (Knizetova et al., 2008). This indicates VEGF's prominent role in glioblastoma cell proliferation and reducing its cytokine levels could prove to be effective in opposing glioblastoma aggressive growth capacity.

As seen from prior and current observations, glioblastoma tumor cells are a great source of VEGF (Pore et al., 2003). VEGF which acts via paracrine signals on vascular endothelial cells, activating cellular processes such as cell proliferation and angiogenesis, is a current paradigm for targeting in several malignancies (Villegas et al., 2005). Emerging from this, the notion of autonomous cell proliferation signaling in glioblastoma has been postulated as discussed in Chapter 1 (Pathogenicity of Glioblastoma Multiforme). The criteria for autonomous cell signaling stem from co-expression of VEGFRs and VEGF. Although, Mesti et al. (2014) showed little to no expression of VEGFR-1 and VEGFR-2 in U87 glioblastoma cells, some studies have opposed this. Knizetova et al. (2008) showed VEGFR-1 and VEGFR-2 co-expressed with all 3 VEGF isoforms ($VEGF_{189}$, $VEGF_{121}$, $VEGF_{165}$) in the U87 cell line. The co-expression of these RTKs further suggests that the VEGF/VEGFR pathways in glioblastoma function under autonomic cell signaling for tumor cell proliferation.

VEGF expression and secretion is well-regulated in glioblastoma neoplasms. Pore et al. (2003) showed that when U87 cells were exposed to EGFR or PTEN wild-type PI3K/Akt pathway inhibitors, VEGF mRNA levels and VEGF secretion were reduced. Similarly, glioblastoma cells exposed to a selective VEGFR-2 inhibitor, abrogated the prominent phosphorylated state of intracellular signaling pathways such as PI3K/Akt and MAPK pathways (Knizetova et al.,

2008). In fact, sunitinib was shown to reduce the phosphorylated state of these intracellular pathway intermediates in glioblastoma cell models (Martinho et al., 2013, Moeckel et al., 2014). Based on the evidence from the literature, and placed within the context of current study, we hypothesize that the observed anti-VEGF activity in U87 cells could be influenced by sunitinib's ability to inhibit RTKs such as VEGFR resulting in intervention in the major intracellular signaling pathways known to be role players in enhanced cell growth. However, this postulation requires further discretion which could form part of impending studies.

4.3.8 PDGF-BB Secretion Undetected in U87 Glioblastoma Cells

In contrast to VEGF secretion analysis, the study found undetected PDGF-BB cytokine secretion from U87 glioblastoma cells after exposure to increasing concentrations of sunitinib. This was true for both the experimental and control groups. Although it was highly anticipated that PDGF-BB will be expressed and secreted by tumor cells (Takeuchi et al., 2004, Hosaka et al., 2013), our findings are contradictory to previous reports, but nonetheless supported by Karcher et al. (2006). The authors showed via immunohistochemical analysis that all PDGF isoforms were weakly expressed in glioblastoma cells, but more specifically immunosorbent analysis showed no detectable PDGF-BB cytokines, whilst moderate levels of PDGF-AB levels and extensive VEGF-A secretions were detected (Karcher et al., 2006). Further in corroboration of the current study, neuroblastoma cell secretions contained no detectable PDGF-BB cytokines (Hosaka et al., 2013). Therefore, based on our results, we can support the notion that U87 glioblastoma weakly secretes PDGF-BB. However, further confirmatory analysis is required to support our current findings which could possibly form part of experimental designs for further exploration of the current study.

Several studies have proposed an autonomous cell signalling pathway via glioblastoma-derived PDGF activation of PDGFRs expressed on tumor cell surfaces (Takeuchi et al., 2004, Martinho et al., 2009). For this to be true, it is imperative for both PDGF and PDGFR to be co-expressed to allow for further enhanced tumor cell proliferation (Hermanson et al., 1992). However,

considering the undetected U87 PDGF-BB cytokine levels, the present study could possibly dismiss this phenomenon. Instead, the lack of PDGF-BB cytokines could rather potentiate paracrine glioblastoma cell growth whereby extracellularly-sourced-PDGF stimulates PDGFR expressed on tumor cells itself. Indeed, PDGFR is highly expressed in glioblastoma tumors and cell lines (Fleming et al., 1992). It is noteworthy that although this study suggests the paracrine cell stimulus hypothesis, extensive research is required for further validation of such a mechanism and thus our findings would serve as a preliminary set of experimental results.

4.3.9 Overall Effect of Sunitinib on U87 Glioblastoma Cell Proliferation

After investigating the effects of sunitinib on U87 cell growth by analysis of cellular morphological changes, viable cell counts and measurement of mitochondrial dehydrogenase activity in viable cells, sunitinib was demonstrated to exert U87 cell growth inhibition. The overall greatest decrease in glioblastoma cell viability was shown to occur at higher concentrations of sunitinib along with increased treatment duration.

CHAPTER 5

CONCLUSION AND STUDY LIMITATIONS

5.1 Conclusion

The current study determined sunitinib's cytotoxic efficacy against neuroblastoma and glioblastoma cell proliferation. Sunitinib induced similar cellular morphological changes in both cell lines which induced cellular distress and visible cell death at high concentrations. However, when considering the quantitative measurement of cell viability, U87 glioblastoma cells were more responsive to sunitinib treatments as opposed to SK-N-BE(2) neuroblastoma cells. This could be due to the biological nature of each malignant cell line such as increased resistance capacity towards selective drug treatments. Nonetheless, both SK-N-BE(2) and U87 cells exhibited significant reduced cell viability most notably after treatment with high doses of sunitinib. Based on the present findings, sunitinib showed the greatest cell growth inhibition at higher concentrations. Additionally, sunitinib's effectiveness was further explored against VEGF and PDGF-BB cytokine secretions. Overall, sunitinib induced the greatest reduction in VEGF secretions from U87 cells when considering the outcome of SK-N-BE(2) VEGF secretions. More interestingly, PDGF-BB cytokine secretions were undetected for both U87 and SK-N-BE(2) cells. Concluding from the results of the current study, sunitinib's inhibition of selective RTKs (e.g. VEGFR) resulted in a consequential reduction in VEGF cytokine secretion which, based on previous literature, can be directly linked to reduced cell viability. The study suggests sunitinib as a possible anti-proliferative agent for neuroblastoma and glioblastoma cell lines via the VEGF/VEGFR signaling pathway. However, further studies are required to validate the current study's findings.

5.2 Limitations

As much as the outcome of the present study was significant, limitations and insights emerged:

- The study was limited to the selected assays utilized due to funding constraints. Additional assays are often incorporated into experimental designs to evaluate the proliferative effects and efficiency of selected drug treatments on cells such as apoptosis, cell cycle arrest analysis and multidrug resistance analysis.

- ELISA kits are designed with high precision which allows for highly accurate results. However, after cytokine analysis, Western blot analysis is often required to further support and confirm ELISA results. It is unfortunate that the current study was constrained and therefore could not perform these supporting proteomic analyses.

- This study was limited to the use of sunitinib, and although sunitinib is a multitargeted receptor tyrosine kinase inhibitor (TKIs), combination therapy has been reported to have a higher pharmacological efficacy (potency). Additionally, a comparative study between various selected TKIs would have provided a much broader spectrum of possible treatment strategies.

- The current study was limited to VEGF and PDGF cytokine analysis. Evaluating additional growth factors and their receptors such as EGF/EGFR which are often increased in glioblastoma and neuroblastoma, would have provided additional malignant proliferative targets.

- Nonetheless, due to the nature of the study and availability of resources and funding opportunities, the study was restricted to *in vitro* analysis and therefore the findings could not be relayed to *in vivo* or possibly clinical studies. However, these shortcomings may inform and refine an array of prospective studies.

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