microenvironment has classically been associated with "space clearance" for GBM via excitotoxic damage. However, an increase in glutamate activation of mGluR5 can also increase the NAS/melatonin ratio. As such, much of the plasticity within the GBM/GSC microenvironment may be driven by processes that control mitochondrial metabolism and the mitochondrial melatonergic pathway. Mutations, epigenetic alterations and changes in the diverse array of receptors and intracellular signalling pathways may mediate their effects via their interactions with higher-order processes acting to regulate the mitochondrial melatonergic pathway.

Chemo-resistance may be seen in this context, whereby resistance to temozolomide or tamoxifen that often emerge following surgery for GBM/GSC may be seen as a mechanism in which GBM/GSC manage to maintain this control over the mitochondrial melatonergic pathway across different cells of the tumour microenvironment. This does not necessarily suggest total inhibition of melatonin production in the cells of the GBM/GSC microenvironment, but it does indicate that regulation of this pathway is of crucial importance. Future research should clarify the regulation of NAS and melatonin in different cell compartments. For example, melatonin uptake into mitochondria in oocytes is mediated by the peptide transporter (PEPT) 1/2[133], the regulation of which may be crucial to the compartmental regulation of melatonin under specific conditions. Other changes in the cell may arise as a consequence of this, and possibly correlate with GBM/GSC maintenance, but would be arising from the need to regulate the mitochondrial melatonergic pathway and not because these other changes are crucial per se. Changes in circadian genes and the impact of the circadian rhythm may also be seen in this context. Such a model highlights the hierarchical influence of patterned transcriptions driven by mitochondrial function, and the key role that alterations of the mitochondrial melatonergic pathways have in driving such patterned changes.

As 14-3-3 stabilizes AANAT, the mitochondrial melatonergic pathway can also be regulated by 14-3-3 protein levels. 14-3-3 is expressed in mitochondria, with down-regulation of 14-3-3ζ induced by ceramide, sensitizing GBM to apoptosis, indicating a role for 14-3-3ζ in GBM/GSC chemoresistance[65]. Heightened expression levels of 14-3-3ζ in GBM patients are associated with a poor prognosis[64]. As to whether this is mediated by 14-3-3ζ stabilization of AANAT, leading to enhanced activation of the mitochondrial melatonergic pathway that is biased towards an increase in NAS production and TrkB activation requires investigation. A decrease in 14-3-3γ inhibits the stem-like qualities of GSC[13], whilst the downregulation of 14-3-3β induces senescence in GBM/GSC[134]. Clearly, different 14-3-3 isoforms are important to GBM/GSC survival, which may be closely linked to 14-3-3 regulation of the mitochondrial melatonergic pathway.

Overall, the mitochondrial melatonergic pathway may be intimately linked to the plethora of diverse data associated with GBM/GSC pathophysiology. The melatonergic pathway has been evident from the beginning of cell evolution, being present in the first bacteria to become integrated into an early cellular structure that ultimately evolved into mitochondria[135]. Consequently, the melatonergic pathway has been an integral aspect of mitochondrial and cellular evolution and therefore, with the various mitochondrial factors, such as sirtuins, and processes such as metabolism, that underpin the function and survival of GBM/GSC and the cells of the tumour microenvironment.

FUTURE RESEARCH

Does the increased YY1 in tumours associate with heightened levels of CYP1B1, mGluR5, P2Y1, *O*-demethylation and CYP2C19, and thereby with the "backward" conversion of melatonin to NAS and TrkB-driven GSC, survival and proliferation?

Does YY1-miR-135b inhibition of Bmal1 modulate OXPHOS in GBM/GSC over the circadian rhythm?

What is the influence of the circadian rhythm on gene expression in GBM/GSC, and in the cells of the tumour microenvironment, including miRNAs?

Do GBM/GSC determine the nature of the tumour microenvironment via the realignment of immune cell circadian rhythms and associated regulation of mitochondrial metabolism and the mitochondrial melatonergic pathway?

Does YY1-induced miR-135b regulate TNF receptor associated factor (TRAF) 2, given both miR-135b[136] and TRAF2[137] attenuate the transcriptional activity of Bmal1?

The AhR is an important regulator of the circadian rhythm, including by forming a heteromer with Bmal1, thereby inhibiting Bmal1's influence on the circadian amplitude and metabolism[138]. AhR expression levels and activation over the circadian rhythm in GBM and GSC will therefore be important to determine.

As mGluR5 activation on microglia/macrophages can increase TrkB activation and BDNF production[139], is this mediated via increased NAS?

As butyrate, via HDAC inhibition, modulates not only mast cell activation[34] but increases GBM and GSC apoptosis[24,25], do inducers of gut dysbiosis/permeability, such as stress, alcohol and diet, then impact on GBM/GSC pathoaetiology and pathophysiology via gut dysbiosis/permeability?

In some cells, sodium butyrate can increase AhR-induced induced CYP1[140]. This will be important to determine in GBM/GSC, especially the impact, if any, of sodium butyrate on CYP1B1-driven 'backward' conversion of melatonin to NAS over the circadian rhythm.

Do activated mast cells suppress GSC pathoaetiology, as indicated by the negative correlation of allergies and GBM development[141]?

Is there a role for mast cells in GBM/GSC pathophysiology, given mast cell suppression of GBM proliferation and migration, as well as their suppression of GSC self-renewal capacity and stemness markers[142]? What is the role of mast cell melatonin production[143]?

As wild-type p53 induces AhR-driven CYP1B1, does the resulting NAS suppress the apoptotic effects of wild-type p53 in GBM/GSC?

The roles of the ceramide/S1P ratio in the regulation of mitochondrial function, metabolism and melatonergic pathway in GBM/GSC and the cells of the tumour microenvironment will be important to determine.

Leucine zipper-EF-hand containing transmembrane protein (LETM) 1 is classically associated with mitochondria ionic regulation via pore formation across the mitochondrial membranes. LETM1 is highly expressed in many different types of tumours, especially in cancer stem cells, and is associated with poor prognosis[144]. As the C-terminal of LETM1 in the mitochondrial matrix has a 14-3-3-like motif, can this motif stabilize mitochondrial AANAT [145]?

As PTEN-induced kinase (PINK) 1 phosphorylates and optimizes LETM1 function, the loss of PINK1 in GBM/GSC[146] will modulate not only mitochondrial ionic regulation but potentially impact upon the mitochondrial melatonergic pathway. This requires investigation as potentially this links previously diverse bodies of data pertaining to GBM/GSC survival and chemoresistance, especially as Ca^{2+} dysregulation is evident in GBM mitochondria[147].

Given Bmal1 and SIRT1 mutually induce each other in non-neoplastic cells[129], it requires investigation as to the interactions of Bmal1 and sirtiuins in the regulation of mitochondria and the mitochondrial melatonergic pathway. Resveratrol, a SIRT1 inducer, affords protection in GBM/GSC and has recently been proposed as an adjunctive in GBM/GSC treatment[148], with the induction of SIRT1 having effects that include regulation of the GBM/GSC microenvironment[149]. As noted above, resveratrol also inhibits AhR, suggesting that it will have an impact on the NAS/melatonin ratio. The interactions of sirtuins with resveratrol and the melatonergic pathway will be important to determine.

TREATMENT IMPLICATIONS

It is highly likely that melatonin per se, as well as its adjunctive use with chemotherapy, will have positive benefits on GBM/GSC patient outcomes[150].

Ultrasound-induced local BBB disruption may allow for an increased availability of the wide array of factors that have been shown in preclinical studies to suppress GBM/GSC[151], and may allow for an increased invasion of mast cells as well as other melatonin producing cells into the GBM/GSC microenvironment. Whether mast cells or other cells chemoattracted to the GBM/GSC microenvironment can be primed for an increase in melatonin release and/or for the inhibition of the 'backward' conversion of melatonin to NAS will be interesting to investigate.

Melatonin increases miR-149[152], which is epigenetically suppressed in GBM[153], with miR-149 and miR-128 increasing chemosensitivity to temozolomide[154].

Given the efficacy of butyrate in the induction of senescence in GBM[25] and apoptosis in GSC[24] as well as increasing chemosensitivity and suppressing YY1[31], it requires investigation as to the clinical utility of sodium butyrate in the management of GBM/GSC, including as an adjunctive to chemo-and radio-therapy.

Given that the maximal toxicity of temozolomide is optimized by the upregulation of the circadian gene, *Bmal1*[5], it would seem likely that research to clarify the roles of circadian genes, circadian rhythm and the melatonergic pathway, will provide ways of improving clinical utility and treatment outcomes.

CONCLUSION

Chemoresistance is common in GBM/GSC, being reflective of the plasticity of response and adaptation that is inherent in the tumour microenvironment. The above would indicate that the mitochondrial melatonergic pathway might be an important aspect, if not driver, of the plasticity in the intercellular interactions of the cells of the tumour microenvironment. The incorporation of the mitochondrial melatonergic pathway provides a conceptual frame of reference that better integrates the diverse array of previously disparate data on the biological underpinnings of GBM/GSC. This has implications for understanding the ubiquitous radio- and chemo-resistance that are evident in GBM/GSC as well as providing novel, and readily achievable, treatment targets.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

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The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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