Metabolic Complications in Childhood Cancer Survivors

School of Women's & Children's Health

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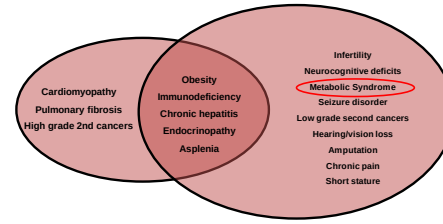
The Cost of Cure

Life-threatening ⟷ Life-altering



Severe/life -threatening conditions:
Oeffinger K : NEJM 2006;355:1572 – 42.4% at 30 years after diagnosis
Hudson M :JAMA 2013 – 80.5% at 45 years

Hyperinsulinemia, Impaired Glucose Tolerance, and Diabetes Mellitus in Survivors of Childhood Cancer: Prevalence and Risk Factors

Kristen A. Neville, Richard J. Cohn, Katharine H. Steinbeck, Karen Johnston, and Jan L. Walker

The Journal of Clinical Endocrinology & Metabolism 91(11):4401–4407

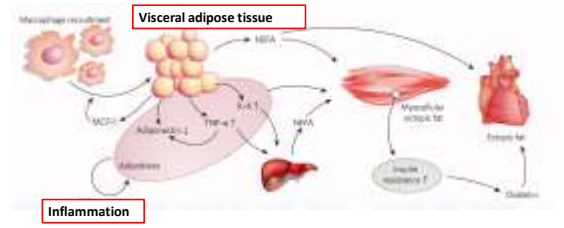
n = 212 pubertal and adult CCS

- Median 12.9 (2.3 -33) yrs from diagnosis
- 18% (39/212) cf controls 4.9%

- Multivariate analysis

TBI	p<0.001
Abdominal adiposity (w/ht >0.5)	p<0.001

Obesity and metabolic disorders



Van Gaal et al., Nature, 2006

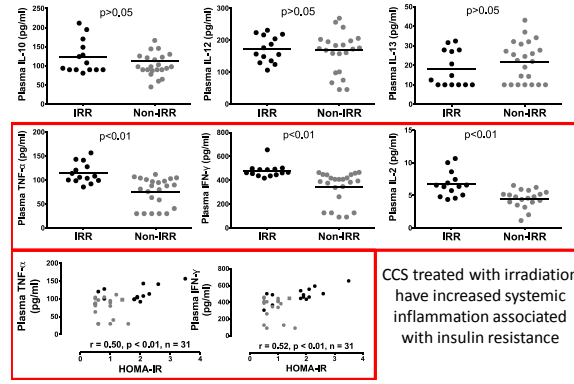
Main mechanisms in development of Insulin Resistance:
Deposition of intracellular lipids
Proinflammatory state

Radiotherapy and insulin resistance in CCS

	Total body irradiation (N=14)	Non Irradiated (N=27)
Age (yr)	24.6 (16-44)	22.8 (17-34)
Gender (M/F)	5/9	14/13
BMI (kg/m²)	23.9±6.8	25.6±5.8
Waist to height ratio	0.51±0.11	0.50±0.08
Triglycerides (mmol/l)	1.93±1.74*	0.96±0.46
Cholesterol (mmol/l)	5.28±0.97*	4.78±0.77
HDL-C (mmol/l)	1.28±0.41	1.58±0.72
LDL-C (mmol/l)	3.09±0.97	2.84±0.51
Insulin (mU/l)	9.24±8.02	5.62±4.61
Glucose (mmol/l)	5.87±3.40*	4.77±0.47
Insulin resistant (%)	7 (50%)*	2 (7.4%)

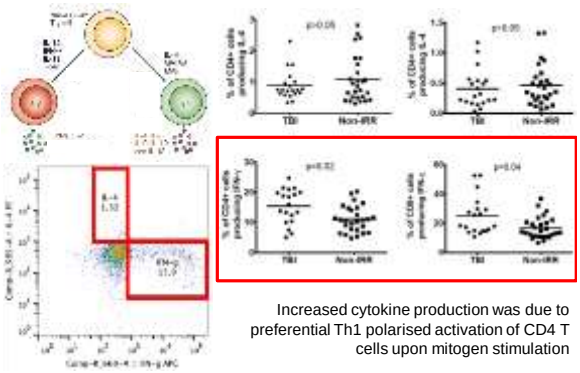
*: p<0.05, TBI vs. non irradiated, BMI: body mass index, HDL-C: high-density

CCS and TBI - increased levels of pro-inflammatory cytokines



CCS treated with irradiation have increased systemic inflammation associated with insulin resistance

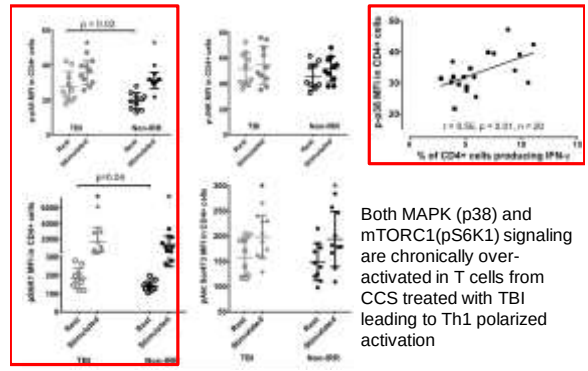
CCS and TBI - increased T cells polarised activation towards Th1



Increased cytokine production was due to preferential Th1 polarised activation of CD4 T cells upon mitogen stimulation

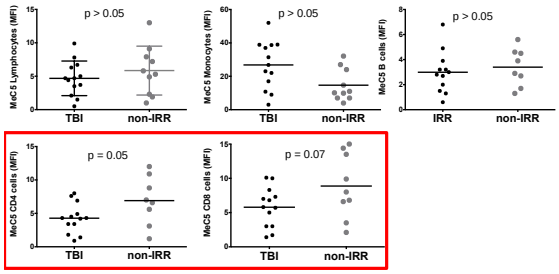
Schwartzberg et al., Nat Rev Immunol, 2005

CCS and TBI – over-activation of intra-cellular pathways



Both MAPK (p38) and mTORC1(pS6K1) signaling are chronically over-activated in T cells from CCS treated with TBI leading to Th1 polarized activation

Epigenetic changes in PBMCs in CCS



T cells from childhood cancer survivors treated with radiation characterized by unique epigenetic signature
Role in long-term memory of treatment?

Metabolic complications in childhood cancer survivors

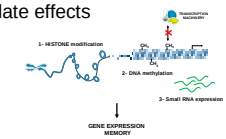
Insulin resistance in CCS treated with total body irradiation:
Neville, Cohn et al., J Clin Endo Metab, 2006

Systemic inflammation in CCS:

- increased levels of pro-inflammatory cytokines
- increased T cells polarized activation towards Th1
- increased intracellular signaling due to a bystander effect

Identification of an unique epigenetic signature:

- understanding pathogenesis of late effects
- long-term memory
- early diagnosis
- treatment
- prevention.



Acknowledgements:

- Richard Cohn
- Karen Johnston

- **School of Medical Science, UNSW**
  - Dr David Simar
  - Dr Saghar Eslami
- **Novo Nordisk Foundation**
  Centre for Basic Metabolic Research
  - AProf Romain Barres,
  -Vibe Nylander,