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Gcn5: The Quintessential Histone Acetyltransferase

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INTRODUCTION:

The concept of chromatin as a regulator of gene expression has been the foundation for nearly all studies of eukaryotic transcription over the past 25 years since the discovery of the first nuclear histone acetyltransferase, Gcn5, by Jim Brownell and David Allis [1,2]. The histone proteins that form the building blocks of chromatin restrict access to the underlying DNA, and as early as the 1950s and 1960s it was clear that the presence of histones was inhibitory to RNA synthesis. The observation that histones could be chemically modified by the post-translational addition of acetyl or methyl groups [3,4] led to the idea, first championed by Vincent Allfrey, that histone acetylation could act as a switch to control transcription [5]. Multiple *in vitro* studies in the following decades supported the idea that acetylation of histones could stimulate transcription from a chromatin template (reviewed in [6,7]). Moreover, histone acetylation clearly correlated with active transcription within cells [6,7]. However, the lack of any good candidates for enzymes that could add (or remove) the acetyl mark to histones within the nucleus was a major stumbling block to understanding how histone acetylation could control gene expression.

In [8] in this Special Issue, Jim Brownell and David Allis describe the intense search for this nuclear histone acetyltransferase activity, which succeeded due to clever biochemical approaches combined with use of a underappreciated organism, *Tetrahymena thermophila*, that provided a rich starting material for biochemical purifications in the form of its specialized transcriptionally active macronuclei [1]. Using this approach, the Allis group tracked this nuclear histone acetyltransferase down to a 55 kDa protein that was homologous to a yeast protein, Gcn5 [2]. Gcn5 was not the first histone acetyltransferase to be identified; that distinction falls to the cytoplasmic histone acetyltransferase Hat1 that was cloned just one year earlier by Rolf Sternglanz and colleagues [9,10]. However, Gcn5 provided a much stronger link between histone acetylation and transcription because Gcn5 had already been identified as an “adaptor protein” in the yeast *Saccharomyces cerevisiae* that was necessary for transcription activation by transcription factors such as Gcn4 [11]. Thus, the identification of Gcn5 as a nuclear histone acetyltransferase provided a clear connection between an enzyme that modified histones within chromatin and gene expression, supporting Allfrey’s original hypothesis that histone acetylation could act as a switch to control RNA synthesis. A new era in transcription research quickly emerged with the discovery of enzymes that deacetylate histones (HDAC1/Rpd3) [12], or add other chemical moieties like methyl groups (SUV39H1) [13]. At the last count, more than 16 different histone modifications have been identified in mammalian cells [14], providing a complex combinatorial network that defines chromatin structure and biology.

In this Special Issue, we bring together many of the original researchers involved in the initial studies to identify and characterize Gcn5, together with leaders from the field who have contributed to our understanding of this quintessential histone acetyltransferase. First, Jim Brownell and David Allis describe the discovery of Gcn5 [8], followed by Brittany Albaugh and John Denu who highlight key structural and catalytic attributes of Gcn5 as the defining member of the Gcn5-related N-acetyltransferase (GNAT) protein superfamily [15]. Next, Michael Sack and colleagues describe a protein that is closely related to Gcn5, Gcn5L1, which lacks intrinsic histone acetylation activity but is still involved in protein acetylation as part of multi-subunit complexes that regulate aspects of vacuolar organelle function [16]. Gcn5, like Gcn5L1, is also found as part of large multi-subunit complexes, and in [17], Shelley Berger, Patrick Grant, and Fred Winston describe the genetic and biochemical studies that led to the identification of the most famous of these Gcn5 complexes, the Spt-Ada-Gcn5 acetyltransferase (SAGA) complex in

the yeast *S. cerevisiae*. Next, Jose M. Espinola Lopez and Song Tan describe the close interactions between Gcn5 and its immediate binding partners, the Ada2, Ada3 and Sgf29 proteins, that influence Gcn5 activity and control its incorporation into different complexes [18] . A recent series of cryo-EM studies have provided a window into SAGA structure and function, and our current understanding of the structure of the Gcn5 complexes and their function is outlined in the Special Issue by Dominique Helmlinger, Gabor Papai, Didier Devys, and László Tora [19]. The discussion of SAGA's role in transcription is elaborated on by Brian Strahl and Scott Briggs in [20], who also discuss the interplay between histone modifications catalyzed by SAGA and other chromatin marks including histone phosphorylation, ubiquitination, and methylation.

Strikingly, many subunits of the Gcn5 complexes are shared with other chromatin or transcription regulatory complexes. In particular, several of the TAF subunits in SAGA are shared with the general transcription factor TFIID. In [21], Marc Timmers describes the shared and specialized TAF subunits in SAGA, while in [22] Carme Nuño-Cabanes and Susana Rodríguez-Navarro discuss other SAGA subunits that are shared with other complexes, or that may have independent biological functions. Although SAGA was first characterized as an acetyltransferase, this multi-subunit complex also possesses a second histone modifying activity: deubiquitination of mono-ubiquitinated histone H2B. In [23], Ryan Mohan's group describe how SAGA's deubiquitinase activity was first identified, and provide insight into its potential biology roles in transcription and other cellular processes.

Gcn5 is highly conserved across eukaryotes, and also forms part of large multi-subunit complexes in plants, insects, and in mammalian cells. In [24], Klaus D. Grasser, Vicente Rubio, and Fredy Barneche describe the plant SAGA complex, which although similar to other organisms, contains some striking differences with regards to the deubiquitination module. In [25], Eliana Torres-Zelada and I describe how studies in the model insect *Drosophila melanogaster* led to the identification of a metazoan-specific Gcn5 complex (ATAC), and discuss how insects contain an additional Gcn5 complex that is absent from yeast or mammalian cells [25]. In [26], Evangelia Koutelou, Aimee Farria, and Sharon Dent describe how studies in mammalian cells and in mice have led to new insight into the roles that Gcn5 and its paralog, PCAF, play during development and in disease. This focus on Gcn5's role in human disease is further elaborated by Beste Mutlu and Pere Puigserver in [27] who discuss how Gcn5's role in acetylating non-histone targets, particularly PGC-1α, contributes to its function as a nutrient sensor that regulates energy metabolism.

Although histones were the first targets of Gcn5 to be identified, hundreds of non-histone proteins are also acetylated by Gcn5. In [28], Michael Downey describes the approaches used to identify Gcn5 substrates, providing a comprehensive list of the Gcn5 substrates that have been currently identified in different species. Intriguingly, this list includes transcription factors, chromatin remodelers and cell cycle proteins, leading to the question of how broadly these non-histone substrates contribute to Gcn5's function. Genetic studies in *S. cerevisiae*, highlighted in this Special Issue by Emily Petty and Lorraine Pillus in [29] provide clues as to many of the roles for Gcn5 in cell cycle control, potentially due to acetylation of both histone and non-histone targets. The revised nomenclature of Gcn5 as a lysine acetyltransferase (KAT2 in *S.cerevisiae* and *Drosophila*, KAT2A and KAT2B in mammals) [30] reflects this broader substrate specificity, although readers will find Gcn5 referred to by both terms within articles in this Special Issue – reflecting its initial characterization as a histone acetyltransferase.

Throughout the past 25 years, many different scientific researchers have contributed to studies on Gcn5, and it has been a joy to work with many of these authors in putting together the current Special Issue. In particular, my own interest in Gcn5 and in chromatin biology owes much to my postdoctoral training with Jerry Workman and Susan Abmayr. Sadly, Susan passed away on July 18, 2019, and this BBA Special Issue on *Gcn5, the quintessential histone acetyltransferase* is dedicated to her memory.

CAPTION:

Susan Abmayr, PhD: March 13, 1956 - July 18, 2019

Susan was a wonderful scientist and mentor who had a passion for the tiny fruitfly, *Drosophila*, and for studying transcription in the context of developmental biology. She had a life-long interest in transcription beginning with her work as a research assistant with Sarah Elgin using *Drosophila* as a genetic model for heterochromatic gene silencing. She then moved to Rockefeller University in New York for her PhD studies with Robert Roeder, where she met her husband and long-time collaborator, Jerry Workman. During her postdoctoral training with Tom Maniatis at Harvard University, she discovered some of the key transcription factors that control muscle development including Mef2. Susan continued to study muscle development during her independent research career first in the Department of Biochemistry and Molecular Biology at Penn State University, and later at the Stowers Institute for Medical Research in Kansas City. Although Susan was well recognized for her studies on muscle development, she was also instrumental in expanding the studies on Gcn5 in the Workman group into *Drosophila*. Her expertise in *Drosophila* genetics and developmental biology culminated in over 25 co-authored papers that shed light on SAGA, ATAC and ADA function in particular tissues to control developmental processes such as oogenesis, embryo development, and neuronal targeting. Susan was a rigorous and occasionally, when needed, a tough mentor, but she also exemplified the qualities of persistence and hard work – leading by example and working side-by-side in the fly room to demonstrate techniques and teach her students. Given her life-long interest in transcription and her substantial contributions to understanding Gcn5 function, it is fitting to celebrate her life and achievements in this Special Issue on Gcn5.

BIOGRAPHY:

Vikki Weake is an Associate Professor in the Department of Biochemistry at Purdue University. She graduated from Massey University in New Zealand and obtained her PhD in Genetics from the same institution for work on dosage compensation in *Drosophila* with Max Scott. Following her graduate work, she moved to the Stowers Institute in Kansas City, USA to work as a postdoctoral fellow with Jerry Workman and Susan Abmayr where her work focused on characterizing tissue-specific functions of SAGA. She moved to the Department of Biochemistry at Purdue University in West Lafayette, Indiana in 2012 to establish her own lab. During her postdoctoral work, she had shown that mutations that disrupt SAGA cause defects in neuronal development in the eye. This connection between chromatin, transcription and neuroscience initiated her interest in the interplay between these fields, and her lab now works on the transcriptional mechanisms involved in aging in neurons using the *Drosophila* eye as a model system. In addition, her lab continues to work on characterizing a recently discovered *Drosophila* Gcn5 complex that is unique to insects. Her work is funded by the National Science Foundation and the National Eye Institute within the National Institutes of Health.

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