HIF1α and ARD1: enemies, friends or neither?

Thomas Arnesen

Department of Molecular Biology and Department of Surgical Sciences, University of Bergen, Bergen, Norway.

e-mail: Thomas.Arnesen@mbi.uib.no

In the interesting review article by Minucci and Pelicci[1], there was a small section on the ARD1–hypoxia inducible factor-1α (HIF1α) link that needs some clarification. This information is based on the original research by Jeong *et al.* describing that mouse ARD1 acetylates the lysine residue 532 within the oxygen-dependent degradation domain of HIF1α[2]. This acetylation was demonstrated to increase its interaction with the von Hippel–Lindau protein and thereby increase the degradation rate of HIF1α. So, ARD1 was defined as a negative regulator of HIF1α. Hypoxia was found to downregulate the mRNA expression of ARD1 and also to decrease the interaction between ARD1 and HIF1α. In this way, hypoxia would release HIF1α from the negative ARD1-mediated effect.

However, there have been several reports contradicting the original findings, including one that was cited in the Minucci review[3]. First, downregulation of human ARD1 was not found to coincide with increased expression of genes downstream of HIF1α[4]. Two independent reports have also established that endogenous human ARD1 protein is not downregulated by hypoxia, that overexpression or knockdown of human *ARD1* does not have any effect on the HIF1α protein stability, and that human ARD1 is not capable of significant HIF1α acetylation[3,5].

Recently, the group behind the original findings stated that the mouse ARD1 found to destabilize HIF1α was a special isoform of ARD1 with a completely different C-terminal region than the mouse and human wild-type ARD1 (REF. 6.). This splice variant has not yet been identified in humans, and the question is whether ARD1 has any effect at all on HIF1α stability in the human system. In all studies using RNA interference (RNAi)-mediated knockdown of human ARD1, target sequences in the common region between wild-type and the special splice variant were used[3,4,5]. So, if such a splice variant existed in human cells, this would also be silenced. However, no effect on HIF1α stability was observed. Wild-type human ARD1 was also found to potentially interact with HIF1α under normal physiological conditions[5], and the presence of human ARD1 and HIF-1α in the same complex would indicate a biological connection, but the consequences of such an interaction, if any, remains to be elucidated.

ARD1 function seems to be conserved during evolution, and conservation is supported by phylogenetic analyses[7]. Studies in yeast[8,9,10], mice[11] and humans[12] demonstrate that ARD1 is an N-terminal acetyltransferase (NAT) that is involved in co-translational acetylation of nascent polypeptides. So, until further evidence is presented, ARD1 should be denoted as a 'NAT' and neither a 'HAT' nor a 'NAT/HAT'.

1. Minucci, S. & Pelicci, P. G. Histone Deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. *Nature Rev. Cancer* **6**, 38–51 (2006).
2. Jeong, J.-W. *et al.* Regulation and destabilization of HIF-1α by ARD1 mediated acetylation. *Cell* **111**, 709–720 (2002).
3. Bilton, R. *et al.* Arrest-defective-1 protein, an acetyltransferase, does not alter stability of Hypoxia-inducible Factor (HIF)-1α and is not induced by hypoxia or HIF. *J. Biol. Chem.* **280**, 31132–31140 (2005).
4. Fisher, T. S. *et al.* Analysis of ARD1 function in hypoxia response using retroviral RNA interference. *J. Biol. Chem.* **280**, 17749–17757 (2005).
5. Arnesen, T. *et al.* Interaction between HIF-1α (ODD) and hARD1 does not induce acetylation and destabilization of HIF-1α. *FEBS Lett.* **579**, 6428–6432 (2005).
6. Kim, S.-H. *et al.* Characterization of ARD1 variants in mammalian cells. *Biochem. Biophys. Res. Comm.* **340**, 422–427 (2006).
7. Polevoda, B. & Sherman, F. N-terminal acetyltransferases and sequence requirements for N-terminal acetylation of eukaryotic proteins. *J. Mol. Biol.* **325**, 595–622 (2003).
8. Mullen, J. R. *et al.* Identification and characterization of genes and mutants for an N-terminal acetyltransferase from yeast. *EMBO J.* **8**, 2067–2075 (1989).

9. Park, E. C. & Szostak, J. W. Ard1 and Nat1 proteins form a complex that has N-terminal acetyltransferase activity. *EMBO J.* **11**, 2087–2093 (1992).
10. Polevoda B. *et al.* Identification and specificities of N-terminal acetyltransferases from *Saccharomyces cerevisiae*. *EMBO J.* **18**, 6155–6168 (1999).
11. Sugiura, N. *et al.* An evolutionarily conserved N-terminal acetyltransferase complex associated with neuronal development. *J. Biol. Chem.* **278**, 40113–40120 (2003).
12. Arnesen, T. *et al.* Identification and characterization of the human ARD1–NATH protein acetyltransferase complex. *Biochem J.* **386**, 433–443 (2005).