Delineating the DNA damage response using systems biology approaches

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Stellingen

behorende bij het proefschrift

Delineating the DNA damage response using systems biology approaches

1. A balance between p53-mediated elimination of stem cells, through loss-of-pluripotency and apoptosis, and Wnt signaling that attenuates this response tunes the outcome of the DDR (this thesis).

2. ARIH1 mediates DNA-damage-induced translation arrest, which protects stem and cancer cells against genotoxic stress (this thesis).

3. In response to DSB-inducing genotoxic stress, ARIH1 protein accumulates and interacts with 4ehp leading to increased recruitment of 4ehp to the 5'mRNA cap.

4. The integration of transcriptionally regulated metabolic enzymes and significantly affected metabolites allows identification of integrated metabolic networks that are responsive to genotoxic stress (this thesis).

5. The DDR, through the action of sensors, transducers, and effectors, orchestrates the appropriate repair of DNA damage and resolution of DNA replication problems, coordinating these processes with ongoing cellular physiology (Harper & Elledge, Mol Cell, 2007).

6. A better understanding of the cellular response to DNA damage will not only inform our knowledge of cancer development but also help to refine the classification as well as the treatment of the disease (Lord & Ashworth, Nature 2012).

7. Tumors with specific DNA repair defects can be completely dependent on back-up DNA repair pathways for their survival, which can be exploited therapeutically to induce synthetic lethality in tumor cells (Bouwman & Jonkers, Nature Reviews Genetics, 2012).

8. Given the functional interdependencies between the molecular components in a human cell, a disease is rarely a consequence of an abnormality in a single gene, but reflects the perturbation of the complex intracellular and intercellular networks that links tissue and organ systems (Barabasi et al., Nature Reviews Genetics, 2011).

9. Failure is a way of learning. If everything works perfectly from the start you will never have to question the route you are taking.

10. Systems biology – it feels as exciting as it sometimes feels impossible to understand the system as a whole, but that's no reason to quit trying.

11. If you feel lost in the smaller problems, it is important to take a step back and remember what you were aiming for: contributing a small part to the study of life and cure of disease.

Louise von Stechow , Leiden, 20 June 2013