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Geneeskunde & Farmacie

GF

Doctoraat Medische Wetenschappen
PhD in Medical Sciences
2012-2013

Openbare verdediging van/*Public defence of*

Dehui XU

Voor het behalen van de academische graad van
'**DOCTOR IN DE MEDISCHE WETENSCHAPPEN**'
To obtain the academic degree of
'***DOCTOR IN MEDICAL SCIENCES***'

The Role of Dll1/Notch Pathway in Multiple Myeloma Cell Proliferation, Engraftment and Drug Resistance

Promotors: Prof. K. Vanderkerken and Prof. E. Van Valckenborgh

Friday 14 December 2012
Auditorium Brouwer, 16:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

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Situering van het proefschrift/*Summary of the dissertation*

Multiple myeloma (MM) is an incurable B cell malignancy characterized by accumulation of malignant plasma cell (PC) in patients' bone marrow (BM). Relapse and drug resistance are two main challenges in MM treatments. The BM microenvironment plays a critical role in MM pathogenesis and development. The Notch pathway is a highly conserved pathway regulating cell fate determination, stem cell self-renewal, proliferation and apoptosis. Notch receptors and ligands are expressed both in MM cells and the BM microenvironment. In this study, we demonstrated that Dll1 is present on BM stromal cells and Notch1 and Notch2 receptors were expressed by MM cells. Moreover, Dll1/Notch interaction could activate Notch signaling in MM cells mostly by Notch2 activation.We found that Dll1/Notch interaction could promote MM clonogenic growth and accelerate MM development in vivo. MM colony forming ability and MM initiation was significantly inhibited by the Notch pathway inhibitor, DAPT. This resulted in a delayed in vivo engraftment. Furthermore, we demonstrated that Dll1/Notch activation accelerates MM development mainly by promoting MM cell proliferation predominantly in CD138+ MM cells, by reducing the expression of p21 and p27 thus accelerating MM cell cycling. Next, we described that Dll1/Notch activation could induce drug resistance to bortezomib and DAPT could reverse the effect. Furthermore, CYP1A1, which is involved in drug metabolism, was upregulated by Dll1/Notch interaction. We further confirmed that inhibiting CYP1A1 by either α-Naphthoflavone (inhibitor) or CYP1A1-siRNA increases the sensitivity to bortezomib, suggesting that CYP1A1 is involved in bortezomib resistance. In addition, in vivo data showed that combination treatment of DAPT with bortezomib was able to increase bortezomib sensitivity and prolonged overall survival in the 5T33MM mouse model. Our study provides a potential strategy not only to overcome bortezomib resistance but also to delay or avoid relapse by Notch inhibition in MM therapy.

Curriculum Vitae

Dehui Xu was born on 8 May 1983 in Fujian province, China. From 2000 to 2005, he studied clinical medicine at Xi'an Jiaotong University in Shaanxi and obtained his Master degree on Genetics in May 2008. From October 2008, he started his PhD research about Multiple Myeloma in the Laboratory of Hematology and Immunology (HEIM), at the Myeloma Center Brussels of the Vrije Universiteit Brussel (VUB). His research resulted in publications in peer-reviewed life science journals. He has also presented his research data in national and international congresses.