Releasing the brakes: validating a new target for cancer drug development

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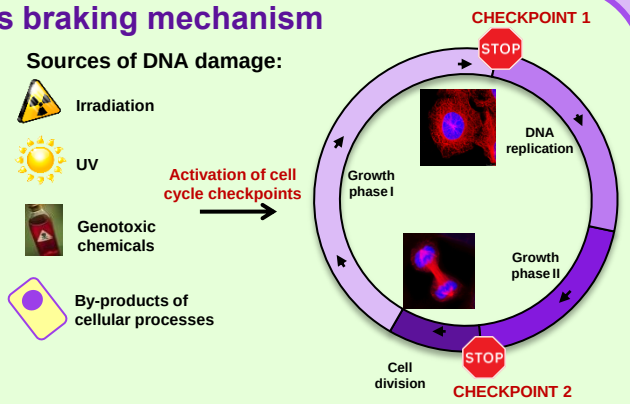
Checkpoints: the cell's braking mechanism

- Cell division is an essential process required by all living organisms to reproduce, grow and repair damaged tissue.
- This process is **highly regulated** to ensure the accurate generation of identical daughter cells. If this process becomes uncontrolled it can lead to **cancer**.
- Normal human cells have a set of inbuilt **control mechanisms** called **checkpoints**. These put a brake on cell division in the presence of damaged DNA to allow **time to repair** the damage before duplicating and dividing their DNA between daughter cells.

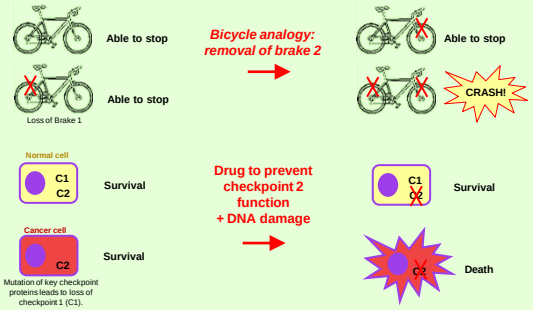
Sources of DNA damage:



The cell cycle is highly controlled to ensure identical daughter cell production upon cell division. In response to DNA damage, checkpoints are activated to brake the division process.

How can we target cancer cells?

- Many cancer cells have either **missing or weakened checkpoints** due to the mutation of proteins required for checkpoint activation.
- If you target the remaining checkpoints with specific drugs then the brakes are released and cells will die when exposed to DNA damaging treatments such as radiotherapy.



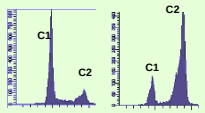
- **This project focuses on the protein, Nek11, which plays a role within checkpoint 2 in response to ionising radiation.**

Research aims

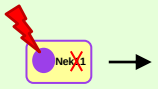
- **To investigate the role that Nek11 plays in colorectal cancer in response to DNA damage.**
- **To explore the potential of Nek11 as a target for colorectal cancer treatment.**

Methodology

- Using RNAi – a method to remove your protein of interest from the cell – we can investigate the effect on checkpoint activation after different types of DNA damage when Nek11 is missing.



Graph to the left shows the cell population profile for untreated cells. The graph on the right is the population of cells at each stage after irradiation treatment. Upon DNA damage most of the cells have now stopped at checkpoint 2.

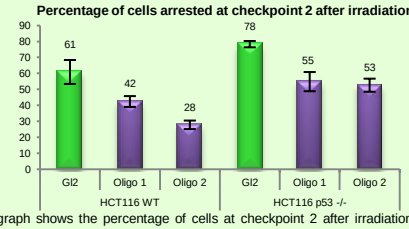


Are cells able to arrest at checkpoint 2?

Nek11 is removed from cells and exposed to DNA damaging agents. Cell cycle analysis will then be carried out to see if checkpoint function is affected upon removal of Nek11.

Results

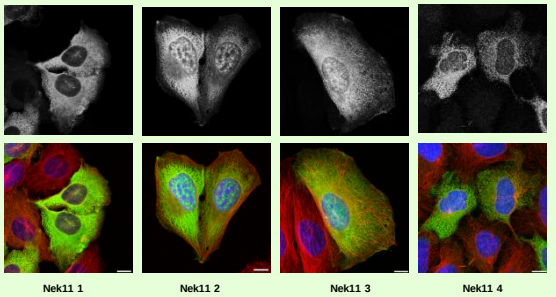
- **Nek11 is required for checkpoint 2 arrest after irradiation**



The graph shows the percentage of cells at checkpoint 2 after irradiation. When Nek11 is removed (oligo 1 and 2) we see a reduced fraction of cells at checkpoint 2 as compared to control (Gl2).

Q. What is the response of Nek11 depleted cells to other types of DNA damage?

- **Nek11 exists as four closely related variants. These show distinct localisation patterns in the cell.**



Images show localisation of four protein variants of Nek11 (green). Variants 1 and 4 show cytoplasmic localisation, whereas 2 and 3 show localisation to the nucleus (blue). These data suggest that the variants may play different roles within the cell.

Q. Do all variants play a role in checkpoint activation?

Conclusions

- Our findings to date support the hypothesis that Nek11 is essential for colorectal cancer cell survival after DNA damage and so could be an exciting target for the development of new anti-cancer drugs.
- Nek11 variants show different localisation patterns suggesting that they may have different roles within the cell.