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Geneeskunde & Farmacie

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PhD in Medical Sciences
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Openbare verdediging van/*Public defence of*

Shasha LV

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'**DOCTOR IN DE MEDISCHE WETENSCHAPPEN**'
To obtain the academic degree of
'***DOCTOR IN MEDICAL SCIENCES***'

Role of molecular alterations in targeted therapies in patients with recurrent glioma

Promotor: Prof. J. De Grève
Co-promotor: Prof. B. Neyns, dr. E. Teugels

Wednesday 10 October 2012
Auditorium Brouwer, 15:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

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Situering van het proefschrift/*Summary of the dissertation*

This thesis studied the role of the deletions in epidermal growth factor receptor (EGFR) gene and the point mutations in isocitrate dehydrogenase 1 (IDH1) gene in formalin-fixed paraffin-embedded (FFPE) glioblastoma samples as well as the functional effect of IDH1R132H mutation *in vitro*. The deletion mutation of the N-terminal domain of EGFR, EGFR variant III (EGFRvIII) and the deletion of C-terminal domain of EGFR, EGFR variant IV (EGFRvIV) were investigated in FFPE glioblastoma tumor samples from the patients treated with anti-EGFR monoclonal antibody, cetuximab. EGFRvIII and EGFRvIV were both discovered exclusively in tumor with EGFR gene amplification. Additionally, a particularly favourable survival for the subgroup of patients with EGFR amplification but without EGFR variant III gene expressions was demonstrated (chapter 3).

Apart from EGFR deletions that were found frequently in secondary glioblastoma, IDH1 mutation was correlated with secondary glioblastoma and a younger age of patients. In addition, IDH1 mutation was correlated with the gene copy number increase of vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor alpha (PDGFRA) and stem cell growth factor receptor (KIT) but inversely correlated with EGFR gene alteration status. Furthermore, it was shown that patients with IDH1 mutation were prone to have a longer overall survival when treated with anti-VEGF(R) agents, however, a shorter overall survival after treated with anti-EGFR agents (chapter 4).

Distinguishing from the translational investigations, the next part of this thesis focused on in vitro study of IDH1 R132H mutation, which demonstrated the contribution of IDH1 R132H mutation to the growth and invasion of glioblastomas cells as well as to the targeted treatments. Cells transfected with IDH1 R132H mutation grow more slowly than cells without and a similar result was observed in a cell invasion assay. Limited effect of anti-EGFR agents was found on inhibiting cell growth whereas anti-VEGF agent did inhibit cell growth in a dose-dependent manner, and independent of the IDH1 mutation status. (chapter 5). The in vitro model could be used in the future to investigate therapeutic interventions for glioma carrying an IDH1 mutation.

Curriculum Vitae

Shasha Lv was born on 26 June 1983 in Shaanxi, China. From 2001 to 2008, she studied clinical medicine at Xi'an Jiaotong University in Shaanxi and obtained her Master degree on Ophthalmology at May 2008. From October 2008, she started her PhD research on translational cancer research of glioma in the Laboratory of Medical and Molecular Oncology (LMMO) of the Medical Oncology Department, at the Oncology Center of the Vrije Universiteit Brussel (VUB). Her research resulted in publications in peer-reviewed life science journals. She has also been invited to present her research data in some national and international congresses. Her thesis resulted from the investigations of the biomarkers that contribute in the targeted therapy of high-grade recurrent gliomas.