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► To cite this version:

Elodie Blondel-Tepaz, Hervé Enslen, Mark G.H. Scott. Control of the Mdm2-p53 signal loop by β -arrestin 2: the ins and outs. *Oncotarget*, 2021, 12 (26), pp.2543-2545. 10.18632/oncotarget.28065 . inserm-03853538

HAL Id: inserm-03853538

<https://inserm.hal.science/inserm-03853538>

Submitted on 15 Nov 2022

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Control of the Mdm2-p53 signal loop by β -arrestin 2: The ins and outs

Elodie Blondel-Tepaz, Hervé Enslen and Mark G.H. Scott

Comment on: The RanBP2/RanGAP1-SUMO complex gates β -arrestin2 nuclear entry to regulate the Mdm2-p53 signaling axis by Blondel-Tepaz et al. *Oncogene*. 2021; 40:2243–57. <https://doi.org/10.1038/s41388-021-01704-w>. [PubMed]

Mdm2 is a major cellular inhibitor of p53. Small molecules designed to block the Mdm2-p53 interaction have been developed as an approach for the treatment of cancer with wild-type p53 [1]. In light of this therapeutic interest continued study of mechanisms that control the Mdm2-p53 signal loop is therefore of central importance.

The β -arrestins (β -arrests) are two scaffold proteins initially appreciated for their roles in the desensitization and endocytosis of G protein-coupled receptors [2, 3]. They also dynamically regulate the activity and/or

subcellular distribution of key intracellular signalling partners including Mdm2 [4–6]. Despite strong sequence homology, β -arr 1 and β -arr 2 present differential subcellular distributions. While β -arr 1 is found distributed both in the nucleus and cytoplasm, β -arr 2 displays an apparent cytoplasmic localization. This is due to constitutive ejection of β -arr 2 from the nucleus through a leptomycin B-sensitive pathway, directed via a nuclear export signal (NES) harboured by β -arr 2 (Figure 1A) that is absent in β -arr 1 [7, 8]. In addition, β -arr 2 is actively

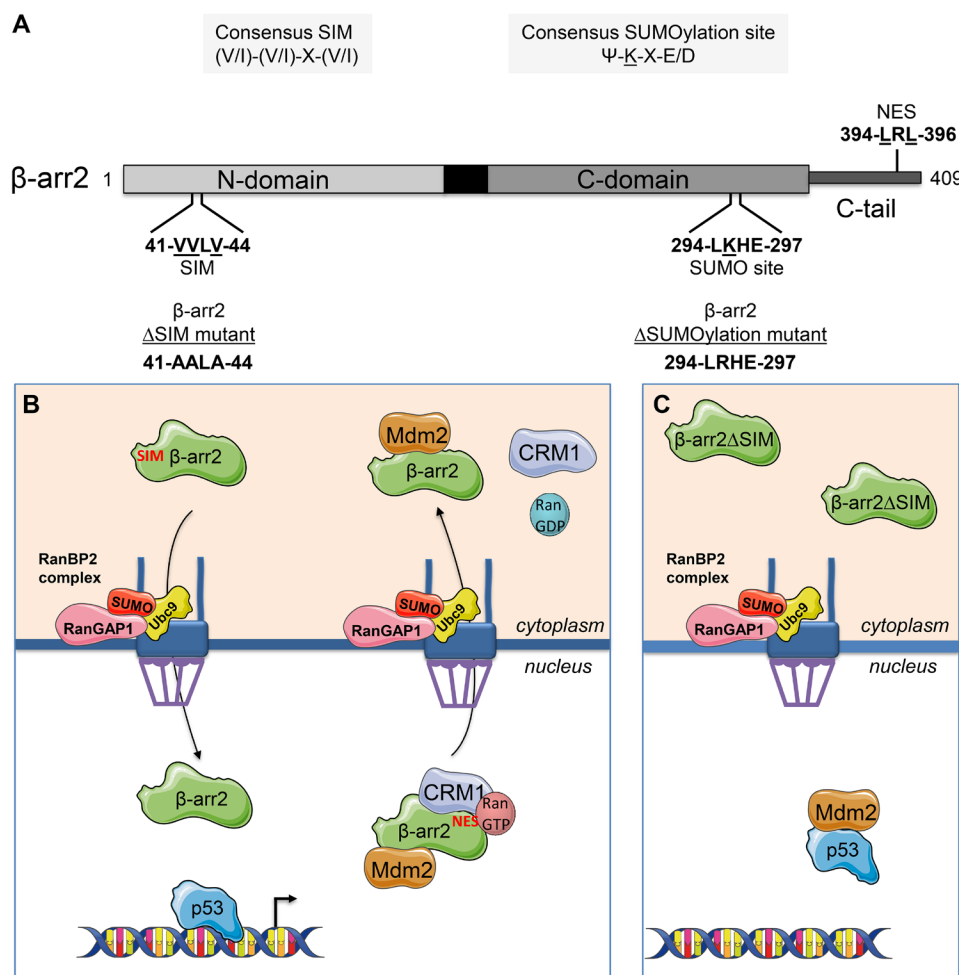


Figure 1: Model outlining the nucleocytoplasmic function of β -arr 2. (A) Schematic diagram indicating the SIM, SUMOylation site and NES in β -arr 2, and the Δ SIM and Δ SUMOylation site mutants used in the study. (B) Nucleocytoplasmic shuttling function of β -arr 2 with active import and export events results in displacement of Mdm2. (C) Defective nuclear import with the β -arr 2 Δ SIM mutant results in loss of Mdm2 displacement.

imported into the nucleus indicating that it undergoes continual nucleocytoplasmic trafficking. This shuttle function of β -arr 2 results in the displacement of Mdm2 from the nucleus to the cytoplasm, with an associated increase in p53 signalling and cell cycle arrest [5, 6].

Contrasting with the well characterized nuclear export mechanism of β -arr 2, knowledge on its entry mechanism(s) into the nucleus and functional impact on Mdm2-p53 signalling remains incomplete. SUMOylation is a post-translational modification that regulates the activity and localization of protein targets including nuclear targeting. β -arr 2 can be SUMOylated [9–11], but no information was available on how small ubiquitin-like modifier (SUMO) might regulate β -arr 2 nucleocytoplasmic shuttling. We therefore explored if SUMO could participate in controlling β -arr 2 nucleocytoplasmic shuttling function. In addition to SUMOylation sites for covalent conjugation of SUMO on a lysine residue, SUMO interaction motifs (SIMs) composed of a short stretch of hydrophobic residues can mediate non-covalent interaction with SUMO resulting in targeting of SIM-containing proteins to SUMOylated protein partners [12, 13]. Using a variety of *in vitro*, *in silico* and cell-based approaches we characterized both a SUMOylation site and SIM in β -arr 2 [14] (Figure 1A). Fusion of SUMO to β -arr 2 was recently found to increase its targeting to the nuclear rim [11]. We found, however, that SUMOylation was not required for nuclear import but that the SIM contained in β -arr 2 was [14]. We also found that the β -arr 2 SIM promotes association with the multimolecular RanBP2/RanGAP1-SUMO nucleocytoplasmic transport hub that resides on the cytoplasmic filaments of the nuclear pore complex. RanBP2 has been shown to act as a platform for nuclear import of a subset of import cargos [15]. We therefore tested the effect of depletion of the RanBP2/RanGAP1-SUMO complex on β -arr 2 nuclear import and indeed found it to be required, indicating its functional importance in β -arr 2 cytonuclear trafficking. RanBP2 has been proposed to enhance nuclear import by at least two mechanisms. Firstly, import receptor-independent interaction of selected cargos with RanBP2 can increase efficiency of nuclear import [15]. Secondly, it serves as a binding site for importin β 1 retaining the transport receptor in association with the nuclear pore complex and reducing the active concentration of import receptors required for efficient transport [16, 17]. Interestingly, in this context, a recent study identified a nuclear localization signal in β -arr 2 and importin β 1-dependent nuclear import [18] indicating that β -arr 2 nuclear import probably involves multiple steps coordinated by RanBP2. In summary, our findings demonstrate that the β -arr 2 SIM targets it to the RanBP2/RanGAP1-SUMO complex, which gates β -arr 2 nuclear entry (Figure 1B).

We next analyzed the function of the β -arr 2 SIM on the downstream Mdm2-p53 signal loop. Due to the defective nuclear import of a β -arr 2 Δ SIM mutant it lost the capacity to titrate Mdm2 from the nucleus to the cytoplasm observed with wild-type β -arr 2 (Figure 1B and 1C). Using non-small cell lung carcinoma and breast tumour cell lines we also found the enhancing effect of β -arr 2 on p53 signalling was lost with the β -arr 2 Δ SIM mutant. The Δ SIM mutant therefore gives rise to the same defective p53 signalling effect as a β -arr 2 Δ NES mutant, which also fails to displace Mdm2 from the nucleus. Our study [14] uncovering the role of a β -arr 2 SIM nuclear entry checkpoint, coupled with its active nuclear export provide an emerging picture of regulatory points that influence β -arr 2-mediated regulation of the Mdm2-p53 axis (Figure 1B). Further studies will be required to determine the full role of the SIM in β -arr 2 compartmentalization and if β -arr 2 cytonuclear function is disrupted in cancer settings.

ACKNOWLEDGMENTS

Work in the Scott group at the Institut Cochin has been supported by grants from the Fondation ARC pour la recherche sur le cancer, La Ligue contre le cancer, The Royal Society, France Canada Research Fund, the Who am I? laboratory of excellence (grant ANR-11-LABX-0071), funded by the “Investments for the Future” program operated by the French National Research Agency (grant ANR-11-IDEX-0005-01), CNRS, and INSERM.

CONFLICTS OF INTEREST

Authors have no conflicts of interest to declare.

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Keywords: β -arrestin; Mdm2; p53; RanGAP1; SUMO

Received: August 06, 2021

Published: December 21, 2021

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