Proyecto PID2020-112526RB-I00 financiado por MCIN/ AEI /10.13039/501100011033

Identificación del proyecto:

Estudio de las funciones específicas de PARP-1 y PARP-2 en tumores mediados por c-Myc (ONCOPAR)

Descripción del proyecto:

Replication stress, a hallmark of cancer cells, is characterized by slowing or stalling of replication fork progression, and represents a major driver of genomic instability. Dysregulated expression of oncogenes, such as c-Myc, is a key source of replication stress leading to tumour development. c-Myc-dysregulation occurs in a wide variety of cancers and its overexpression has been linked to aggressiveness and poor prognosis. Recently, we have shown that Poly(ADP-ribose) polymerases (PARP)-1 and PARP-2 exert distinct and opposing effects on the development of c-Myc-driven B cell lymphoma in mice. PARP-1 and PARP-2 catalyse the transfer of ADP-ribose units onto amino acid residues of acceptor proteins in response to DNA-strand breaks, playing a central role in the response to DNA damage. Accordingly, PARP inhibitors have emerged as promising new cancer therapeutics. However, the inhibitors currently available for clinical use are not able to discriminate between individual PARP proteins. Nevertheless, we found that genetic deletion of PARP-2 prevents c-Myc-driven B cell lymphomas, while PARP-1-deficiency accelerates lymphomagenesis in the EuMyc mouse model of aggressive B cell lymphoma. The challenge is now to find out the intrinsic mechanisms, both at the level of the tumour cell itself and its environment, by which PARP-1 and PARP-2 play an opposite role on oncogene-driven tumorigenesis that will provide a basis for the rational exploitation of isoform-specific PARP inhibitors. An open question is whether PARP-2 deficiency leads to an exacerbation of replicative stress induced by c-Myc leading to an accumulation of DNA damage, resulting in the activation of the ATMH2AX/ CHK2-p53/p21 pathway, and how all this impacts on tumour development. Moreover, a link has been established between replication stress, genomic instability and the accumulation of DNA in the cytoplasm, which triggers the modulation of the immune system through activation of the cGAS/STING signalling pathway and the production of key mediators. In addition, cGAS/STING signaling pathway also triggers other biological processes including various forms of programmed cell death. However, there is currently a very poor understanding of how replication stress can lead to the accumulation of cytosolic DNA and to what extent this contributes to tumorigenesis. The hypothesis of this project is that PARP-1 and PARP-2 are playing different roles in the link between oncogenic stress with genomic instability and its connection to the cGAS/STING cytosolic DNA sensing pathways, modulating distinct downstream effector programs. In addition, PARP-1 and PARP-2 are also playing different roles

in modulating tumour escape mechanisms such as MHC class I expression. All of this might contribute to the opposite effect of PARP-1 and PARP-2 on c-Myc-driven tumour development and progression. We propose to capitalize our expertise in mouse models of cancer, PARP-signalling pathways, and immunology, and perform a comprehensive project that helps to understand the specific contribution of PARP-1 and PARP-2 in the context of oncogene-driven replication stress, genomic instability, cytoplasmic DNA signalling, immune response and cancer. The execution of the proposed project may help to design new PARP-centred therapeutic strategies with selective PARP-2 inhibition potentially representing a new approach for the treatment of c-Myc-driven tumours.

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