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Nucleosome remodelers in double-strand break repair

Andrew Seeber[1,2,4], Michael Hauer[1,3,4] and Susan M Gasser[1,2]

ATP-dependent nucleosome remodelers use ATP hydrolysis to shift, evict and exchange histone dimers or octamers and have well-established roles in transcription. Earlier work has suggested a role for nucleosome remodelers such as INO80 in double-strand break (DSB) repair. This review will begin with an update on recent studies that explore how remodelers are recruited to DSBs. We then examine their impact on various steps of repair, focusing on resection and the formation of the Rad51-ssDNA nucleofilament. Finally, we will explore new studies that implicate remodelers in the physical movement of chromatin in response to damage.

Addresses
[1] Friedrich Miescher Institute for Biomedical Research, Maulbeerstrasse 66, CH-4058 Basel, Switzerland
[2] University of Basel, Faculty of Natural Sciences, Klingelbergstrasse 50, CH-4056 Basel, Switzerland
[3] University of Tuebingen, Interfaculty Institute for Cell Biology, Department of Molecular Biology, Auf der Morgenstelle 15, D-72076 Tuebingen, Germany

Corresponding author: Gasser, Susan M (susan.gasser@fmi.ch)
[4] These authors contributed equally to this work.

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Introduction

In eukaryotic cells, the genomic DNA is wrapped around histone proteins to form a compact nucleosomal fiber. This form of chromatin is bound and protected by a variety of factors, yet is nonetheless susceptible to environmentally induced damage. Once damaged, repair and checkpoint signaling machineries recruit chromatin modifying enzymes to render damaged DNA accessible to repair. This is mediated both by enzymes that modify histones and by ATP-dependent nucleosome remodelers that can shift, evict and exchange histone dimers or octamers, facilitating the different steps of the repair process. Histone modifications coordinate repair with other DNA-based functions, such as transcription and replication. Recent work also suggests that nucleosome remodelers enhance micromovement [1•] and possibly evict proteins that inhibit the repair process [2••]. Finally, the re-establishment of the initial chromatin structure requires histone chaperones and various modifying enzymes that deposit or remove acetyl-groups, methyl-groups and ubiquitin from histone tails [3]. It is likely that active nucleosome remodeling is required as well for proper recovery after repair.

All remodelers of the SWI2/SNF2 family contain related, large catalytic ATPase subunits. A new phylogenetic analysis has replaced the classical grouping (SWI/SNF, ISWI, CHD and INO80) of the various remodelers, splitting them into six major families, namely the Snf2-like, Swr1-like, SMARCAL1, Rad54-like, Rad5/16-like and ERCC6/SSO1653-like [4] (Table 1). SWI/SNF members of the Snf2-like family contain a bromodomain which binds acetylated histone tails. ISWI remodelers have HAND, SANT and SLIDE domains involved in DNA binding in the context of nucleosomes. The Snf2-like family also includes CHD remodelers, which contain a tandem chromodomain that mediates binding to methylated histones. INO80 complexes fall into the Swr1-like class, which has a characteristic insert in the middle of the ATPase domain, and contain a RuvB-like DNA helicase, Rvb1/2 in yeast or TIP49a,b in mammals. Most remodeling complexes harbor a number of additional subunits, among them actin and actin related proteins (Arps), some of which are shared, others unique to specific remodelers (Table 1) [5].

Previous work had shown that mutation or down-regulation of some remodeler subunits renders cells hypersensitive to DNA damage [6]. This phenotype, however, can stem from effects either on transcription, replication, or the repair pathway itself. To study the direct involvement of chromatin remodelers in double strand break (DSB) repair, chromatin immunoprecipitation (ChIP) and fluorescent imaging studies have monitored whether or not a given ATP-dependent nucleosome remodeler was recruited to a unique DSB or to a zone of laser-induced damage. These approaches have implicated many remodelers directly in steps of repair, and most frequently in repair by homologous recombination (HR), but more recently, also by non-homologous end joining (Table 2). Given the broader effect of remodelers on chromatin composition, we will hereafter refer to them as chromatin remodelers, rather than nucleosome remodelers. In this review, we provide an overview about the various roles that remodeling complexes play during DSB repair. Crucial to understand is how remodelers are initially recruited to DSBs, how they impact the various steps of repair and how they affect the formation of the Rad51-ssDNA nucleofilament. Recent studies also implicate chromatin remodelers in changing the physical movement of DNA in response to damage.

Table 1

Composition and classification of nucleosome remodelers in *S. cerevisiae* and Human.

Grouping			Organism							
Family	Subfamily & Composition		*S. cerevisiae*			Human				
Swr1 like	**Ino80**	Complex	**INO80**			**INO80**				
		ATPase	Ino80			hINO80				
		Orthologous subunits	Rvb1*, Rvb2*			TIP49A*, TIP49B*				
			Arp4*, Arp5*, Arp8, Act1			BAF53a*, ARP5, ARP8				
			Taf14							
			Ies2			hIES2				
			Ies6			hIES6				
		Unique	Ies1, Ies3-5, Nhp10			Amida, NFRKB, MCRS1, FLJ90652, FLJ20309				
	Swr1	Complex	**SWR1**			**SRCAP**	**TRRAP/Tip60**			
		ATPase	Swr1			SRCAP	p400			
		Orthologous subunits	Rvb1*, Rvb2*			Tip49a*, Tip49b*	Tip49a*, Tip49b*			
			Arp4*, Arp6, Act1			BAF53a*, Arp6	BAF53a*, Actin			
			Yaf9			GAS41*	GAS41*			
			Swc4/Eaf2			DMAP1*	DMAP1*			
			Swc2/Vps72			YL-1*	YL-1*			
			Bdf1				BRD8/TRCp120			
			H2AZ, H2B			H2AZ, H2B				
			Swc6/Vps71			Znf-HIT1				
		Unique	Swc3,5,7				Tip60, MRG15, MRGX, FLJ11730, MRGBP, EPC1,EPC-like, ING3			
	Etl1	Complex	**FUN30**			**SMARCAD1**				
		ATPase	Fun30			SMARCAD1				
		Subunits	Not identified			Not identified				
Snf2 like	**Mi-2**	Complex	**No homolog**			**NuRD**				
		ATPase				CHD3/Mi-2α CHD4/Mi-2β				
		Subunits				MBD2,MBD3, MTA1-3, HDAC1-2, RbAp46 or 48, p66α, p66β				
	Chd1	Complex	**CHD1**			**CHD1**				
		ATPase	Chd1			CHD1				
		Subunits	monomeric			monomermic				
	Alc1	**Complex**	**No homolog**			**ALC1**				
		ATPase				ALC1				
		Subunits				Not identified				
	Snf2	Complex	**SWI/SNF**	**RSC**		**BAF**	**PBAF**			
		ATPase	Swi2/Snf2	Sth1		BRG1/SMARCA4 or hBRM/SMARCA2	BRG1			
		Orthologous subunits				BAF250a/ARID1A or BAF250b/ARID1B or				
				Rsc1, Rsc2, Rsc4		BAF180*, BAF200/ARID2*	BAF180*, BAF200/ARID2*			
			Swi3	Rsc8		BAF155/SMARCC1* and/or BAF170/SMARCC2*	BAF155/SMARCC1* and/or BAF170/SMARCC2*			
			Swp73	Rsc6		BAF60a/SMARCD1*	BAF60a/SMARCD1*			
			Arp7*, Arp9*	Arp7*, Arp9*		BAF53a*	BAF53a*			
			Snf5	Sfh1		BAF47/hSNF5/SMARCB1*	BAF47/hSNF5/SMARCB1*			
						BAF57/SMARCE1*	BAF57/SMARCE1*			
						β-actin*	β-actin*			
		Unique	Swi1/Adr6, Swp82, Taf14, Snf6, Snf11	Rsc3, Rsc5, Rsc7, Rsc9, Rsc10, Rsc30, Htl1, Lbd7, Rtt102		BAF45a or BAF45d				
	Iswi	Complex	**ISW1a**	**ISW1b**	**ISW2**	**ACF**	**CHRAC**	**NURF**		
		ATPase	Isw1*	Isw1*	Isw2	hSNF2H		hSNF2L		
		Orthologous subunits			Itc1	WCRF180/ hACF1*	WCRF180/ hACF1*	BPTF		
					Dpb4		hCHRAC17	RbAp46		
					Dls1		hCHRAC15	RbAp48		
		Unique	Ioc3	Ioc2, Ioc4						
Rad54 like	**Rad54**	Complex	**Rad54**			**Rad54**				
		ATPase	Rad54			Rad54				

*Subunits shared within different remodeling complexes of the same organism.

Recruitment of chromatin remodelers to a DSB

The INO80 nucleosome remodeler is recruited to DSBs in both yeast and man. In yeast, the INO80 complex is made up of 15 subunits including Ino80, Rvb1/2, Arp5/8, Arp4, Act1, Nhp10 and Ies3. Its recruitment to DSBs in yeast requires an interaction with phosphorylated H2A (γH2A); mutation of the phosphoacceptor site on yeast H2A reduced INO80 binding at an induced DSB [7]. The subunits implicated in this interaction are Nhp10 and Ies3