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The SDR superfamily: functional and structural diversity within a family of metabolic and regulatory enzymes

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Abstract. Short-chain dehydrogenases/reductases (SDRs) constitute a large family of NAD(P)(H)-dependent oxidoreductases, sharing sequence motifs and displaying similar mechanisms. SDR enzymes have critical roles in lipid, amino acid, carbohydrate, cofactor, hormone and xenobiotic metabolism as well as in redox sensor mechanisms. Sequence identities are low, and the most conserved feature is an α/β folding pattern with a central beta sheet flanked by 2–3 α-helices from each side, thus a classical Rossmann-fold motif for nucleotide binding. The conservation of this element and an active site, often with an Asn-Ser-Tyr-Lys tetrad, provides a platform for enzymatic activities encompassing several EC classes, including oxidoreductases, epimerases and lyases. The common mechanism is an underlying hydride and proton transfer involving the nicotinamide and typically an active site tyrosine residue, whereas substrate specificity is determined by a variable C-terminal segment. Relationships exist with bacterial haloalcohol dehalogenases, which lack cofactor binding but have the active site architecture, emphasizing the versatility of the basic fold in also generating hydride transfer-independent lyases. The conserved fold and nucleotide binding emphasize the role of SDRs as scaffolds for an NAD(P)(H) redox sensor system, of importance to control metabolic routes, transcription and signalling.

Keywords. Short-chain dehydrogenases/reductases, reaction mechanism, protein family, oxidoreductase, Rossmann fold, enzyme evolution.

Dehydrogenase family relationships: the ADH paradigm

Based on sequence analyses of insect, yeast and mammalian alcohol dehydrogenases (ADHs) distinct families of NAD(P)(H)-dependent dehydrogenases were postulated well over 25 years ago [1]. This and further studies demonstrated multiple evolutionary steps of 'enzymogenesis' leading to the current system of distinct oxidoreductase families, classes and isozymes [2, 3]. The initial observations have held true, and through genome sequencing projects it is now clear that distinct families of dehydrogenases/reductases represent a large group of gene products within nearly every genome [3, 4]. This large representation of oxidoreductases highlights their importance and functional diversity in the physiology of organisms reaching from prokaryotes to mammals [3]. The variety of particular biochemical roles is enormous and comprises many intermediary metabolic functions. Examples are utilization and detoxification of ethanol and xenobiotics in general, regulation of hormones and signalling molecules (e.g. by hydroxysteroid and prostaglandin dehydrogenases in mammals) or sensing of the redox status in metabolism or transcription, thereby regulating vital cellular processes [5–9].

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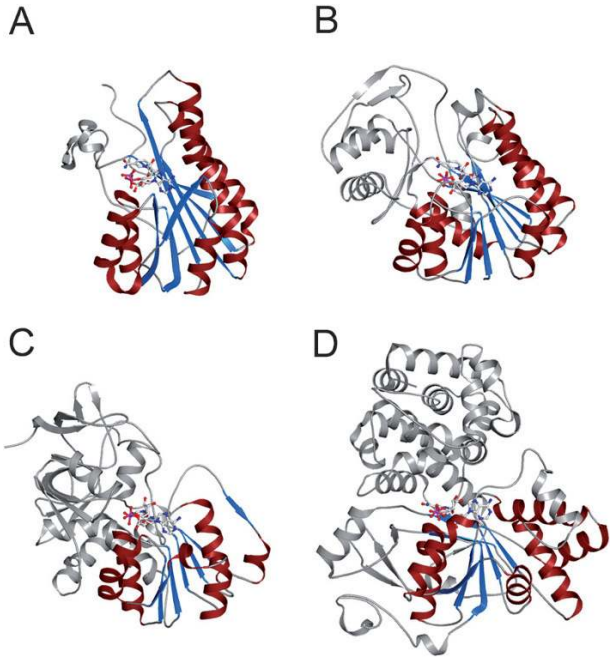

Figure 1. Ribbon diagram comparison of classical SDR, extended SDR, MDR and LDR enzymes. The Rossmann-fold motif is depicted with beta strands in blue and helices in red; additional domains and secondary structural elements are shown in grey. The nucleotide cofactor is drawn in ball-and-stick representation. (*A*) Classical SDR (3α/20β HSD; PDB 2hsd). (*B*) Extended SDR (galactose epimerase; PDB 1xel). (*C*) MDR (horse liver ADH; PDB 1hld). (*D*) LDR (mannitol DH; PDB 1m2w).

Whereas the Zn-containing yeast and liver alcohol dehydrogenases (ADHs; members of the family of medium-chain dehydrogenases/reductases, MDRs) have been well characterized [10–12], insect and bacterial alcohol and polyol dehydrogenases initially received less attention. At first, these enzymes were found to be different [13, 14] and were considered only of prokaryotic and lower eukaryotic origin. However, the discovery of similarities between these enzymes and human or mammalian prostaglandin, hydroxysteroid and other dehydrogenases changed the view dramatically [15–18]. Based on distinct sequence motifs, protein chain length, mechanistic features and structural comparisons, a system of short-, medium- and long-chain dehydrogenases/reductases has now been established [16, 19, 20]. A typical member of the short-chain dehydrogenases/reductases (SDRs) is *Drosophila* ADH, while prokaryotic polyol dehydrogenases and eukaryotic glucose 6-phosphate dehydrogenases or UDP-glucose dehydrogenases are now classified into the heterogenous group of long-chain dehydrogenases/reductases (LDR) [20, 21].

Common to all three types of oxidoreductases is the occurrence of a 'Rossmann-fold' dinucleotide cofactor binding motif (Fig. 1) initially described in lactate, alcohol, malate and glyceraldehyde 3-phosphate dehydrogenases [22–26], and now found to be one of the most common protein folds [4, 27]. The Rossman-fold structural element is composed of a central, twisted parallel β-sheet consisting of 6–7 β-strands [28, 29], which are flanked by 3–4 α-helices from each side. The strand topology is 3-2-1-4-5-6-7 with a long crossover between strands 3 and 4, creating a characteristic binding site for the nicotinamide [29]. This structural motif is characterized by a highly variable Gly-rich sequence pattern critical for structural integrity, and enables accomodation and binding of the pyrophosphate portion of the nucleotide cofactor [29]. An acidic residue binding to the 2′ and 3′ hydroxyls of the adenine ribose and located about 20 residues downstream of the Gly-rich motif, directly after the second β-strand, determines NAD(H) specificity. NADP(H) binding is dictated by the presence of a basic residue within the Gly-rich segment, and/or in the loop after the second strand, as observed in the SDR family [29]. All three oxidoreductase families show distinct chemical mechanisms and domain architectures, reflected in well-defined sequence motifs and domain organizations. Common to all families is the ability to interconvert substrates containing hydroxyl/oxo groups. However, considerable additional substrate specificities exist in the SDR family, as detailed below.

A large variability is noticed in the mechanistic and structural details within each family. MDR enzymes either have a Zn-dependent or Tyr-based catalytic mechanism, and consist of two distinct domains (the coenzyme-binding and the catalytic domain). LDRs have a similar domain architecture as MDRs with the active site located in the cleft between the two domains, but frequently utilize a Lys-based catalytic center [21, 30]. Conversely, most SDR members display a simple one-domain architecture with the substrate binding site located in the highly variable C-terminal region, although additional small domains are occasionally observed, as in the case of 'extended' SDRs (cf. below) [6, 16]. The catalytic base in the majority of SDRs is a highly but not strictly conserved Tyr residue, giving rise to significant mechanistic differences in SDR subclasses. The degree of three-dimensional conservation indicates that ancestral dehydrogenases existed within each MDR, SDR or LDR family. After multiple gene duplicatory events, these ancestral dehydrogenases gave rise to the present system of subfamilies and classes found within each family. Interestingly, the aldo-keto reductases (AKRs), although structurally belonging to the $(\alpha/\beta)_8$ or TIM barrel protein family, display an example of convergent evolution with an active site conformation nearly superimposible to that of SDRs with conserved Tyr and Lys residues [8, 16, 31].

Table 1. Characterized SDR members in different domains of life as of January 2007.

Domain of life	SDR forms
Prokaryotes	15698
Archaea	313
Eukaryotes	5019
Viral	48
Total	21078

SDR: a large protein family

The SDR superfamily presently consists of at least 140 different enzymes (from minimally 71 genes in the human) that are active on a wide spectrum of substrates [6, 32–34], most of which have also been characterized in many species to now represent over 20000 depositions in sequence databases as of January 2007 (Table 1). Genome investigations have shown that about 1/4 of all dehydrogenases found are SDRs [27]. The superfamily is present in all domains of life [3], but because of the large number of completely sequenced bacterial genomes (close to 400 in January 2007), about 3/4 of all known SDR forms are of bacterial origin (Table 1).

In human and mouse, about 70 distinct SDR forms are found [35, 36] (Table 2), when adjusted for closely related forms at the 90% identity level. When variants due to different splicing and related isoforms are also included, the gross SDR number is about double. The difference in numbers for rat and mouse might depend upon different stages of the corresponding genome projects. In cress (*Arabidopsis thaliana*), the tetraploidicity and gene multiplicity of its genome [37] contributes to a considerably larger number of SDR forms, whereas yeast only has 25 SDR forms.

Two main types of SDR enzymes, denoted 'classical' and 'extended', are clearly identifiable and were discovered early [16, 38]. The 'classical' type has a chain length of about 250 amino acid residues, while the 'extended' family has an additional 100-residue domain in the C-terminal region. Three further types, denoted 'intermediate', 'complex' and 'divergent' [39], can be distinguished based upon characteristic sequence motifs, for which the cofactor and active site motifs are listed in Table 3. Structural information has increased tremendously over the last few years, with well over 200 SDR structures deposited in the Protein Data Bank, including several high-resolution binary and ternary complexes. Structural data is available for all five types of SDRs, thus allowing interpretations of structure-activity relationships, as summarized below.

Table 2. Number of SDR enzymes in human and model organisms.

Species	Number of SDR enzymes	
	Total	Redundancy-reduced at 90% identity level
Human	143	71
Mouse	152	67
Rat	60	46
Fruit-fly	114	82
Cress	262	149
Yeast	27	25

The right-most column represents SDR members after exclusion of closely related forms (more than 90% identical in pairwise comparisons).

Table 3. Cofactor and active site sequence motifs for the fiveSDR subfamilies.

Subfamily	Cofactor binding	Active site
'classical'	TGxxx[AG]xG	YxxxK
'extended'	[ST]GxxGxxG	YxxxK
'intermediate'	[GA]xxGxx[GA]	YxxxK
'divergent'	GxxxxxSxA	YxxMxxxK
'complex'	GGxGxxG	YxxxN

x, any amino acid residue. Brackets denote alternatives that can be present or absent.

Structural and mechanistic aspects of SDR enzymes

Once identified by sequence patterns, it is now obvious that the only unifying criterion for SDRs is the Rossmann-fold scaffold and its ability to bind NAD(P) dinucleotides. Although the vast majority of SDRs show a Tyr-based catalytic center with adjacent Ser and Lys residues, other types, such as the 'divergent' SDRs, utilize a distinct mechanism. From kinetic studies mainly on *Drosophila* ADH but also on other 'classical' SDRs [40, 41], the SDR reaction appears often to proceed through an ordered 'bi-bi' mechanism, with the coenzyme binding first and leaving last. The dinucleotide cofactor binds in an extended conformation that allows transfer of the '4-pro-S' hydride, in contrast to MDRs that catalyze '4-pro-R' hydride transfer. Hydroxy/carbonyl groups constitute the largest number of SDR substrate chemical groups that are interconverted, but SDR enzymes also catalyze reduction of C=C and C=N double bonds, and mediate dehydratase, as well as sulfotransferase, isomerase and decarboxylation reactions [16, 43–54] (Fig. 2).

Numerous studies show that the central acid-base catalyst in SDRs is a hydroxyl-tyrosinate ion that

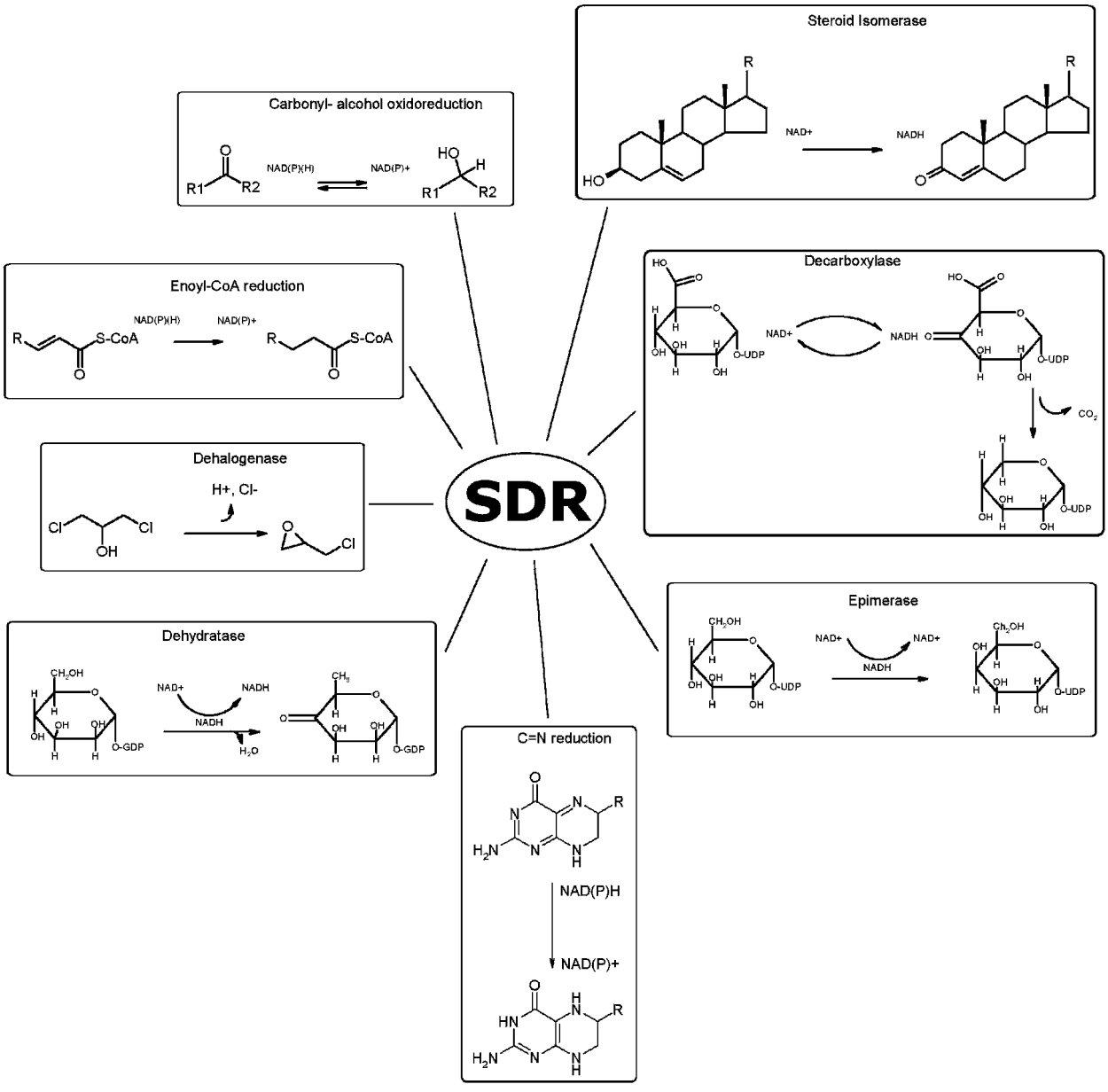

Figure 2. Reactions catalyzed by SDR enzymes.

donates or abstracts a proton to/from the substrate [10, 55–58], although this issue was not undisputed [59]. The property of the Tyr residue to act as a catalytic acid/base is enhanced by an adjacent Lys residue that together with an oxidized, positively charged cofactor nicotinamide lowers the tyrosine hydroxyl pKa [44, 58]. The lysine ε-amino group is also involved in nicotinamide ribose binding, whereas the role of the active site Ser residue is to stabilize and polarize the carbonyl substrate group [10, 56]. A highly conserved active site Asn residue located in helix αE produces a characteristic helical kink, and its main-chain carbonyl group ligates a water molecule that is in H-bonding distance to the active site lysine. In this manner a proton relay system is established [45], connecting bulk solvent to the active site Tyr residue (Fig. 3). As outlined below, many variations on this general scheme exist, and it is likely that more variant mechanistic features will be discovered. Apart from the Gly-rich cofactor motif and these active site residues, other sequence elements are traceable and correlate to scaffold or cofactor binding functions [6].

The majority of SDRs are oligomeric, with either homodimeric or homotetrameric quaternary structures. In most but not all [60] cases, the main dimerization interfaces are across two perpendicular

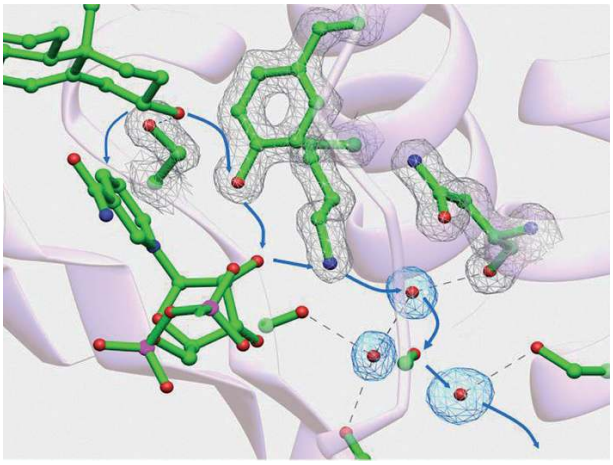

Figure 3. Proton relay in 'classical' SDRs [45]. Shown is the active site architecture of bacterial 3β/17β-hydroxysteroid dehydrogenase (PDB id 1hxh), with NAD+ (lower left) and a modelled 3β-hydroxysteroid (upper left corner). Hydride transfer is to the 4-pro-S of the nicotinamide (left blue arrow), whereas a proton path is generated through side chains of the active site tyrosine, lysine, the nicotinamide ribose hydroxyl and a conserved water molecule, which is stabilized by the main-chain carbonyl of a conserved asparaginyl residue.

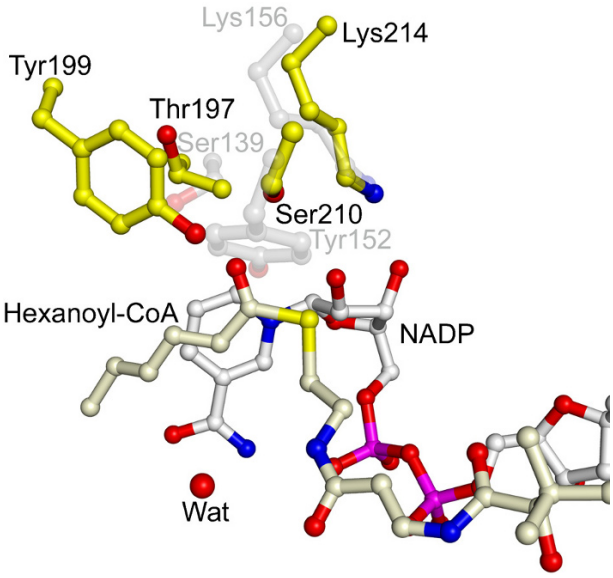

Figure 4. Active site features of the 'divergent' SDR dienoyl-CoA reductase (1w6u). Active site residues are shown with yellow carbons and labelled, while the active site residues of the classical SDR 3α/20β-HSD are superimposed in grey, and shown semi-transparent for comparison. A water molecule that is accessible to bulk solvent and is proposed to be involved in the reaction mechanism is shown as a red sphere.

twofold axes (P and Q), involving a four-helix bundle and a β-sheet that extends across two subunits [61]. Monomeric SDRs such as carbonyl reductase (CBR) have a long segment of 20-odd residues inserted just before the catalytic Tyr that forms an α-helix, which packs against and stabilizes the helical interaction surface [62].

'Classical' and 'intermediate' SDRs

Classical and intermediate SDRs are closely related forms, with 'intermediate' forms representing mostly *Drosophila* ADH. These two classes differ mainly within the Gly-rich cofactor binding region (Table 3), but show a highly similar one-domain architecture. The substrate and reaction spectrum includes mostly NAD(P)(H)-dependent oxidoreduction of hydroxy/keto groups within a large array of small molecules such as steroids, alcohols, polyols, growth factors, xenobiotics and secondary metabolites.

'Divergent' SDRs

'Divergent' SDRs are characterized by an irregular active site motif (Table 3) which in many instances contains an active site tyrosine but no lysyl residue at the usual position downstream of the Tyr. Instead, a methionine or hydrophobic residue is noted there, followed by a Lys residue four residues after the Met position. Despite this, the Tyr and Lys side chains are close in space, and in a similar conformation as in other SDR subfamilies [39]. Members of this subfamily are enoyl-thioester reductases, involved in fatty acid metabolism. Structural and biochemical studies on plant and bacterial enoyl-ACP reductases (InhA, FabI) [63, 64] as well as human dienoyl CoA reductase [43] support a mechanism where double-bond reduction is achieved via hydride transfer to one double-bond carbon center, formation of an enolate intermediate and protonation presumably leading to the reduced acyl species. The active site configuration deviates considerably; the tyrosine residue is in hydrogen bonding contacts to the thioester carbonyl and apparently stabilizes the enolate intermediate [65, 66]. The structural data are compatible with a mechanism where the proton donated to the Cα carbon is derived directly from solvent, implying no acid/base catalytic role for Tyr (Fig. 4). Clearly different mechanisms are operative within this group of SDRs, since human peroxisomal enoyl CoA reductase has the active site Tyr replaced by a Phe residue.

'Complex' SDRs

A subfamily of 'complex' SDRs was identified through sequence pattern searches [39]. Members of this group are part of large multidomain enzymes,

Table 4. Numbers of SDR families and enzymes with assignments of EC classes 1, 4 and 5.

	All SDR types		Extended type	
	Families	Enzymes	Families	Enzymes
EC 1	219	9468	25	217
EC 4	14	1865	13	1861
EC 5	26	1773	26	1773
Total EC 1+4+5	259	13106	64	3851

The left part shows numbers for all SDR types, the right part for the extended type only, establishing this type to contribute most of the non-EC1 class enzymes.

such as mammalian fatty acid synthases and bacterial polyketide synthases. This subfamily displays rudimentary sequence pattern similarities (Table 3) versus the 'classical' or 'extended' SDRs [39]. Structure determination of the ACP-ketoacyl reductase domain of *Streptomyces* erythromycin synthase [67] revealed that all necessary parts of the catalytic machinery, i.e. the Asn, Ser, Tyr and Lys residues, are assembled in a catalytically competent fashion, but are contributed from distinct parts of the general scaffold. Importantly, a previously uncharacterized 'linker' region of the polyketide synthase provides a structural domain for oligomerization with the catalytic domain. Further sequence motifs were identified, allowing prediction of the ACP-hydroxyacyl product stereospecificities [68].

'Extended' SDRs

The initial observation of relationships between 'classical' and 'extended' SDRs [16, 38] brought different enzymatic classes in addition to oxidoreductases (EC 1.-.-.-), namely lyases (EC 5.-.-.-) and isomerases or epimerases (EC 4.-.-.-), into the SDR family (Table 4). Although odd at first, the explanation for this phenomenon is that mechanistically these activities are coupled to initial oxidoreductive steps on specific substrates. This is further emphasized by the NAD(P)(H) nucleotide cofactor dependence of 'extended' SDRs and conservation of their active site residues. This principle allows for a large mechanistic diversity, and individual examples from the main classes of 'extended' SDRs are given below to highlight the large range of activities.

SDR-type epimerases

Mechanistically, the best-characterized member of the extended SDR family is UDP-galactose epimerase (GALE) [52, 57, 69–72]. It catalyzes the interconversion between UDP-glucose and UDP-galactose and constitutes a central step of the Leloir pathway in the metabolism of galactose. The enzyme contains a tightly bound NAD^+ molecule, which stays attached and undergoes different redox state changes during the reaction cycle. In the first step of the reaction, a concerted proton abstraction from the 4′OH of the substrate and hydride transfer from the substrate C4 to the S-face of the nicotinamide cofactor occurs [52, 55, 69, 71, 73–76]. The resulting 4-ketopyranose intermediate rotates within the active site around the phosphate bond by about 180°, thus presenting the opposite side of the sugar to NADH. In the last part of the reaction cycle, the carbonyl substrate is reduced by hydride transfer from NADH in alliance with the initial catalytic base, with the net result being a stereochemical inversion of the substrate hydroxyl group. Variable sizes of the active site pockets between *Escherichia coli* and human GALE give rise to the observed different substrate specificities and also explain the ability of the human enzyme to catalyze conversion of UDP-N-acetylglucosamine and UDP-N-acetylgalactosamine [76].

Extensive mutagenetic, kinetic and crystallographic data confirm the roles of Tyr149 (numbering as in the *E. coli* structure) and Ser124 as central catalysts in the SDR-type of epimerases [52, 55, 69, 71, 73–76]. The presence of a charge transfer band between NAD^+ and the epimerase strongly suggests a deprotonated tyrosine residue of importance, and together with the extensive mechanistic investigations on *Drosophila* ADH enforces the concept of tyrosine as the central acid/base catalyst in SDRs. UDP binding to the nucleotide-diphosphate domain enhances reactivity of NAD^+, suggesting cooperative behaviour between the UDP binding domain and the central catalytic domain. Whether this observation holds true for other extended SDR types such as dehydratases or decarboxylases is unknown at present.

SDR-type isomerases

Another important category of SDR-type isomerases is the mammalian 3β-hydroxy-5ene-steroid isomerases, involved in the synthesis of all classes of steroid hormones and bile acids [77–79]. No crystal structure of these enzymes has been solved yet. Mechanistically best-studied is the type I 3β-HSD-Δ5 isomerase, which in a sequential reaction first oxidizes the 3β-hydroxyl group in a manner involving the conserved Tyr, Lys and Ser residues. This is followed by NADH-induced activation of an isomerase-competent domain, likely to involve Asp and Tyr residues as catalytic acid/base catalysts [79] involved in proton transfer at steroid positions C4 and C6, similar to a mechanism described for a bacterial steroid isomerase [80, 81].

SDR-type dehydratases

Several members of the extended SDR family catalyze dehydration of important diphosphonucleotide-activated carbohydrates like GDP-mannose or dTDP-glucose. For example, in humans the essential carbohydrate GDP-fucose is synthesized from GDP-mannose via two distinct SDR enzymes: first, an intermediate GDP-4-keto-6-deoxymannose is produced in the GDP-mannose dehydratase (GMDH) reaction, and this is then further metabolized via GDP-4-keto-6-deoxymannose epimerase/reductase (TSTA 2) to the GDP-fucose product [82].

The catalytic mechanism of GMDH, based on bacterial and plant orthologs [83, 84], involves an initial $NADP^+$-dependent oxidation of the 4′OH group of the mannose, followed by a proton abstraction from the C5′ carbon, subsequent protonation of the C6′OH, resulting in loss of a water molecule and formation of a 4-keto, 5,6-ene intermediate. Hydride transfer to C6′ and proton transfer to C5′ results in the final GDP-4-keto-6-deoxymannose product. This mechanism implies the presence of 2 distinct catalytic bases; the first step (oxidation of the C4′OH) is conducted by the conserved Tyr residue, while the oxidation/reduction of the C5′ carbon and the C6′OH is presumably carried out by a conserved glutamate residue (Glu157 in the human enzyme, Glu164 in the *A. thaliana* enzyme) [83].

SDR-type decarboxylases

Several decarboxylases have been identified as members of the SDR family and are involved in cellular functions such as lipid A modification with 4-amino-4-deoxy-L-arabinose in Gram-negative bacteria or in production of UDP-xylose necessary for proteoglycan synthesis in eukaryotes [85, 86]. These SDR-type decarboxylases carry out an initial oxidation step at the C4-OH group of nucleotide-diphosphate sugars such as UDP-glucuronic acid. This leads to decarboxylation of the C6-carboxyl group and formation of UDP-4 keto arabinose or, after further reduction using the initially formed NADH, yields UDP-xylose [85, 87]. Structural analyses reveal close relationships to UDP-galactose epimerases, but clear differences exist in the active site geometry and architecture. Structure determination of ArnA, a bacterial decarboxylase, suggests a different mechanism where active site Ser and Arg residues appear to be the key catalytic residues [46]. The eukaryotic xylose synthases utilize a UDP-glucuronic acid decarboxylation reaction with reduction of a 4-keto pentose intermediate. It is conceivable that in these enzymes the initial reaction proceeds through a central proton abstraction through the active site tyrosyl residue. However, further mechanistic details of this class of SDR enzymes are presently unknown and require clarification.

Related SDR enyzme families: conservation of the Rossmann fold with different active sites

From the examples illustrated above it has become evident that the three-dimensional folding pattern of SDRs, like those of most protein families, is more conserved than their underlying sequence motifs. This is further highlighted by structure determination of mammalian biliverdin β reductase [88], transcriptional regulators like fungal NmrA [89], proapoptotic oncogenes such as CC3/Tip30 [90] and prokaryotic halohydrin dehalogenases [91]. All these proteins display close to non-traceable sequence homologies despite a highly similar three-dimensional architecture related to the SDR fold. Out of these examples, biliverdin reductase β, which catalyzes the reduction of tetrapyrroles such as biliverdin IXβ and flavins, was the first to be structurally characterized. The crystal structure revealed binding of NAD(P) as well as a folding pattern with UDP-galactose epimerase as the closest structural neighbour [88]. Although no clear candidate for a catalytic base was identified, proton transfer could be achieved either by a His residue or be directly derived from solvent. Other catalytically important residues found in SDRs, such as Asn, Ser and Lys, are absent, again highlighting the versatility of the Rossmann fold to accomodate separate active site configurations.

The SDR scaffold as redox sensor: NAD(P)(H) binding with non-enzymatic functions

Structure determination of monomeric CC3/TIP30 (human gene name HTATIP2), a proapoptotic oncogene [92] with metastasis suppression properties, revealed close relationships to UDP-galactose epimerase and carbonyl reductases [90]. Although initially suspected to be a kinase [93], bioinformatic predictions suggested clear relationships to SDRs [94], such as galactose epimerase, which was experimentally verified later on [90]. CC3/TIP30 binds NAD(P) and contains the active site residues Ser, Tyr and Lys. At present, no catalytic activity has been demonstrated for the protein. However, it is conceivable that differential NADP(H) binding is involved in regulation of other cellular functions, such as interactions of CC3/TIP30 to nuclear importins or corepressors and transcription factors such as c-myc/CIA [90]. This is in line with observations on other types of oxidoreductases such as aldo-keto reductases (AKRs), where several members regulate potassium channel transport [95], or 2-hydroxyacid dehydrogenases like the C-terminal binding proteins (CTBPs), which regulate transcription by interaction with e.g. the C-terminal region of human adenovirus E1A proteins [96, 97]. In fact, similar properties have been shown for the SDR-fold fungal transcriptional regulator NmrA, which differentially binds oxidized nucleotide cofactors, thus linking redox status to interactions with transcription factors [98]. The recent structure determination of a human ortholog to NmrA [99] (gene symbol NMRAL) revealed a similar SDR-type architecture, lack of classical active site residues and cofactor binding-induced structural rearrangements. Importantly, NMRAL associates with cytoskeleton components, and directly interacts with argininosuccinate synthase, implying a role as redox sensor in NO signalling. This is reminiscent of the function of methionine adenosyl transferase, consisting of catalytically active α-subunits and regulatory SDR-type β-subunits, which differentially bind NADP(H) and are postulated to act as a redox sensor module [100]. Again, these examples demonstrate that the basic nucleotide binding scaffold can adopt other roles than merely promoting catalysis of oxidoreductase functions. This is further highlighted by RNA binding and nuclease activity of the chloroplast factor CSP41 [101], which lacks classical SDR active site residues. This is not the only case of oxidoreductases involved in RNA chemistry, e.g. the MDR enzyme ζ-crystallin and other Rossmann-fold enzymes like GAPDH are able to bind specific mRNAs and can regulate their stability [102].

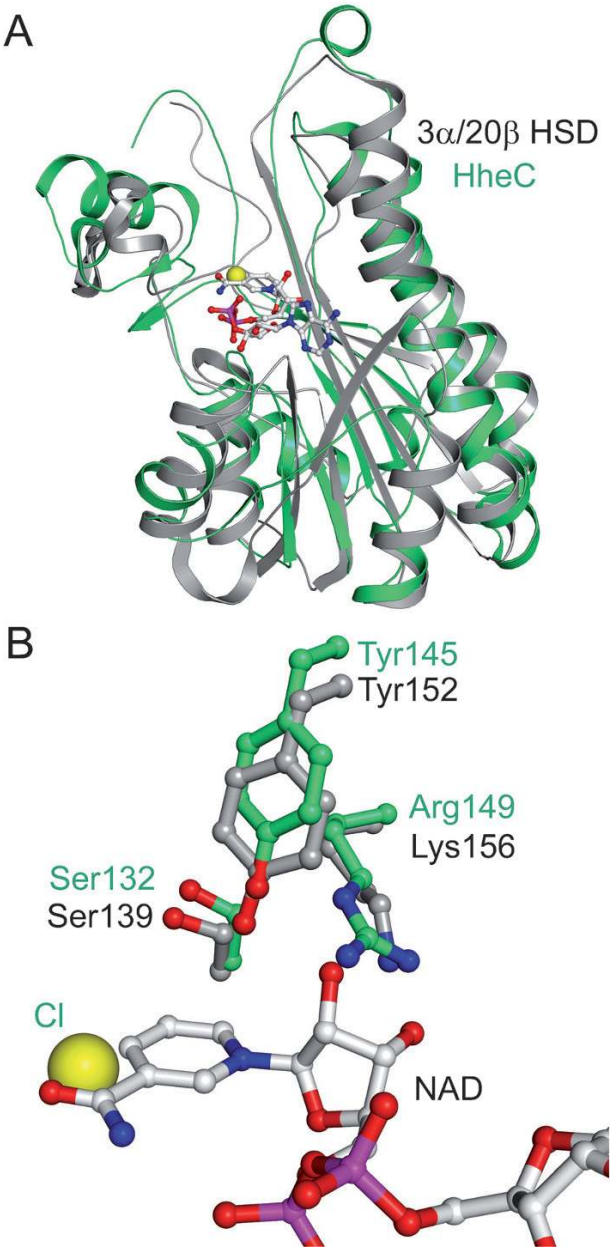

Figure 5. Relationship of halohydrin dehalogenases to the SDR family. (*A*) Superposition of 3α/20β-HSD (grey) with halohydrin dehalogenase HheC (green), showing a similar α/β fold architecture. (*B*) Close-up of the active sites of 3α/20β-HSD and HheC. Residues in the active site of 3α/20β-HSD and HheC are labeled in grey and green, respectively. The NAD molecule from 3α/20β-HSD is shown as well as the chloride ion bound to HheC.

Halohydrin dehalogenases

Structurally and in part mechanistically related to SDRs are prokaryotic halohydrin dehalogenases (halohydrin hydrogen-halide lyases; EC 4.5.-.-), which catalyze the reversible nucleophilic displacement of a halogen by a vicinal hydroxyl group yielding an epoxide, a proton and a halide [103]. These

enzymes are of considerable biotechnological interest and are useful as potential catalysts for the production of optically pure epoxides and halohydrins, as well as in the bioremediation of halogenated aliphatics that are found in polluted soil and water.

Structural analysis of halohydrin dehalogenase HheC from *Agrobacterium radiobacter* revealed an α/β architecture similar to SDR enzymes, despite almost negligible sequence identities [91] (Fig. 5). These dehalogenases lack the characteristic nucleotide cofactor binding motifs and sequence signatures, consistent with the finding that hydride transfer is not a necessary feature for the dehalogenation reaction carried out by the enzymes. However, the Tyr and Ser residues of the active site tetrad are completely conserved, along with a strict replacement of the active site lysine residue usually found in SDRs by an arginine residue [91, 103]. The structural interpretation and mutagenetic data suggest a mechanism where a deprotonated Tyr residue, facilitated by the adjacent Arg residue, removes a proton from the vicinal hydroxyl group. The ensuing alkoxide attacks the adjacent electron-deficient carbon, which results in formation of an epoxide and a leaving halide ion. As in other SDRs, Ser stabilizes the reaction intermediate by forming a hydrogen bond to the hydroxyl group [91, 103] (Fig. 4). A further unusual SDR catalytic triad consisting of Ser-Ser-Arg residues was recently noted for a hyperthermophilic archaeal protein of unknown function, emphasizing the mechanistic and structural variability within the SDR family [104].

Perspectives

Interest in the SDR family centers around at least three different aspects: molecular evolution, enzymology and biotechnological applications. Regarding evolution, SDRs are remarkable in demonstrating a versatile nucleotide binding domain as a central scaffold and combining this with accommodations to fit to hundreds of reactions/substrates and to literally half of all enzyme class types. Bioinformatic and structural analyses have shown huge variability in mechanistic features with no absolutely conserved residue. Instead, the conservation of the three-dimensional fold with conserved cofactor binding properties appears to be the driving force to create an enzymatic platform spanning at least three different EC classes. Regarding biotechnological applications, SDRs constitute a 'druggable' enzyme class, and investigations into human forms have spawned widespread biotechnological and pharmaceutical interests.

An attempt to systematize and provide a repository for the SDR family is currently ongoing, and regular updates will be available through http://www.sdr-enzymes.org.

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