Considering Mechanistic Data

Ted Simon, Ph.D. DABT

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Hypothesis: Ingestion of Cr(VI) acts by inducing DNA damage and subsequent mutations at the next cell division cycle (McCarroll et al., 2010)

- The occurrence of mutations in the k-ras gene in the target tissue in vivo and no dose-related effect was observed (O'Brien et al., 2013)
- Questions
  - Is the kras gene representative of other tumor-associated genes (e.g. p53, VHL)?
  - What is sufficient for a positive control in this study?

Hypothesis: Cr(VI) acts by causing de-differentiation of enterocytes to stem-like cells

- This would be an example of epithelial → mesenchymal transition, essentially a reversal of a developmental process
- Such a transition has been shown to occur in a double-mutant mouse (Schwitalia et al., 2013)
- Questions
  - How likely is such as process to occur in vivo?
  - Is this process consistent with accumulated knowledge of cancer biology (e.g. Trosko, 2014)?

The Hallmarks of Cancer

- Two papers by Hanahan and Weinberg detailed these hallmarks (2000 and 2011)
  - Sustained proliferative signaling
  - Evading growth suppressors
  - Activating invasion and metastasis
  - Enabling replicative immortality
  - Inducing angiogenesis
  - Resisting cell death / apoptosis
- How does any proposed MOA comport with these hallmarks?

Finally …

- Less is more --Mies van der Rohe
- If IRIS would provide details of the thinking about MOAs / AOPs as was done in the iAs effort, I believe the discussions at these meeting would be much more productive.
- Tight timelines and a rigid schedule may hinder the detailed consideration of scientific issues

References

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