PP2A plays a key role in inflammation and cancer through tristetraprolin activation

We have read with great interest the recent work by Ross *et al*,¹ which provides novel relevant findings about the therapeutic efficacy of using protein phosphatase 2A (PP2A)-activating drugs to target tristetraprolin (TTP) in rheumatoid arthritis (RA). In this elegant work, the authors showed that TTP is over-expressed and colocalises with activated mitogen-activated protein kinase (MAPK) p38 in RA synovial tissue. MAPK p38 phosphorylates and inhibits TTP at two serine residues, and Ross *et al* determined that these phosphorylation sites are critical for the role of TTP as a key regulator of inflammatory responses. Since PP2A dephosphorylates TTP at these two serine residues,² they hypothesised and assessed the efficacy of PP2A-activating compounds such as COG1410 and ALL(s) in RA, observing that these agents led to PP2A-mediated TTP activation thereby reducing both inflammation and bone erosion using in vitro and in vivo models of this disease. These results highlight the potential clinical usefulness of PP2A activation as a novel strategy to develop potent anti-inflammatory treatments.

PP2A is a well-known tumour suppressor that has been described commonly inactivated in human cancer.³ Moreover, PP2A has been described as a key regulator of the MAPK signalling⁴ and controls the production of proinflammatory chemokines.⁵ Of importance, the risk of developing cancer is higher in people with inflammatory diseases such as colitis or hepatitis. The reason may be that the molecular events generated by the inflammatory response predispose to transformation from chronic inflammation to neoplasia.⁶ Thus, TTP could represent a key linker between inflammation and cancer due to its role as modulator of the expression of both cytokines and proto-oncogenes.⁷ Therefore, the function of PP2A as a TTP activator could be of high relevance and further reinforced by the fact that this phosphatase also targets MAPK signalling, which is responsible for the inhibitory phosphorylation of TTP.⁵

In conclusion, the study by Ross *et al*¹ highlights that PP2A plays a relevant role in inflammation through TTP dephosphorylation and activation. Importantly, these findings would suggest the potential benefits derived from the clinical use of PP2A-activating drugs as anti-inflammatory therapy as well as a novel strategy to prevent cancer development in those patients with chronic inflammatory diseases.

Ion Cristóbal,¹ Blanca Torrejón,¹ Juan Madoz-Gúrpide,² Federico Rojo,² Jesús García-Foncillas¹

¹Translational Oncology Division, Oncohealth Institute, IIS-Fundación Jiménez Díaz, UAM, University Hospital 'Fundación Jiménez Díaz', Madrid, Spain

²Pathology Department, University Hospital 'Fundación Jiménez Díaz', Autonomous University of Madrid, Madrid, Spain

Correspondence to Dr Ion Cristóbal and Professor Jesús García-Foncillas, Translational Oncology Division, Oncohealth Institute, IIS-Fundación Jiménez Díaz, UAM, University Hospital 'Fundación Jiménez Díaz', Avda. Reyes Católicos-2, E-28040 Madrid, Spain; ion.cristobal@fjd.es, jgfoncillas@fjd.es

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