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Mitochondrial sirtuin 5 (SIRT5) controls glutamine metabolism and ammonia-induced autophagy in breast cancer cells

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Cirtuins (SIRT1 to SIRT7) are a protein family of NAD⁺-dependent deacetylases. In hepatocytes SIRT5 has been shown to Ocontrol ammonia utilization by modulating the first step of urea cycle. Recently, in cancer cells, ammonia produced by glutaminolysis has been shown to increase autophagy and to contribute to the overall tumor survival by eliminating damaged and toxic macromolecules. However, it is not known if SIRT5 can modulate ammonia-induced autophagy and survival in cancer cells. To address this possibility, clones of breast cancer cells, MDA-MB-231 overexpressing and silenced for SIRT5 were produced. Our results show that SIRT5 overexpression decreased ammonia concentration in cell culture medium, an event that resulted in inhibition of ammonia-induced autophagy. By contrast, SIRT5 silencing increased ammonia concentration and autophagy in cancer cells. Similarly, SIRT5 pharmacological inhibition prevented ammonia-induced autophagy. Ammonia regulation was achieved by SIRT5 by controlling glutamine metabolism. In fact, we found that SIRT5 and glutaminase coimmunoprecipitated and that SIRT5 inhibition resulted in an increased succinylation of glutaminase. We next determine that autophagy and mitophagy were increased by ammonia with an increase of autophagy markers LC3, GABARAP and GATE16, mitophagy markers BNIP3 and PINK1/Parkin system as well as mitochondrial morphology and dynamics. We observed that, autophagy and mitophagy increased in SIRT5 silenced cells and in wt cells treated with the SIRT5 inhibitor and decreased in SIRT5 overexpressing cells. In conclusion we propose that the control of glutamine metabolism and ammoniainduced autophagy by SIRT5 might represent a survival strategy in tumor cells to survive to chemotherapy, hypoxia or nutrient starvation.

Biography

M Tafani has received his PhD in 2004 from the Sapienza University. He completed his PhD and Postdoctoral studies at Thomas Jefferson University in Philadelphia. In 2010, he was appointed as Associate Professor at Sapienza University of Rome. He has published 50 papers on peer-reviewed journals. He serves as an editorial board member of Cancer Research Journal of the Science Publishing Group.