Response to: 'Correspondence on "Glucosamine and O-GlcNAcylation: a novel immunometabolic therapeutic target for OA and chronic, low-grade systemic inflammation?' by Angelides and Manolios

We have read with interest the comment from Angelides and Manolios in which they propose an alternative way to account for the potential mechanism of action of glucosamine in osteoarthritis (OA) and other chronic inflammatory diseases.[1] Recent and robust epidemiological data suggest that sustained glucosamine intake could partially prevent cardiovascular disease and cancer.[2] Our editorial made some hypothetical considerations about the mechanism of action of this compound.[3] The editorial also commented on the difficulty of detecting a beneficial effect of glucosamine in OA, due to the modesty of the therapeutic effect, as well as the weakness of the methodological tools employed in OA clinical trials.[3]

In some way, the relationship between glucosamine and OA takes us fully into the pathophysiology that revolves around immunometabolic regulation, a driver that can account for tissue deterioration in various chronic diseases and still with many aspects to be elucidated. The hexosamine biosynthesis pathway (HBP), through which glucosamine can be metabolised in the cell, integrates the main cellular metabolic molecules, such as carbohydrates, amino acids, lipids and nucleotides, and regulates the inflammatory response through many mechanisms.[3] It is an example of what immune-metabolic integration means in diverse and varied circuits of the organism, an essential concept to decipher the pathogenesis of many human diseases. These integrating processes have been scarcely studied in OA, despite its association with obesity, low-grade systemic inflammation and cardiovascular disease.[4]

Angelides' contribution is relevant suggesting the tropism of glucosamine for inflamed tissues in human diseases.[1] The radiolabelled glucosamine was deposited along the hyaline cartilage of OA knee, but not in the healthy cartilage. The tracer deposit was also diffusely present in the synovium of patients with more advanced knee OA. The greater uptake in rheumatoid arthritis than in OA synovium was another data indicating a direct relationship between the intensity of inflammation and glucosamine uptake. Finally, the inflammation of an extra-articular tissue such as muscle also showed an increase in glucosamine accumulation in patients with myositis.

The accumulation of glucose and its analogues has been associated to the upregulation in glucose consumption during different chronic inflammatory diseases, such as rheumatoid arthritis or sepsis, and cancer, in order to fulfil the increase in energy demand when this nutrient is only partially oxidised.[5–7] The metabolic shift from mitochondrial oxidative phosphorylation to aerobic glycolysis observed in these tissues links metabolism to inflammation.[8] Lactate accumulation and aerobic glycolysis impedes inflammation resolution and blocks macrophage polarisation towards an anti-inflammatory phenotype.[6] However, the metabolic alteration associated to inflammation goes beyond cell glucose catabolism. An altered management of fatty acids, cholesterol and glucose has been described during systemic chronic inflammation such as that occurring in rheumatoid arthritis.[6 8 9] Inflamed macrophages accumulate cholesterol and mismanage carbohydrate metabolism, likely attempting to ensure energy store due to the enormous cost involved in the production of pro-inflammatory mediators and cell proliferation.[10] In experimental models of joint inflammation, an excess of lipids modifies the course of the disease.[11 12] Furthermore, a hypercholesterolaemic diet per se slightly inflames the intra-articular fat in the knee of healthy rabbits. The same diet produces an intense synovitis, and lipodystrophy with severe destruction of joint fat.[12]

It should be explored whether glucosamine could inhibit oxidative phosphorylation. However, as authors point out, limited success has been observed in the treatment of inflammatory conditions with agents that suppress glucose metabolism. Our hypothesis is that, regardless of the amount of glucosamine that can reach the cartilage or the synovium, glucosamine microshocks could alter a key nutrient sensor pathway, such as the HBP, and the incorporation of its final product by O-N-Acetylglycosylation to protein residues, with a final net effect of an anti-inflammatory nature.

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