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A low protein diet to target cardiovascular disease and cancer in one shot?

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This commentary refers to ‘Low-protein diet induces IRE1 α -dependent anticancer immunosurveillance’ by Rubio-Patiño *et al.*, *Cell Metab*, 2018.¹

The Western countries face an obvious paradigm when talking about lifespan increase and medication use. Concomitantly with the population lifespan increased in the last 50 years, the number of chronic diseases such as cancers and hypertension has greatly expanded. Beside the conventional medication, biologists investigate alternative methods to improve lifespan and prevent a growing variety of chronic diseases. Sometimes, these methods are simple and ancestral. Dietary restriction, including fasting and caloric restriction, is recognized to prevent and reduce many disorders including tumour cell proliferation.² While such diet is hardly applicable in some cases, finding alternative methods to gain the similar healthy benefits without reducing caloric intake is a challenge.

In this way, Rubio-Patiño *et al.*¹ brought a different method without impacting total caloric intake. By feeding mice with a low-protein isocaloric diet (i.e. 25% reduction in protein), they demonstrated a positive effect in reducing tumour growth in three independent immunocompetent mouse models bearing lymphoma, melanoma, and colorectal cancer. Interestingly, their findings provided new insights in the mechanism behind tumour reduction. This involved the activation of the unfolded protein response (UPR) through an adaptive mechanism dependent of the inositol requiring enzyme 1 (IRE1). IRE1 is a ribonuclease required to catalyse X-box binding protein 1 (XBP1) mRNA.³ In cancer cells, IRE1 α RNase activity is involved in the regulation of IRE1-dependent decay (RIDDD) or mRNA, rRNA, and microRNA that leads to retinoic acid inducible gene 1 (RIG1) activation pathway which was shown to affect adaptive immunity by stimulating the endoplasmic reticulum (ER) stress (also called UPR), a highly conserved quality-control mechanism protecting against ER unfolded/misfolded protein overload.

Rubio-Patiño *et al.* observed a new concept in diet benefits based on stimulating the immune system whereas most of the studies so far showed decrease cell tumour proliferation. Even though some cancer cells are able to resist chronic ER stress activation, several evidences showed that environmental or therapy-induced ER stress can release major immunostimulatory signals leading to immunosurveillance.⁴ In the present study, activated IRE1 α /RIG1 triggers ER stress thus promoting immunosurveillance through CD8⁺ T cell activation and an anticancer immune response in mice. To validate their hypotheses on the critical role of IRE1 α in the cancer cells, the authors invalidated this transcription

factor through the CRISPR/Cas9 technology, resulting in blunted reduction in mouse tumour growth.

Their results reinforce the theory that macronutrient intake modulates protein homeostasis (proteasins) and UPR. Both processes contribute to eliminate cancer cells through activation of the immune system and T cell recruitment. This study highlights the therapeutic potential of accurately controlling macronutrient intake. In fact, protein intake reduction by only 25%, may be enough to substitute dietary restriction and notably carbohydrate restriction. How low protein diet triggers IRE1 α activation and ER stress in tumour cells remains unclear. Future complementary methods for cancer prevention and treatment may suggest specific diet by modulation of the macronutrient intake.

Cardiovascular diseases (CVD) and cancers are the main public health issues in occidental countries. While they share similar risk factors (e.g. chronic inflammation, age, obesity, diabetes, and infectious agents), they may also share complementary therapeutic strategies. Although misfolded protein accumulation and ER stress remain less explored in CVD, their role have long been clearly demonstrated in neurodegenerative and age-related diseases, thus pointing out another area of interest.

Cardiomyocytes require both ER and sarcoplasmic reticulum (SR) for general cellular function and excitation–contraction coupling. These two compartments can activate UPR. Prola *et al.* evaluated the early cardiac consequences of ER stress by pharmacological activation in mice, and revealed that it rapidly led to cardiac dysfunction characterized by ER and SR membrane impairment. They also showed downregulation of some key actors of the mitochondrial biogenesis including the same IRE1 transcription factor and decrease mitochondrial calcium uptake and metabolism.⁵

Intriguing support for a role for UPR in the human heart is the very recent findings of Lui *et al.* using human induced-pluripotent stem cell-derived cardiomyocytes. Their results revealed that activated UPR in human cardiomyocytes downregulated key cardiac ion channels, leading to electrical remodelling and arrhythmia susceptibility that could be reversed especially by inhibiting IRE1.⁶

Furthermore, cancer treatments targeting ER stress and proteasome inhibition have substantial cardiac consequences leading to heart failure in patients. Hence, such anticancer agents cause ER stress in the heart. Fu *et al.*⁷ addressed this issue and demonstrated that proteasome inhibitors (e.g. epoxomicin) activates ER stress and apoptosis in neonatal rat cardiomyocyte, partially via CCAAT/enhancer-binding protein homologous protein (CHOP)-dependent pathway. Inhibiting the particular CHOP

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transcription factor in cardiomyocyte partially reduces apoptosis. This indicates that other more complex mechanisms related to ER stress, and potentially involving IRE1, could induce cardiac death.

In vessels, ER stress appeared to be a relevant factor in arterial cells by facilitating the development of atherosclerosis. Pathologically chronic ER stress associated with oxidative stress, inflammation and apoptosis was reported in atherosusceptible regions. Importantly, the oxidation-related ER stress pathways were demonstrated to be a determinant in macrophages in the progression of atherosclerosis by contributing to the formation of atherosclerotic plaques.⁸ In this way, antioxidant therapies constitute some of the current strategies to delay the progression of atherosclerosis. Moreover, the large-scale CANTOS clinical trial showed a significant effect to reduce atherosclerosis by inhibiting the pro-inflammatory IL-1 β pathway using canakinumab.⁹ Interestingly, the CANTOS anti-inflammatory trial showed beneficial effects to prevent lung cancer in patients with atherosclerosis.¹⁰

Finally, could we modulate ER stress in CVD by modulating macronutrient uptake similarly to cancer treatment? According to a Finish group recently analysing data from 2240 middle-aged men, on a high-protein rich diet from animal proteins, concluded to be unhealthy for the heart. They found that men in the highest overall protein intake have a 33% higher risk of heart failure when compared to those with the lowest protein intake.¹¹ However, the cellular pathways involved in this process remain to be studied.

To conclude, the findings reported in the study of Rubio-Patiño *et al.* in mice demonstrate that a specific protein intake reduction induces ER stress, which in turns stimulates T cell recruitment to eliminate the tumour cells. How applicable such strategy is in cancer patients suffering from weakness and cachexia has to be taken with caution. Alternative methods may help activating similar IRE1 α /RIG1-dependent ER stress pathways to fight cancer. In contrary inhibiting them might be of potential in future treatments to fight CVD.

Conflict of interest: none declared.

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Biography: Albano C. Meli received his PhD in Neurobiology at the Faculty of Pharmacy in Montpellier (France) in 2007. He then worked as a postdoctoral research scientist at Columbia University Medical Center in New York City (USA) for 4 years where he got mainly trained in basic cardiology. He was granted a European Marie-Curie Fellowship (2011) and a European Society of Cardiology grant (2012) to build up a team on human pluripotent stem cell-derived cardiomyocytes at Masaryk University Faculty of Medicine in Brno (Czech Republic). Albano was recruited as a permanent researcher by the French National Institute for Health and Medical Research (INSERM) in 2014. He has experience in basic cardiac physiology, calcium handling, ion channel biophysics as well as in human pluripotent stem cell-derived cardiomyocytes to model inherited cardiac arrhythmias. He is also a nucleus member of the Scientist of Tomorrow of the European Society of Cardiology.