Comparing total-body metabolic PET imaging signatures of lung cancer cachexia to other wasting conditions

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Cancer cachexia (CC) is a debilitating wasting condition. While anorexia and muscle wasting are features of cachexia, CC is a distinct and poorly understood metabolic syndrome[1]. We harnessed preclinical models of lung cancer to study how glucose uptake changes during CC and performed comparative analyses with anorexia and muscle wasting.

Lung K-ras$^{G12D/+}$;Lkb1$^{-/-}$(KL) mice suffering CC were imaged using [^{18}F]fluorodeoxyglucose (FDG) PET at 15-19% weight loss alongside K-ras wild-type (WT) non-tumour bearing controls. Mice were injected with 12-18MBq of FDG, imaging 80-100 minutes post injection with the Mediso nanoScan® PET/MRI 1T.

In non-tumour bearing male animals, we modelled anorexia, muscle wasting, and circulation of cachexia factor GDF15 as follows, respectively: fasted overnight for 20 hr, treated with dexamethasone 21-phosphate (dexa) (2mg/kg, i.p. daily, 21 days) and single injection of recombinant human GDF15 hormone (0.1 mg/kg s.c.).

FDG *ex vivo* biodistribution showed increased uptake in myocardium ($p<0.05$), brain and liver (both $p<0.01$) of KL cachexic animals with no significant change in FDG blood pool.

Like cachexic KL animals, FDG uptake in fasted animals increased in brain ($p<0.0001$), perhaps due to increased FDG blood pool. FDG uptake in skeletal muscles and brown adipose tissue decreased (both $p<0.05$) in fasted state suggesting lower muscle activity and decreased thermogenesis respectively. Dexa-induced muscle atrophy also resulted in decreased FDG uptake in gastrocnemius/soleus muscles (SUV_{mean} 0.63 vehicle vs. 0.45 dexa, $p<0.05$) but no changes in skeletal muscle FDG uptake were noted in cachexic animals. In contrast to KL animals, GDF15 injection resulted in decreased FDG uptake in myocardium ($p<0.05$).

Overall, the cachexic FDG signature showed differences to other wasting conditions in this mouse model, suggesting different underlying mechanisms.

Total-body PET can reveal diverse metabolic wasting states. We aim to elucidate mechanisms of metabolic changes in cachexia to allow metabolic subtyping and personalised treatment options.

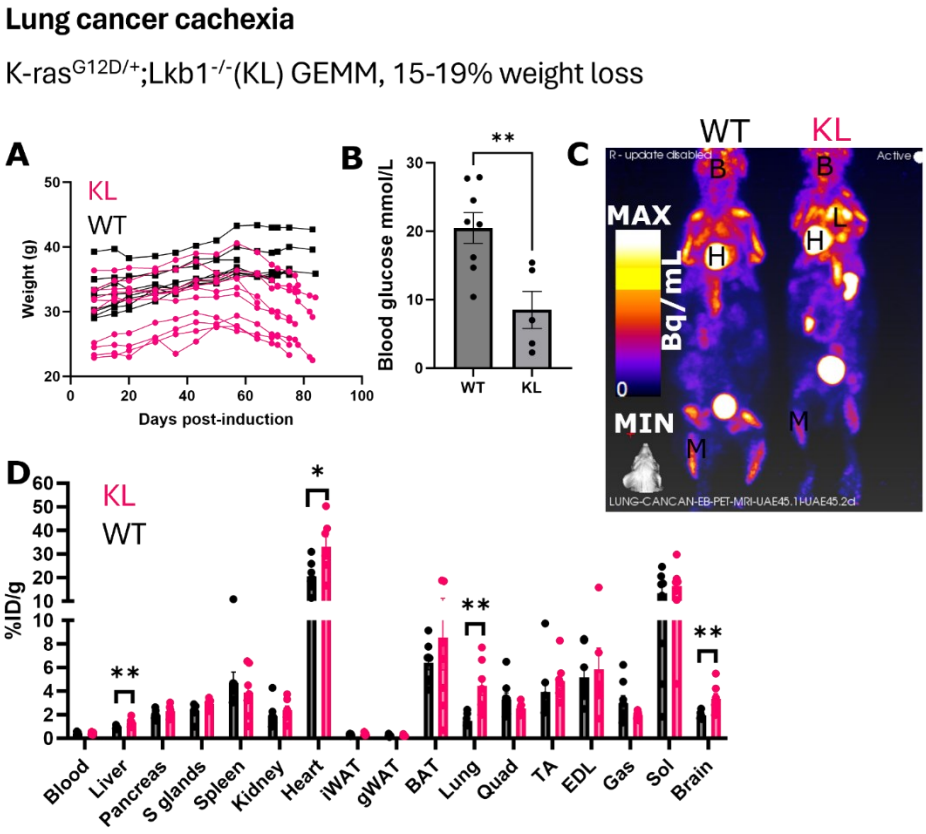

Figure 1. FDG metabolic PET phenotype in lung cancer cachexia KL mouse model. A) Weight trajectories in KL (pink) and non-tumour bearing controls (WT, black). Imaging conducted at end-point, 15-19% body weight loss. Each line corresponds to one animal. B) Blood glucose mmol/L measured by ACCU-CHEK® from cardiac blood at end-point. C) Exemplar maximum intensity projection of 18-F FDG uptake across WT and KL animals. Major organs of interest are labelled as follows B=brain, H=heart, L=lung tumour, M=muscles, lower limb. D) Ex vivo biodistribution of FDG measured in % injected dose (ID) per gram of tissue. In B and D each dot corresponds to data from one animal. *p<0.05, **p<0.01.

References:

(1) Ferrer M, Anthony TG, Ayres JS, Biffi G, Brown JC, Caan BJ, Cespedes Feliciano EM, Coll AP, Dunne RF, Goncalves MD, Grethlein J, Heymsfield SB, Hui S, Jamal-Hanjani M, Lam JM, Lewis DY, McCandlish D, Mustian KM, O'Rahilly S, Perrimon N, White EP, Janowitz T. Cachexia: *A systemic consequence of progressive, unresolved disease*. Cell. 2023 Apr 27;**186**(9):1824-1845. doi: 10.1016/j.cell.2023.03.028.