Stellingen behorende bij het proefschrift

Redox-Controlled Signaling in Normal Myeloid Cells and Leukemia

1 The membrane distal cytoplasmic region of the granulocyte colony-stimulating factor receptor (G-CSFR) plays an important role in the control of myeloid differentiation. Previously, it was postulated that this region contains a so called 'differentiation domain'. In the light of recent findings it appears that the prominent effect of this region on intracellular routing of activated receptors is most critical for ensuring a balanced signaling response essential for differentiation. (***Chapter 2, this thesis***)

2 Loss of either Prdx4 or Ptp1b; both localized to the endoplasmic reticulum (ER), has similar effects on signaling and proliferation in response to G-CSF arguing that these proteins control the same pathway activated upon stimulation with G-CSF. In order for Prdx4 and Ptp1b to execute their functions endocytosed G-CSFR complexes route via the ER. (***Chapter 2, this thesis***)

3 Inactive oxidized phosphatases are reactivated by antioxidants. The role that phosphatases might also play in reactivation of antioxidants has been vastly underestimated. Phosphatases also reactivate antioxidants by dephosphorylation of their tyrosines. (***Chapter 2, this thesis and In activation of Peroxiredoxin I by Phosphorylation Allows Localized H2O2 Accumulation for Cell; Cell 2010, February 19, 517-528***)

4 Negative regulation of G-CSF signaling by Prdx4 is completely dependent on the presence of cysteines in its catalytic site. (***Chapter 2, this thesis***)

5 The hyper-sensitivity of acute promyelocytic leukemia to G-CSF is not due to higher G-CSFR expression levels but due to reduced expression of peroxiredoxin 4 - the negative regulator of G-CSFR mediated signaling. (***Chapter 3, this thesis***)

6 Virus integrations are commonly found in genes sensitive to reactive oxygen species (ROS). These genes could be directly or indirectly involved in regulation of ROS levels or in ROS mediated signaling. Although viral integrations in these genes may have a direct effect on malignant transformation, it cannot be excluded that these integrations merely enhance the viral replication process. (***Chapter 4, this thesis***)

7 It is generally accepted that increased ROS levels, for instance caused by decreased antioxidant activity, may lead to tumor formation. However, it cannot be excluded that in many tumor types, elevated ROS levels are merely a reflection of the stressed condition of the tumor cells.

8 Cell lines that have adapted to 20% oxygen culture conditions as opposed to 3% oxygen under physiological conditions are not ideal for detecting nanomolar concentrations of ROS produced upon activation of receptors. Insensitive techniques to detect such low quantities of ROS further complicate matters.

9 Contradictory results related to the use of antioxidants as adjuvant therapy exist. The lack of detailed knowledge about the role of externally administered antioxidants in disease prevention and ageing should raise doubts about the generalized use of antioxidants for therapy. (***The antioxidant conundrum in cancer; Cancer Res. 2003 Aug 1; 63(15):4295-8***)

10 No matter how good your theory is, artificial and insensitive experimental conditions can easily prove it wrong.

11 When a man begins working with clear ideas, he always ends up with uncertainties. However only when he addresses the uncertainties, will he end up with clear ideas.

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