GESINAS - ImmunoTools Award 2021

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Exploring the immune-metabolic influences of adipose tissue in Oesophageal Adenocarcinoma

Background:

Oesophageal Adenocarcinoma (OAC) is the most strongly associated cancer with obesity, with the estimation that the numbers of OAC will double in the next two decades, in parallel with increasing obesity rates globally; this has become a worldwide epidemic. Approximately 75% of OAC patients are obese which results in chronic systemic low-grade inflammation, which is believed to drive carcinogenesis as well as influencing treatment response. Consequently, a multi-modal approach to treating this disease involves neoadjuvant treatment (treatment prior to surgery) with either chemotherapy alone or combination chemoradiotherapy (neo-CRT) for locally advanced tumours. Unfortunately, only ~30% of patients show a beneficial response with ~70 of patients receiving a toxic treatment with no benefit. These patients also experience a delay to surgery without therapeutic gain significantly affecting overall patient survival.

Adipose tissue is a regulatory organ with many downstream effects which are still not understood among which is dysregulated fatty acid metabolism. Lipid metabolism has been suggested to play a key role in the tumour microenvironment and in tumour and immune cells promoting tumour progression, with obesity suggested to have a direct effect on impairing immunosurveillance. In addition, adipose tissue conditioned media from obese cancer patients has been shown to significantly enhance the proliferation

of oesophageal cancer cells in vitro, compared with conditioned media from adipose tissue of non-obese cancer or non-cancer patients.

The work from our lab looks to profile the metabolism and secreted pro-inflammatory mediators of both tumour and adipose explants and with the focus on cytokines with key roles in the stimulation and polarisation of immune cells including IL-10 and IL-4. As well as looking at the metabolism of cancer cells and matched metastatic cell line models and immune cells individually and following co-culture having been treated with our adipose and tumour conditioned media.

In previous studies, elevated free fatty acids and utilisation of fatty acid metabolism have both been implicated in promoting migration and invasion of cancer cells. We hope to assess the influence of the adipose secretome on the metabolism and invasive capabilities of a matched cancer and metastatic cell model.

Objective:

Will obesity alter the metabolism of adipose tissue explants and will the secretome of these explants effect cancer cell and immune cell function and metabolism?

Methodology:

- To support the growth and stimulation of NK cells in culture the following cytokines will be utilized: IL-12 and IL-15
- To support the growth and maturation of Dendritic Cells in culture the following cytokines will be utilized: GM-CSF and IL-4
- To support the growth and polarisation of Macrophages in culture the following cytokines will be utilized: M-CSF, IL-4 and IL-13
- Immune cells will then be co-cultured to assess the effect on their biological functionality particularly pro-inflammatroy response in macrophages via flow cytometry using IL-6 antibody
- ELISA will be carried out to examine levels of sCD147: in matched cancer and metastatic cell model following treatment with adipose conditioned media

- ELISA will be carried out to examine levels of MCP-2 and MCP-3: in macrophages following treatment with adipose conditioned media and co-culture

Expected outcome

We hope to demonstrate that obesity significantly alters the immune-metabolic influences of adipose tissue. Alterations in the secretome of adipose tissue could potentiate the tumour microenvironment and deleteriously effect immune cell function therefore further interrogation is required to fully elucidate the influence adipose tissue may have in treatment response. Particularly as the epidemic that is obesity increases to rise, it is impertaive that we now assess how the obese tumour microenvironement may help or hinder cancer treatement particularly immmunotherapy based ones that rely so heavily on an effective immune cell response.

GESINAS – **ImmunoTools** **Award Social Commitment:**

Scientific outreach for me is one of the most important associations of research. I am currently a member of my Institutes Outreach Committee and have carried out both in-house and community engaged outreach project with particular focus on engaging students in primary and secondary education to enhance their understanding of the role of research and what we do.

Currently I am developing scientific resources for each class level of primary education and a short course aimed at transition year students in secondary school both of which I am hopeful will be ready for the next academic year.

GESINAS - **ImmunoTools** AWARD for **Fiona O'Connell** includes 20 reagents

PE - conjugated anti-human IL-6

recombinant human rh GM-CSF, rh IFN-g, rh IL-4, rh IL-12, rh IL-13, rh IL-15, rh M-CSF

human ELISA-set (for one 96 plate): human sCD147 (sEMMPRIN), human MCP-3 (CCL-8), human MCP-2 (CCL-8)

DETAILS more AWARDS