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***Cover Letter**

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Molecular and Cellular Endocrinology

23rd March 2017

Dear Editors and Editorial staff,

On behalf of all the co-editors of the MCE Special Issue on Metabolism and Cancer, I am submitting an Editorial entitled " Multifaceted link between metabolism and cancer " which we would like to be considered for publication in the Special Issue/Topic: 'The role and regulation of metabolism in cancer' of Molecular and Cellular Endocrinology.

We declared that there are no conflicts of interest with this manuscript. We also declare that the content of the manuscript is original and that it has not been published or accepted for publication, either in whole or in part, in any form. It is also not being considered by another Journal.

As I am the guest editor of the Special Topic, I suggest Professor Ilpo Huhtaniemi the Editor-in-chief or another Senior Editor handling this manuscript.

We thank you for your consideration.

Yours sincerely,



Eric W-F Lam

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Multifaceted link between metabolism and cancer

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Cancer is a disease characterised by unregulated cell proliferation and survival. Cancer Cells are able to reprogram biochemical pathways to aid these processes (Hiller and Metallo, 2013). Over the last decade, the multifaceted link between metabolism and cancer has been the subject of extensive research; in fact, the metabolic reprogramming is considered a hallmark of cancer (Boroughs and DeBerardinis, 2015; DeBerardinis et al., 2008).

The stromal compartment (that contains cells of the immune system, the tumour vasculature and lymphatics, as well as fibroblasts, pericytes and adipocytes) and the malignant cells together shape the tumour microenvironment (Balkwill et al., 2012; Muppalla et al., 2013). The intercellular communication between malignant and non-malignant cells is driven by cytokines, chemokines, growth factors, and inflammatory and matrix remodelling enzymes (Balkwill et al., 2012). It has been demonstrated that the tumour microenvironment significantly alters the metabolism of cancer cells (DeBerardinis et al., 2008; Hiller and Metallo, 2013); for example, oncogenic signalling pathways directly enhanced nutrient acquisition and facilitate assimilation of carbon into macromolecules such as lipids, proteins and nucleic acids (Boroughs and DeBerardinis, 2015). This altered metabolism contributes to cancer initiation, progression and resistance to treatment (Boroughs and DeBerardinis, 2015; DeBerardinis et al., 2008; Muppalla et al., 2013). The present Special Research Topic of Molecular and Cellular Endocrinology is devoted to exploring this relationship between microenvironment and the malignant cells, focusing on the role of the metabolism in cancer initiation, progression, and drug resistance.

The microenvironment involves the generation of cancer-associated fibroblasts (Allen and Louise Jones, 2011). These fibroblasts produce growth factors, chemokines and cytokines and are associated with cancer progression, enhanced angiogenesis, increased tumour growth and invasion (Allen and Louise Jones, 2011; Kalluri and Zeisberg, 2006)**.** In this Special Research Topic, Lopes-Coelho and colleagues demonstrated how cancer-associated fibroblasts are a source of fatty acids to breast cancer cells covering their metabolic needs and increasing the disease progression (Lopes-Coelho et al., 2017). It is well known that fatty acids per se play an important role in cancer as they are involved in different processes such as cellular proliferation. Furthermore, cancer cells rely on fatty acids as cellular building blocks for membrane formation, energy storage, and the production of signalling molecules (Currie et al., 2013)**.** In addition, Saavedra-García and colleagues discuss the implications of the fatty acid metabolism and cancer, linking these implications with the FOXO3-FOXM1 Forkhead transcription factor axis (Saavedra-Garcia et al., 2017). FOXO3 and FOXM1 have antagonistic roles in cancer; FOXO3 behaves like a typical tumour

suppressor, meanwhile FOXM1 functions as a potent oncogene (Bella et al., 2014; Lam et al., 2013; Zona et al., 2014). Referred to this paper, Fan and colleagues matched the DAF-16/FOXO3 downstream genes in *Caenorhabditis elegans* with their respective human orthologues and reviewed the roles of these targeted genes in fatty acid metabolism (Fan et al., 2017).

Fatty acids are mainly released into circulation by adipocytes (Frayn et al., 2006; Summers et al., 2000), but adipose tissue does not only release fatty acids, it is a highly dynamic endocrine organ that also secretes a number of different molecules that can communicate with other cells (Booth et al., 2015; Li et al., 2011) and can dysregulate the microenvironment and alter the peripheral tissue metabolism (Booth et al., 2015). There are many proposed mechanisms that link obesity/adiposity to high cancer risk such as adipokine production (Booth et al., 2015; Nimptsch and Pischon, 2015). Fatty acid-binding protein 4 and 5 are two proteins expressed in adipose tissue and associated with cancer (Furuhashi and Hotamisligil, 2008; Guaita-Esteruelas et al., 2016; Thumser et al., 2014). In their review, Guaita-Esteruelas and colleagues discuss the recent findings relating to Fatty acid-binding protein 4 and 5 and cancer under obesity and normal weight conditions (Guaita-Esteruelas et al., 2017).

Deregulated fatty acid metabolism and other stress conditions can disturb folding of proteins in the endoplasmic reticulum (ER) (Cunha et al., 2012; Sano and Reed, 2013). These disturbances in ER homeostasis (ER stress) lead to a cell stress response termed unfolded protein response (UPR), which initially restores the imbalance and promote cell survival, but can eventually trigger cell death (Xu et al., 2005). It is well known that ER stress contributes to the development and progression of many diseases such as cancer (Ozcan and Tabas, 2012). In their review, Alasiri and colleagues discuss how ER stress affects cancer through FOXO3-FOXM1 axis interactions (Alasiri et al., 2017).

On the other hand, environmental factors, diet, and lifestyle play a crucial role in the development of cancer (Muscaritoli et al., 2016). A good example of how external stimuli is related with cancer development is acrylamide. Acrylamide is a white odourless water soluble crystal employed as a water-soluble thickener to produce a water soluble gel (useful in electrophoresis), but also it is used as a papermaking, tertiary oil recovery, and the manufacturing of permanent press fabrics (Kahkeshani et al., 2015). Furthermore, acrylamide can be found in many foods, mainly in fried and baked foods (Kahkeshani et al., 2015; Katen and Roman, 2015; Pelucchi et al., 2015; Virk-Baker et al., 2014). Acrylamide has been classified as carcinogen for humans (Katen and Roman, 2015; Pelucchi et al., 2015; Virk-Baker et al., 2014). Wang and colleagues demonstrated that low levels of acrylamide do not produce obvious symptoms, but it can alter some metabolic parameters

that highlight the link existed between metabolism and cancer (Wang et al., 2017). Together, this collection of articles underscores the intimate relationships that exist between metabolism and cancer and how the dissection of this intertwined connections can be instrumental in unveiling new therapeutic targets and strategies.

Conflict of interest statement

The authors declare that they have no competing interests.

Disclosure statement

The authors have nothing to disclose.

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