LIX JCET LECTURE, 20.03.2015, 9.00

Nicotinamide N-methyltransferase: from disease to 3D structure

Dr. Davide Sartini
Università Politecnica delle Marche
Ancona, Italy

The enzyme nicotinamide N-methyltransferase (NNMT) catalyses the N-methylation of nicotinamide, pyridine and structurally related compounds, using S-adenosyl-L-methionine (SAM) as methyl donor. NNMT has been found to be overexpressed in several malignancies, including clear cell renal cell carcinoma (ccRCC), oral squamous cell carcinoma (OSCC), bladder urothelial carcinoma (BUC), and non-small cell lung cancer (NSCLC). Moreover, NNMT upregulation has been recently reported in metabolic syndrome and in cancer stem cell (CSC)-enriched populations obtained from human cancer cell lines.

Results obtained from studies carried out to investigate the functional significance of alterations in enzyme expression associated with disease, and the role of NNMT in cancer cell metabolism, demonstrated that NNMT knockdown led to a significant decrease of anchorage-independent cell growth and cell proliferation, both *in vitro* and *in vivo*, in several human cancer cell lines.

The crystal structure of human NNMT as a ternary complex bound to both the demethylated donor S-adenosyl-L-homocysteine (SAH) and the acceptor substrate nicotinamide has been determined. These studies revealed the structural basis for nicotinamide binding and highlight several residues in the active site which may play a fundamental role in nicotinamide recognition and NNMT catalysis. The functional importance of these residues was probed by site-directed mutagenesis and enzyme kinetics analysis.

References

1. **Sartini D**, Muzzonigro G, Milanese G, Pierella F, Rossi V, Emanuelli M. Identification of **nicotinamide N-methyltransferase** as a novel tumor marker for renal clear cell carcinoma. J Urol. 2006 Nov;176(5):2248-54.
2. **Sartini D**, Santarelli A, Rossi V, Goteri G, Rubini C, Ciavarella D, Lo Muzio L, Emanuelli M. **Nicotinamide N-methyltransferase** upregulation inversely correlates with lymph node metastasis in oral squamous cell carcinoma. Mol Med. 2007 Jul-Aug;13(7-8):415-21.
3. Emanuelli M, Santarelli A, **Sartini D**, Ciavarella D, Rossi V, Pozzi V, Rubini C, Lo Muzio L. **Nicotinamide N-methyltransferase** upregulation correlates with tumour differentiation in oral squamous cell carcinoma. Histol Histopathol. 2010 Jan;25(1):15-20.
4. Pozzi V, Mazzotta M, Lo Muzio L, **Sartini D**, Santarelli A, Renzi E, Rocchetti R, Tomasetti M, Ciavarella D, Emanuelli M. Inhibiting proliferation in KB cancer cells by RNA interference-mediated knockdown of **nicotinamide N-methyltransferase** expression. Int J Immunopathol Pharmacol. 2011 Jan-Mar;24(1):69-77.
5. Peng Y, **Sartini D**, Pozzi V, Wilk D, Emanuelli M, Yee VC. Structural basis of substrate recognition in human **nicotinamide N-methyltransferase**. Biochemistry. 2011 Sep 13;50(36):7800-8.
6. **Sartini D**, Pozzi V, Renzi E, Morganti S, Rocchetti R, Rubini C, Santarelli A, Lo Muzio L, Emanuelli M. Analysis of tissue and salivary **nicotinamide N-methyltransferase** in oral squamous cell carcinoma: basis for the development of a noninvasive diagnostic test for early-stage disease. Biol Chem. 2012 May;393(6):505-11.
7. **Sartini D**, Muzzonigro G, Milanese G, Pozzi V, Vici A, Morganti S, Rossi V, Mazzucchelli R, Montironi R, Emanuelli M. Upregulation of tissue and urinary **nicotinamide N-methyltransferase** in bladder cancer: potential for the development of a urine-based diagnostic test. Cell Biochem Biophys. 2013 Apr;65(3):473-83.
8. Pozzi V, **Sartini D**, Morganti S, Giuliante R, Di Ruscio G, Santarelli A, Rocchetti R, Rubini C, Tomasetti M, Giannatempo G, Orlando F, Provinciali M, Lo Muzio L, Emanuelli M. RNA-mediated gene silencing of **nicotinamide N-methyltransferase** is associated with decreased tumorigenicity in human oral carcinoma cells. PLoS One. 2013 Aug 21;8(8):e71272.

9. **Sartini D**, Morganti S, Guidi E, Rubini C, Zizzi A, Giuliante R, Pozzi V, Emanuelli M. **Nicotinamide N-methyltransferase** in non-small cell lung cancer: promising results for targeted anti-cancer therapy. Cell Biochem Biophys. 2013 Dec;67(3):865-73.
10. **Sartini D**, Seta R, Pozzi V, Morganti S, Rubini C, Zizzi A, Tomasetti M, Santarelli L, Emanuelli M. Role of **nicotinamide N-methyltransferase** in nonsmall cell lung cancer: in vitro effect of shRNA-mediated gene silencing on tumorigenicity. Biol Chem. 2015 Mar 1;396(3):225-34.
11. Giuliante R, **Sartini D**, Bacchetti T, Rocchetti R, Klöting I, Polidori C, Ferretti G, Emanuelli M. Potential involvement of **nicotinamide N-methyltransferase** in the pathogenesis of metabolic syndrome. Metab Syndr Relat D. 2015. In press.