Open Working Group Session on

Biomarkers of radiation sensitivity

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Biomarkers of Low dose – acute or chronic - Radiosensitivity.

Bioassays + genetic markers that can predict radiosensitivity.

+

- bioassays that can monitor radiation exposure.

Transciprional profiling, proteomics and miRNA profiling have all said genes activated after low doses are distinct to those after high doses – therefore processes may be different and hence biomarkers may be different.

What do we mean by radiosensitivity

- Main impact of high dose radiation exposure is extensive cell or tissue damage
- For low doses there is unlikely to be extensive cell or tissue damage.
- .accumulative Tissue damage (eg heart)
- carcinogenesis
- senescence or shortened lifespan
- stress response leading to any of the above.
- Sensitivity at developmental stages or specific tissues– eg developing brain, cataracts

Multiple end-points.

- Multiple end points and multiple tissues
- Therefore there will not be a single biomarker
- Should we focus on certain responses – NO obvious consensus to do this.
- Biomarkers may be superimposed on spontaneous effects eg FOXE biomarker for thyroid cancer.
- Multiple end points means that systems biology approaches may be useful to sort outthe relative contributions of the different processes.

Factors for consideration are:

- Will the damage/changes be accumulative
- Cell type for analysis – are lymphocytes reflective – decided cell types are ok

What are the mechanisms/processes : (1)

- DNA damage responses –

  Although the role may differ to high doses, they should still be considered - ROS damage may be more significant.

  If DNA damage persists longer it may activate signals for longer.

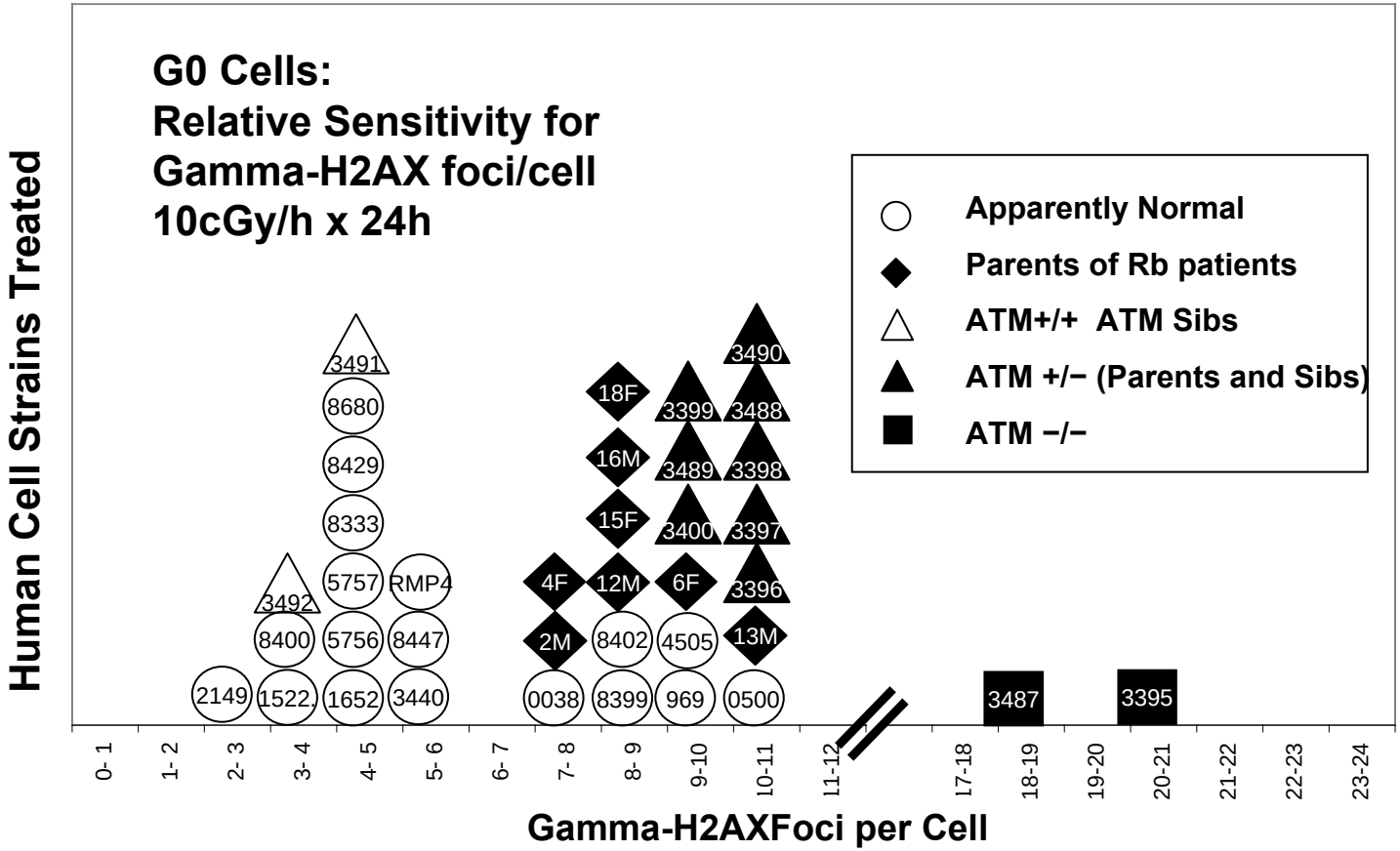
  g-H2AX assay is a useful test and studies have shown they can detect sensitivity to chronic low dose exposure in A-T hets, eg.

  High throughput and further endpoints of damage response signalling possible markers – but only likely to detect some aspect of sensitivity.

Can gH2AX foci predict over responders to chronic low dose IR

- Joel Bedford used gH2AX foci analysis following chronic low dose exposure of non-replicating fibroblasts

Used 10 cGy/h for 24 h. Then analysis of accumulated DSBs in Control, ATM-/- and ATM+/- cells (patient cells) and Rb+/- individuals



Kato, et al, DNA Repair 6, 818-829 (2007)

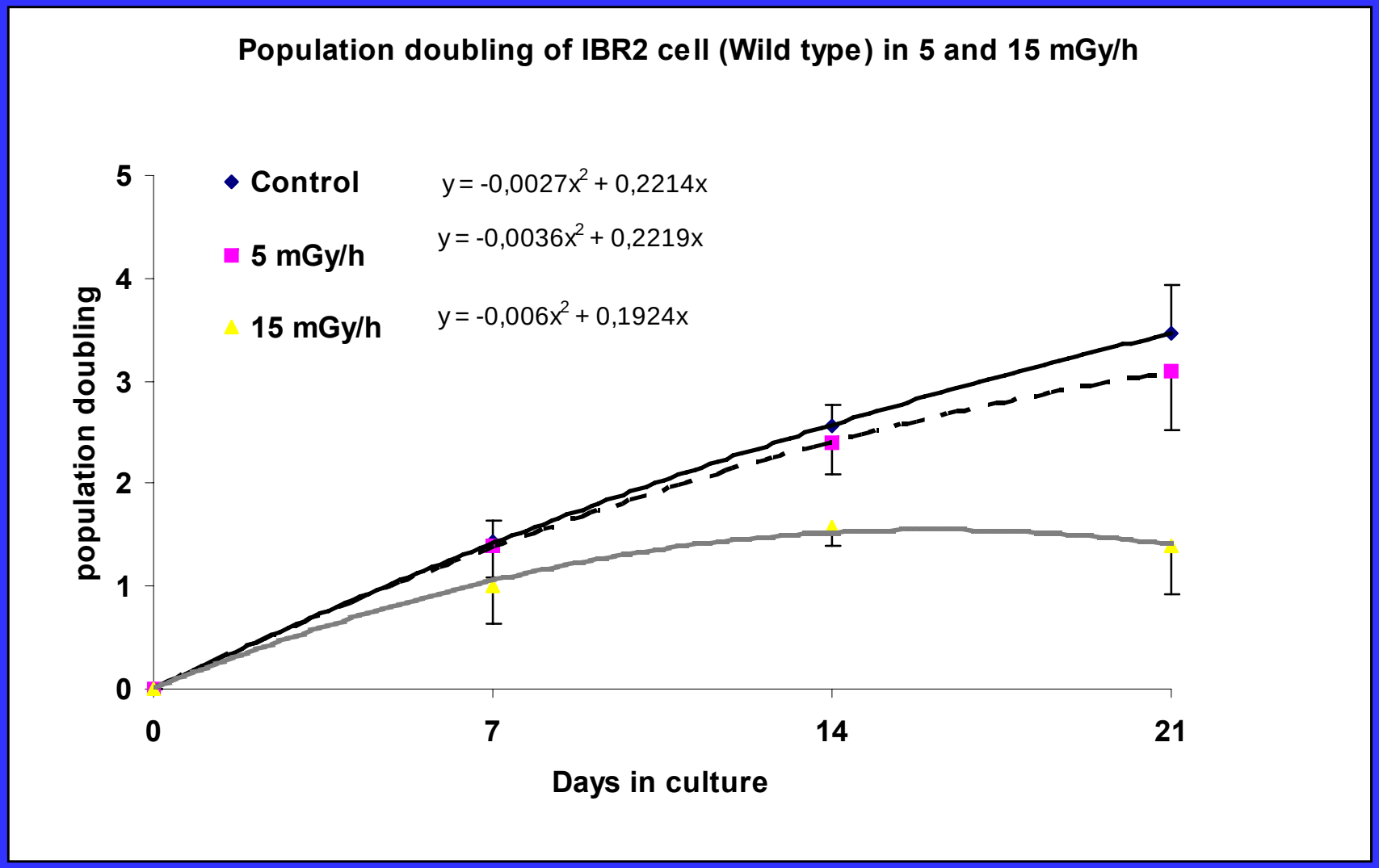
Activation of signalling: signalling responses may play a greater role than for high dose exposure

- Eg inflammatory response/cytokine signalling– could be very important for eg tissue sensitivity – TGFb or EGF15. – eg correlation with heart disease.
- Need to understand more about the inflammatory response but if hyperactivation is a correlate then could identify predictive assays.
- Bystander response – is it distinct from or same as inflammatory responses/cytokine signalling.
- This represents an important area for future research and for possibility of identifying/considering biomarkers

Activation of stress responses

- What do we mean by stress responses – need to know more
- Release of ROS likely to be important
- Premature senescence is induced by chronic low dose exposure (Harms-Ringdahl) – could be due to activation of stress response – can this predict biomarkers.

Control cells exposure ot 5 and 15 mG/H show enhance premature senescence or loss of proliferation



Mouse studies

- Can provide information for mechanisms + examine utility of biomarkers.
- Eg possibility to use Gfp-tagged proteins that are activated by low dose exposure – can see in what tissues the gene is activated – hence help to identify optimal tissues/systems for analysis.
- Mice eg ptch mouse which shows sensitivity can be combined with other backgrounds to identify additional sensitivity genes

Sensitivity of different tissues

- Discussed this for developmental sensitivity
- Possible immune system cells can be exploited since very sensitive, easy to examine and may provide a good biomarker cell type.

Epidemiology

- Use of epidemiology to predict past exposure may be difficult if end points are transient – ie window of analysis.
- What populations are sensitivity to low dose exposure?
- Can be exploited more usefully when we have more mechanisms

Long term identification of biomarkers.

- Need to know more about the mechanisms conferring sensitivity
- Need to know exactly what end points are caused by low dose exposure – eg all (or specific) carcinogenesis, specific tumours, heart disease, developmental stages.
- Need to understand more about stress responses and inflammatory response and impact of ROS activation
- May need to identify markers that superimpose on a spontaneous level of the same end points (or activated by other stresses).

Long term techniques

- Omics approaches
- Biomonitoring of plasma/urine – if metabolism altered in any way (short term exposure only maybe?).
- Markers of cytokine/stress signalling
- Systems biology because clearly a multi system response