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"Modification web" & "Signal router" theories on histone modification network system in eukaryotic gene regulation: An imaginative, creative, original, competitive and non-competitive science journey with nature's mysterious cell

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James Friesen | Cecil Yip Red Seminar Room

Abstract:

"Histone code hypothesis" is inadequate to explain the complexity and robustness against various perturbations. We developed a theory of the regulatory network of histone modifications in which we encode histone modifications as nodes and regulatory interactions between histone modifications as edges (1). This network has scale-free like property, which supports its complexity and robustness. We further show that the intrinsically disordered tail regions (IDR) are suitable for the acquisition of this scale-free like property (1). The "Modification web" of IDR may function as "signal router" for the complex and robust processing of the large amounts of signaling information (1). In the network, the compensatory pathways are created to acquire the robustness against any defects. B ecause of this robustness, it is difficult to determine the significance of the histone modifications in IDR. To overcome this issue, we created a strategy using drugs coordinately to inhibit modification enzymes and observed the mutant phenotypes when the compensatory pathways are largely interrupted. We analyzed our developed histone-GLibrary (2-4) using HDAC inhibitor and identified novel phenotypic mutants. We also examined the phenotypic changes through the combined use of an HDAC inhibitor and an inhibitor of DNA-mediated reactions (5). This strategy reveals how histone "modification web" network is robust and its characteristics should be utilized for drug development (6). Before discussing of my current research on histone modification network system, I will briefly talk about the essence of my studies on eukaryotic gene regulation concentrated on RNA polymerase II/S-II (7,8) and TBP/TFIID/GTF (9-19), MYST-HAT/CIA(ASF1)/histone chaperones (20-30). Because these past world-leading studies inevitably affect on my present studies on histone modification network system based on many-to-many reactions.

(1) Genes Cells, 14, 789 (2009), (2) Genes Cells, 12, 13 (2007), (3) Genes Cells, 14, 1271 (2009),
(4) EMBO J., 30, 3353 (2011), (5) Genes Cells, 15, 553 (2010), (6) Curr.Pharm.Design, 19, in press (2013),
(7) JBC, 259, 608 (1984), (8) JBC, 260, 5739 (1985), (9) Cell, 54, 665 (1988), (10) Cell, 54, 1033 (1988),
(11) Nature, 341, 299 (1989), (12) Proc.Natl.Acad.Sci.U.S.A., 88, 9553 (1991), (13) Nature, 354, 398 (1991),
(14) Nature, 354, 401 (1991), (15) Nature, 360, 40, (1992) (16) Proc.Natl.Acad.Sci.U.S.A., 89, 11809 (1992),
(17) Nature, 362, 179 (1993), (18) Nature, 367, 484 (1994), (19) Nature, 369, 252 (1994),
(20) J.Biol.Chem., 272, 30595 (1997), (21) Genes Cells, 5, 221 (2000), (22) Cell, 102, 463 (2000),
(23) Proc.Natl.Acad.Sci.U.S.A., 99, 9334 (2002), (24) Nature Genet., 32, 370 (2002),
(25) Nature Struct.Mol.Biol., 11, 275 (2004), (26) Genes Cells, 9, 499 (2004),
(27) Nature Struct.Mol.Biol., 13, 331 (2006), (28) Proc.Natl.Acad.Sci.U.S.A., 104, 4285 (2007),
(29) Nature, 446, 338 (2007), (30) Proc.Natl.Acad.Sci.U.S.A., 107, 8153 (2010)

Host: Dr. Jack Greenblatt