**Summary of Sirtuin Structures**

**(12-30-2013)**

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| **Protein(+small molecule)** | **PDB ID** | **Major Findings** | **Reference** |
| Sir2Af1 + NAD+ (ADPR observed) | 1ICI | Overall sirtuin fold and NAD+ binding site | Xu group, Cell 2001 |
| hSIRT2 apo | 1J8F | Overall sirtuin fold | Pavletich group, NSMB 2001 |
| Sir2Af2 + p53K382Ac | 1MA3 | Mode of p53 substrate binding | Wolberger group, Mol Cell 2002 |
| Sir2Af1 + NAD+ (ADPR observed) | 1M2G | Overall sirtuin fold | Cho group, J Biol Chem 2002 |
| Sir2Af1(S24A) + NAD+ (ADPR observed) | 1M2H | Local conformation change around S24A |
| Sir2Af1(H80N) + NAD+(ADPR observed) | 1M2J | Local conformation change around H80N |
| Sir2Af1(F159A) + NAD+(ADPR observed) | 1M2K | F159 is proposed to participate in substrate binding |
| Sir2Af1(D102G, F159A, R170A) + NAD+ | 1M2N | 2’-O-Ac-ADP-ribose product observed after the crystal was incubated with N-acetyl lysine |
| yHst2, full length | 1Q14 | Overall Hst2 fold. C- and N-terminal extensions interact with NAD+ and acetyllysine binding sites, respectively to autoinhibit the enzyme | Marmorstein group, NSMB 2003 |
| yHst2 + NAD+(ADPR observed) | 1Q17 | Cofactor binding loop becomes ordered compared to apo structure | Marmorstein group, Structure 2003 |
| yHst2 + NAD+ (2’-O-Ac-ADPR observed) +H4K16Ac peptide | 1Q1A | Model for 2’-O-Ac-ADP-ribose product and acetyllysine substrate binding in the same structure |
| CobB (E. Coli) +H4K16Ac peptide | 1S5P | Model of acetyllysine peptide substrate binding | Marmorstein group, J Mol Biol 2004 |
| Sir2Af2 + NAD+ | 1S7G | Active NAD+ binding with nicotinamide moiety ound in the C pocket | Wolberger group, Mol Cell 2004 |
| yHst2 + H4K16Ac peptide + carba-NAD+ (non-hydrolyzable analogue) | 1S7C | Nicotinamide moiety binds in C pocket; N-ribose planar to acetyllsine supporting an SN1 catalytic mechanism | Marmorstein group, PNAS 2004 |
| yHst2 +ADPR+H4K16Ac peptide | 1SZD | Model of ADPR binding and proposal of a D pocket for free nicotinamdie binding |
| Sir2Af2 + NAD+ + NAM | 1YC2 | Free nicotinamdie binding observed in the C pocket | Wolberger group, Mol Cell 2005 |
| Sir2Tm +p53K382Ac peptide + NAM | 1YC5 | Free nicotinamide binding observed in the C pocket |
| Sir2Tm + polypropylene glycol | 2H2I | Approximation of the apoenzyme | Wolberger group, Biochemistry 2006 |
| Sir2Tm +p53K382Ac peptide | 2H2D | Residues at -1 and +2 positions of the peptide make side chain interactions with Sir2Tm |
| Sir2Tm +p53K382 peptide | 2H2F | Residues at -1 and +2 positions of the peptide make side chain interactions with Sir2Tm |
| Sir2Tm +H4K79Ac peptide | 2H2H | Residues at -1 and +2 positions of the peptide make side chain interactions with Sir2Tm |
| Sir2Tm +H4K115Ac peptide | 2H2G | Residues at -1 and +2 positions of the peptide make side chain interactions with Sir2Tm |
| SirTm + NAD+ +p53K382Ac peptide | 2H4F | Putative Michaelis complex suggesting an SN2 catalytic mechanism | Wolberger group, Structure 2006 |
| SirTm(H116Y) + NAD+ +p53K382Ac peptide | 2H4H | Identical to wild type and NAD+ orientation is not dependent on contacts with the His116 general base |
| (Sir2Tm + p53K382Ac peptide) crystal soaked with NAD+ | 2H4J | Deacetylated p53 observed |
| Sir2Tm(H116A) + NAD++p53K382Ac peptide | 2H59 | 3’-O-Ac-ADP-ribose +p53K382 observed in one molecule |
| yHst2+ADP-HPD + H4K16Ac peptide | 2OD7 | Binding model of an oxocarbenium intermediate mimic | Marmorstein group, Mol Cell 2007 |
| yHst2+ADP-HPD + H4K16Ac peptide +NAM | 2OD9 | Nicotinamide is observed to bind in the D pocket (valid issues were raised regarding the crystallographic evidence) |
| yHst2(I117F) + carba-NAD++H4K16Ac peptide | 2OD2 | Isomorphous to wild type; I117 is proposed to participate in nicotinamdie binding in D pocket |
| hSIRT5 +NAD+ (ADPR observed) | 2B4Y | Sirtuin fold | Plotnikov group, Structure 2007 |
| hSIRT5 + suramin | 2NYR | Suramin binding model |
| Sir2Tm +DADMe-NAD+ +p53K382Ac peptide | 3D4B | Binding model of a dissociative intermediate | Wolberger group, Structure 2008 |
| Sir2Tm + S-alkylamidate | 3D81 | Binding model of an O-alkylamidate intermediate mimic |
| Sir2Tm + p53 peptide(KAcXXR) | 3JR3 | Putative nucleophilic attack from Arg at +2 of acetyllysine peptide for ADP-ribosylation | Wolberger group, J Biol Chem 2009 |
| hSIRT3 apo | 3GLS | Sirtuin fold | Perni group, J Biol Chem 2009 |
| hSIRT3 + AceCS2-KAc | 3GLR | Model of acetyllysine binding |
| hSIRT3 +AceCS2-KS-Ac-ADPR | 3GLT | Binding model of an S-alkylamidate intermediate |
| hSIRT3+AceCS2-K | 3GLU | Binding of a dethioacetylated AceCS2 peptide |
| hSIRT5+H3K9 (thioacetyl) peptide | 3RIG | Binding model of an Succinyl-lysine peptide | Lin group, Science 2011 |
| hSIRT5 +NAD++H3K9 (N-succinyl) peptide | 3RIY |  |
| Sir2Tm + p53K382 (propionyl) peptide) | 3PDH | Binding model of propionyl-lysine | Wolberger group, Protein Sci 2011 |
| hSIRT6 +NAD+ (ADPR observed) | 3K35 | Sirtuin fold(lacks the helical module in the smaill domain); ADPR binding | Denu group, J Boil Chem 2011 |
| hSIRT6 + ADPR | 3PKI |  |
| hSIRT6+2’-N-acetyl-ADP-ribose | 3PKJ | Sirtuin bound to 2’-N-acetyl-ADP-ribose, a non-hydrolyzable analog of O-acetyl-ADP-ribose |
| hSIRT3 + Ac-ACS +Carba-NAD | 4FVT |  | Dai, H. J. Org. Chem. 2012 |
| hSIRT5+Succ-IDH2+Carba-NAD | 4G1C |  |
| hSIRT3+Fluor-de-Lys peptide +piceatannol | 4HD8 |  | Steegborn group, Plos One 2012 |
| hSIRT3+Bromo-Resveratrol+ACS2 peptide | 4C78 |  | Steegbon group, Chem Biol. 2013 |
| hSIRT3+Bromo-Resveratrol + Fluor-de-Lys peptide | 4C7B |  |
| hSIRT3+Ex-527+NAD | 4BV3 |  | Steegborn group, PNAS 2013 |
| hSIRT3+Ex-527+ADP-Ribose | 4BVB |  |
| hSIRT3+Ex-527+2O’Acetyl-ADP Ribose | 4BVH |  |
| hSIRT3+thioalkylimidate formed from thio-acetyllysine ACS2-peptide | 4BVE |  |
| hSIRT3+thioalkylimidate formed from thio-acetyllysine ACS2-peptide in the presence of Ex527 | 4BVF |  |
| hSIRT3+native alkylimidate formed from thio-acetyllysine ACS2-peptide in the presence of Ex527 | 4BVG |  |
| Sir2+Ex-527+2O’Acetyl-ADP Ribose+deacetylated p53-peptide | 4BV2 |  |
| Sir2+Ex-527+products /substrates p53 peptide + NAD | 4BUZ |  |
| hSIRT3+ELT inhibitor11c | 4JSR | [N-{2-[1-(6-carbamoylthieno[3,2-d]pyrimidin-4-yl)piperidin-4-yl]ethyl}-N'-ethylthiophene-2,5-dicarboxamide] | Dai, H.J. Med. Chem. 2013 |
| hSIRT3+ELT inhibitor 28 | 4JT8 | 28 [4-(4-{2-[(2,2-dimethylpropanoyl)amino]ethyl}piperidin-1-yl)thieno[3,2-d]pyrimidine-6-carboxamide] |
| hSIRT3+ELT inhibitor 3 | 4JT9 | [14-(4-{2-[(methylsulfonyl)amino]ethyl}piperidin-1-yl)thieno[3,2-d]pyrimidine-6-carboxamide] |
| hSIRT3+ADP-Ribose | 4BN4 |  | Steegborn group, Acta Crystallogr., 2013 |
| hSIRT3+SRT1720 inhibitor | 4BN5 |  |
| hSIRT3+acetyl p53+4-amino-7methylcoumarin | 4FZ3 |  | Liu D et al, J. Med. Chem. 2013 |

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**PubMed Abstract:**
Sirtuins are protein deacetylases regulating metabolism, stress responses, and aging processes, and they were suggested to mediate the lifespan extending effect of a low calorie diet. Sirtuin activation by the polyphenol resveratrol can mimic such lifespan extending effects and alleviate metabolic diseases. The mechanism of Sirtuin stimulation is unknown, hindering the development of improved activators. Here we show that resveratrol inhibits human Sirt3 and stimulates Sirt5, in addition to Sirt1, against fluorophore-labeled peptide substrates but also against peptides and proteins lacking the non-physiological fluorophore modification. We further present crystal structures of Sirt3 and Sirt5 in complex with fluorogenic substrate peptide and modulator. The compound acts as a top cover, closing the Sirtuin's polypeptide binding pocket and influencing details of peptide binding by directly interacting with this substrate. Our results provide a mechanism for the direct activation of Sirtuins by small molecules and suggest that activators have to be tailored to a specific Sirtuin/substrate pair.

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