

VU Research Portal

Oncogenic properties and targeting of chemokine receptors CXCR4, CXCR7 and US28

Delic, A.

2015

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Delic, A. (2015). *Oncogenic properties and targeting of chemokine receptors CXCR4, CXCR7 and US28*.

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

English Summary

In this thesis I describe the research I performed during my PhD, which focused on oncogenic properties of human chemokine receptors CXCR4, CXCR7 and viral chemokine receptor US28. The aim of my research was to provide a better understanding of chemokine receptor-induced oncogenic signaling and of potential targeting of this network.

Chemokine receptors are members of G protein-coupled receptor (GPCR) family. They bind chemokines, which attract immune cells that express a subset of chemokine receptors, to sites of inflammation and thereby initiate the process of pathogen clearance. Because of this important role in immune cell responses, chemokine receptors contribute to several disease types. In **Chapter 1** a detailed introduction is given on the chemokine receptor system with the focus on several disease types these receptors contribute to. Chemokine receptors can serve as drug targets because of the specific responses that they activate in immune cells. Some examples of successful targeting of the chemokine receptor family are described in the first chapter. In **Aim of the thesis** I explain why we are interested in investigating the oncogenic properties of specifically CXCR4, CXCR7 and US28 and what I hope to achieve with my research.

GPCRs in general, including chemokine receptors, can be targeted by several approaches. Most commonly, small molecules are designed that can bind specifically to the receptor of choice thereby disrupting its signaling ability and positively contributing to the disease state. Other approach is the use of antibody based therapeutics, which is described in **Chapter 2**, mainly focusing on the use of nanobodies. For targeting of chemokine receptor CXCR7 we have developed and characterized specific nanobodies, described in detail in **Chapter 3**. We show in this chapter that CXCR7 nanobodies are specific for this receptor and that they are able to block CXCR7 signaling in head and neck cancer both *in vitro* and *in vivo*.

Chemokine receptors CXCR4 and CXCR7 share the same ligand (CXCL12) and are known to interact by forming heterodimers or by activating and/or inhibiting each other's signaling pathways. In **Chapter 4** the CXCR4/CXCR7/CXCL12 axis is investigated in relation to interactions with epidermal growth factor receptor (EGFR) family in a breast cancer cell line endogenously expressing both CXCR4 and CXCR7. We found that EGFR family member HER2 is phosphorylated by stimulation of CXCR4 receptor by CXCL12, while CXCR7 is able to regulate the endogenous phosphorylation level of HER2. Furthermore in this chapter we outline a hypothesis to explain the cross-talk of CXCR4/CXCR7/CXCL12 axis with HER2 in HER2-positive breast cancer cells.

English Summary

Oncogenic signaling networks activated by CXCR4 and CXCR7 in the same breast cancer cell line are explored further in **Chapter 5** by means of Reverse Phase Protein Array (RPPA). The advantage of such an approach is that a large number of phosphorylated proteins are investigated within the same sample set. The cells were stimulated by CXCL12 for various amounts of time, in the presence or absence of selective inhibitors of CXCR4 and CXCR7. An unsupervised correlation-based analysis found that several phospho proteins were specifically modulated by CXCR4 or CXCR7 and others by both in non-additive ways.

HCMV-encoded viral chemokine receptor US28 is the third receptor that was investigated in this thesis. In previous studies this receptor was shown to promote tumorigenesis by constitutively (in absence of ligand) activating several pathways leading to tumor growth. In **Chapter 6** we show that US28 is able to activate hypoxia induced factor 1 (HIF-1), a regulator of angiogenesis and energy metabolism. By activation of HIF-1 US28 regulates cellular proliferation and secretion of angiogenic factor VEGF.

Finally, in **Chapter 7** the obtained results are discussed and put into a broader perspective to show the relevance of the work described in this thesis. In short, the signaling axis of the investigated receptors CXCR4, CXCR7 and US28 in oncogenic setting is further characterized and the range of control this system exerts on cancer cells is extended. Further exploitation of therapeutic targeting of CXCR4, CXCR7 and US28 should be of interest in combination with already existing therapies.