

Angiogenesis Inhibition in Glioblastoma

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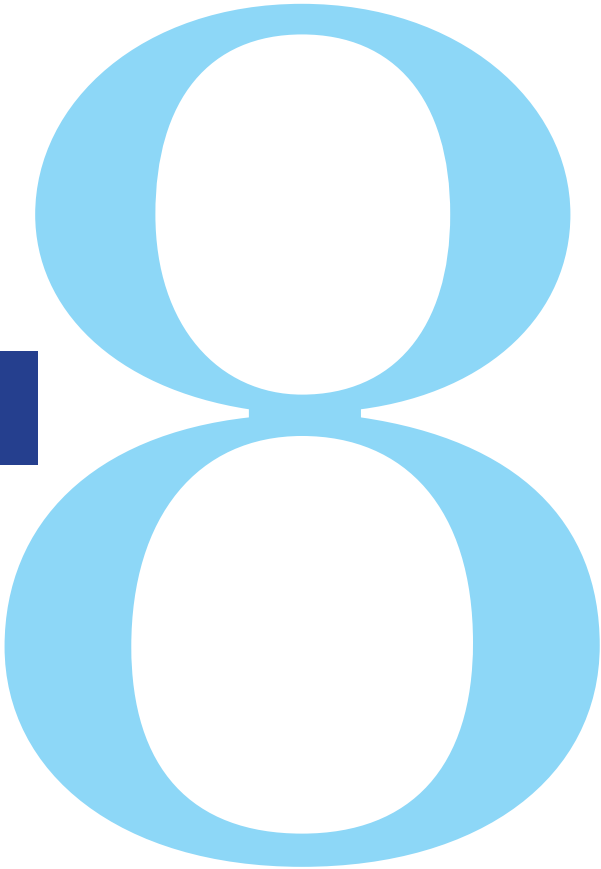
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Chapter 8



Summary en Nederlandse samenvatting

Summary

Taken together these findings highlight the complicated process that underlies angiogenesis in glioblastoma. The clinical challenges for the future will be to use this knowledge to overcome the therapeutic challenges to effectively use the angiogenesis inhibitors in the patients that will most likely respond to the treatment. Based on our data bevacizumab can inhibit the transformation from endothelial progenitor cells to endothelial cells, but has no influence the formation of endothelial progenitor cells from BTSC. It was possible to inhibit this step by a notch inhibitor that was found to be safe in a phase 0/1 trial²¹. It is therefore possible that notch inhibitors can augment bevacizumab to effectively inhibit angiogenesis in future trials. To test these hypotheses the organotypic “explant” system, that is ideally suited for these questions, can be used and may decrease the need for tests in animal models. The finding that EGFR amplification and classical subtype make glioblastoma less likely to respond to bevacizumab can be used to select patients on the basis of molecular characteristics of the tumor of the patient. Additional investigations are required to further validate this finding as well as to investigate the mechanistic basis for bevacizumab propensity to fail in the setting of amplified EGFR. One possibility is that EGFR amplified tumors have a higher percentage of endothelial cells that are derived from BTSC, but this remains to be proven. Despite the lack of effect of overall survival in trials to date, angiogenesis remains a hallmark of cancer and is considered a rate limiting step in carcinogenesis. To be able to effectively interfere in this process will have beneficial therapeutic effect, stand alone or in combination with cytotoxic treatments or immunotherapy, and is without a doubt worth the research effort.

Nederlandse samenvatting

Samengevat laten de bevindingen in deze thesis het gecompliceerde proces dat aan angiogenese ten grondslag ligt zien. De klinische uitdaging voor de toekomst is om deze kennis toe te passen om effectief gebruik te maken van angiogenese remmers bij patiënten die de meeste kans hebben er goed op te reageren. Onze data laat zien dat de VEGF remmer bevacizumab de transformatie van voorloper endotheelcellen naar endotheelcellen kan remmen, maar geen effect heeft op de vorming van voorloper endotheelcellen door hersentumor stamcellen. Dit was wel mogelijk met een notch remmer die veilig was bevonden in een fase 0/1 trial¹. Het is daarom mogelijk dat notch remmers gecombineerd met bevacizumab effectiever angiogenese kan remmen in toekomstige trials. Om deze, en andere hypothesen te testen is het in dit proefschrift beschreven organotypic “explant” model erg geschikt en kan ervoor zorgen dat minder dierproeven nodig zijn. De bevinding dat EGFR amplificatie en glioblastomen met het “classical” subtype minder goed reageren op behandeling met bevacizumab kan gebruikt worden om patiënten te selecteren voor behandelingen op basis van moleculaire eigenschappen van de tumor. Verder onderzoek is nodig om deze bevindingen te bevestigen en om een mechanistische verklaring te vinden voor het falen van angiogenese remming bij tumoren met EGFR amplificatie. Een mogelijke verklaring is dat EGFR geamplificeerde tumoren meer endotheelcellen hebben die van hersentumorstemcellen afkomstig zijn, maar dit is nog niet bewezen.

Ondanks het gebrek aan toename van overleving in trials met angiogenese remmers bij patiënten met een glioblastoom blijft dit proces een essentieel onderdeel bij het ontstaan van kanker. Als het lukt om effectief te interveniëren in dit proces, zal dat ongetwijfeld leiden tot een gunstig therapeutisch effect. Als alleenstaande behandeling of in combinatie met immunotherapie. Het is daarom zonder twijfel de wetenschappelijke inspanning waard.