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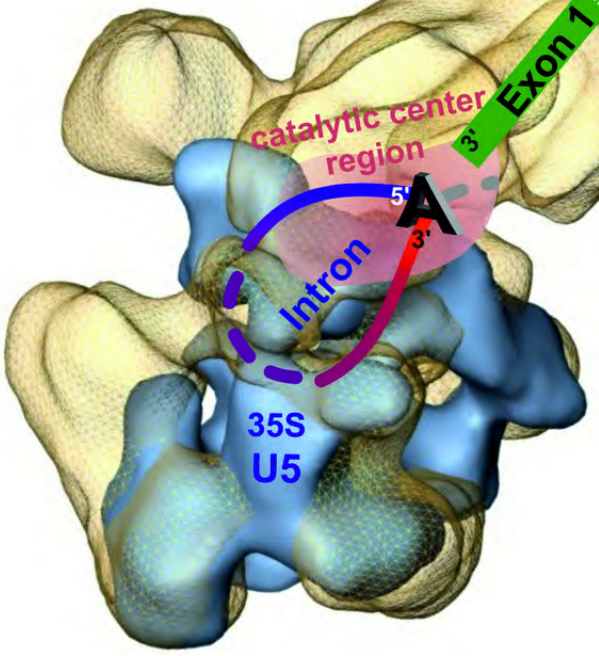
Insights into the 3D spatial organization of the spliceosome and its structural dynamics

Preise

Auszeichnungen für Christian Griesinger, Herbert Jäckle und Thomas Jovin

INHALT



Insights into the 3D spatial organization of the spliceosome and its structural dynamics

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The spliceosome is a complex macromolecular ribonucleoprotein (RNP) enzyme that catalyzes pre-mRNA splicing, the process whereby noncoding introns are removed from a pre-mRNA and the remaining coding regions (exons) are ligated to form mRNA. Pre-mRNA splicing is an essential step in gene expression, and alternative splicing events, where multiple mRNAs are generated from a single pre-mRNA, play a central role in expanding the complexity of the proteomes of higher organisms. Furthermore, errors in the splicing process or defects in splicing regulation are the cause, or modulate the severity of a large number of pathological conditions including cancer and neuro-degenerative diseases.

Spliceosomes are highly dynamic RNP complexes and are assembled anew onto each pre-mRNA intron in a multi-step process during which the small nuclear RNPs (snRNPs) U1, U2, U4, U5, and U6, plus more than 80 additional splicing factors, interact with the pre-mRNA[1] (Fig. 1). U1 and U2 are the first snRNPs that bind to the pre-mRNA, followed by the association of the pre-formed U4/U6.U5 tri-snRNP, which generates the pre-catalytic spliceosomal B complex. Following a number of dramatic rearrangements, including destabilization of the U1 and U4 snRNPs, the spliceosomal B complex is catalytically activated, giving rise first to the B^{act} complex, and then, after the

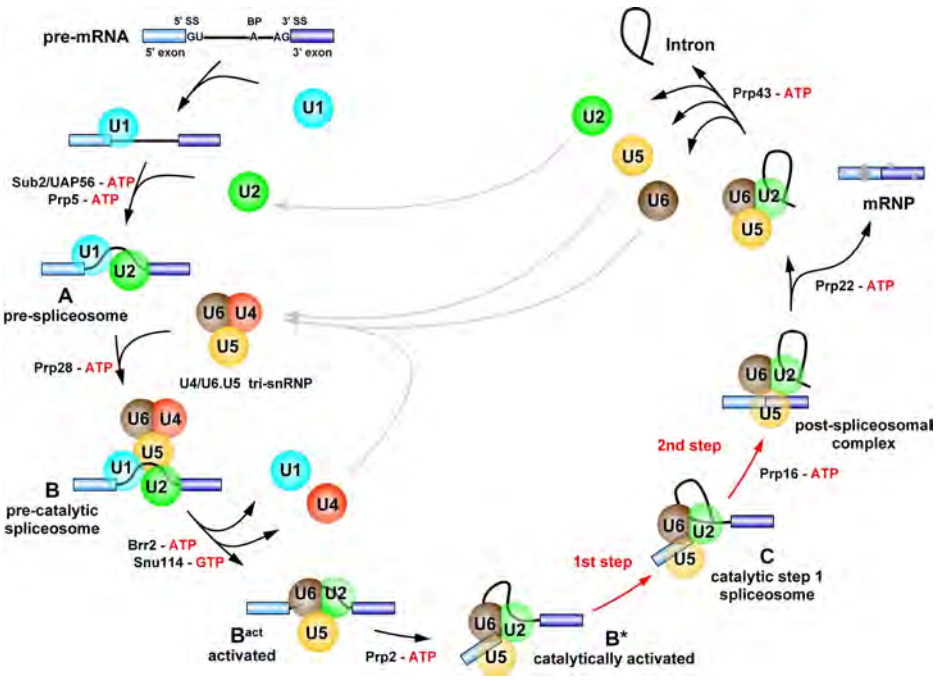

Fig. 1. Spliceosome assembly, catalysis, and disassembly pathway. The U snRNPs are represented by circles and the RNA helicases/ATPases acting at the various stages of splicing are indicated.

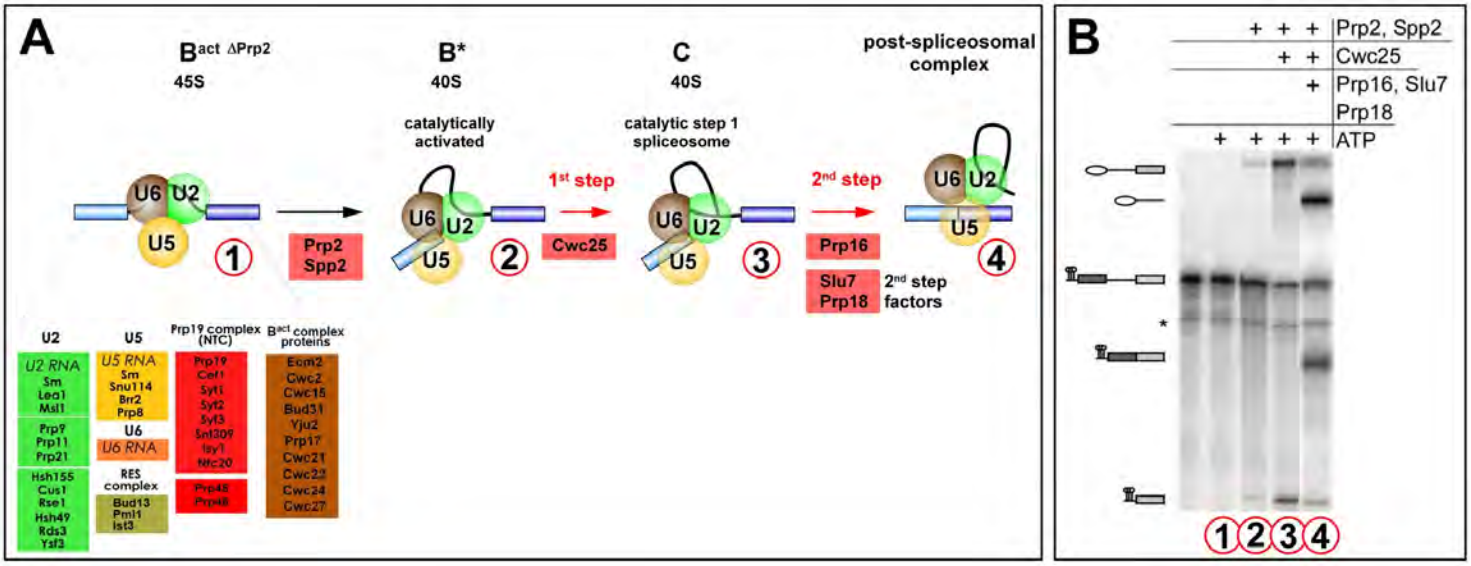

Fig. 2. Reconstitution of the catalytic steps of splicing from highly purified components. **(A)** Schematic of the yeast in vitro splicing reconstitution system and the various spliceosomal complexes (#2-4) that are formed after incubating purified, activated B^{act} spliceosomes lacking Prp2 (#1) with the indicated purified spliceosomal proteins (red boxes). The protein composition of the purified B^{act} complexes lacking Prp2 is shown below with the various spliceosomal proteins grouped according to snRNP association or function. **(B)** Recapitulation of both catalytic steps of splicing from purified activated spliceosomes and recombinant splicing factors. Purified B^{act} spliceosomes lacking Prp2, formed on radiolabeled pre-mRNA, were incubated with ATP alone (lane 1) or additionally with the spliceosomal proteins indicated above lanes 2-4. Splicing of the radiolabeled pre-mRNA was determined by isolating the RNA, and separating it on a denaturing polyacrylamide gel. The unspliced pre-mRNA, splicing intermediates (the free 5′ exon and intron-lariat-3′ exon), and splicing products (mRNA and spliced-out intron) were visualized by autoradiography and are indicated on the left.

action of the RNA helicase Prp2, to the B* complex. The latter catalyzes the first step of splicing, which involves cleavage at the 5′ splice site of the pre-mRNA and formation of an intron lariat, and leads to the formation of the spliceosomal C complex. This complex then catalyzes the second step of splicing during which the 3′ splice site is cleaved (releasing the intron) and the 5′ and 3′ exons of the pre-mRNA are ligated together to form mRNA. During spliceosome assembly, an intricate RNA-RNA network involving the snRNAs (the RNA component of the snRNPs) and the pre-mRNA is formed[1]. This RNA-RNA network plays a central role in juxapositioning the reactive groups of the pre-mRNA (i.e. the 5′ and 3′ splice sites and the branch site). RNA structures involving U2 and U6 snRNA play crucial roles in the catalytic core of the spliceosome, with nucleotides of U6 directly involved in the catalysis of pre-mRNA splicing[2].

The spliceosome undergoes multiple structural rearrangements and extensive changes in its protein composition during its assembly and the subsequent catalytic steps of splicing. These rearrangements are facilitated by a group of spliceosome associated proteins, namely by members of the DExD/H-box family of RNA unwindases/RNPases, that include, among others, U5-200K/Brr2, Prp2, Prp16, Prp22, and Prp43[3], which act at one or more steps of the splicing cycle (Fig. 1). The precise targets of many of these proteins remain largely unknown, but in several cases the mechanisms of their action and regulation are now beginning to emerge.

In recent years, our group has focused on addressing several unanswered key questions regarding pre-mRNA splicing. First, what are the precise roles of spliceosomal proteins, especially RNA helicases, during splicing? Second, what is the molecular architecture of the spliceosome and how does it change at distinct stages of its assembly/function? And finally, what is the catalytic RNP core of the spliceosome comprised of? To address these questions, we use a multiparameter approach, combining biochemical and biophysical strategies with structural biology techniques.

Reconstitution of splicing catalysis/spliceosome disassembly with purified spliceosome components

To investigate the role of RNA helicases and other spliceosomal proteins during the catalytic steps of splicing and the disassembly of the splicing machinery, we recently established an in vitro splicing complementation system using purified yeast spliceosomal complexes stalled prior to catalytic activation (designated $B^{actΔPrp2}$ complexes) and recombinantly expressed proteins needed for activation and/or catalytic step 1 or 2 of splicing[4]. By adding one or more recombinant proteins to the purified, stalled spliceosomes and assaying for splicing catalysis (Fig. 2), we could show that efficient catalysis of step 1 of the splicing reaction requires not only the helicase Prp2 and its binding partner Spp2, but also the splicing factor Cwc25, demonstrating for the first time that Cwc25 promotes step 1 catalysis[4].

During the final catalytic activation of the spliceosomal B^{act} complex (which yields the B* complex), the RNA helicase Prp2 facilitates RNP rearrangements in

the spliceosome, but the nature of this Prp2-mediated remodeling has remained elusive. Using our splicing reconstitution system and fluorescently-labeled spliceosomal proteins, we performed dual color-fluorescence cross-correlation spectroscopy (dcFCCS) in collaboration with Jörg Enderlein (University of Göttingen) to study the dynamics of spliceosomal protein binding. These studies showed that the binding affinity of a surprisingly high number of spliceosomal proteins is significantly changed during catalytic activation, suggesting a high cooperativity between multiple Prp2-mediated, structural rearrangements in the spliceosome's catalytic core[5]. However, RNA structure probing data from our lab suggest that Prp2 action has only a limited effect on the conformation of the spliceosome's RNA network, indicating that it acts primarily by remodeling protein-RNA interactions rather than RNA-RNA interactions (unpublished observations).

A prerequisite for catalysis of step 2 of splicing by the C complex is a poorly understood RNP remodeling event facilitated by the RNA helicase Prp16. Using our purified yeast splicing system, we could demonstrate that Prp16, but not the helicase Prp22, is necessary and sufficient to generate catalytically-activated C* complexes and that it promotes step 2 catalysis[6]. We have also studied the dynamics of spliceosomal protein association by dcFCCS during this step. Our data show that the step 2 factors Slu7 and Prp18 are needed to displace the step 1 factor Cwc25 from the spliceosome and are consistent with the idea that Cwc25 and Slu7/Prp18 stabilize the step 1 and 2 conformation of the spliceosome's catalytic center, respectively[6]. Our dcFCCS studies also revealed that remodeling of the spliceosome by Prp16 appears to be subtle compared to the extensive Prp2-mediated restructuring of the spliceosome during catalytic activation for step 1 catalysis. We have also recapitulated the disassembly stage of the yeast spliceosome using purified components and could show that the RNA helicase Prp43 and its coactivators Ntr1 and Ntr2 are sufficient to dissociate the intron lariat spliceosome into distinct U6, U5, and U2 snRNPs and the intron lariat RNA[7] (see also Figure 1). These studies further demonstrated that, in contrast to previous reports, the ATPase/unwinding activity of the helicase Brr2 is not required for disassembly of the intron lariat spliceosome.

Taken together, these data underscore the power of our splicing reconstitution system for dissecting the function of essential splicing factors during spliceosome activation, catalysis, and disassembly. We are currently modifying this system with the goal of analyzing in detail the decisive but poorly understood spliceosome activation step, during which the pre-catalytic spliceosomal B complex is converted to the B^{act} complex.

Molecular insights into the function and regulation of the spliceosomal helicase Brr2

A key enzyme facilitating the conversion of the pre-catalytic B complex to the activated B^{act} complex is the DExH-box ATPase/helicase Brr2. This enzyme catalyzes the unwinding of the U4/U6

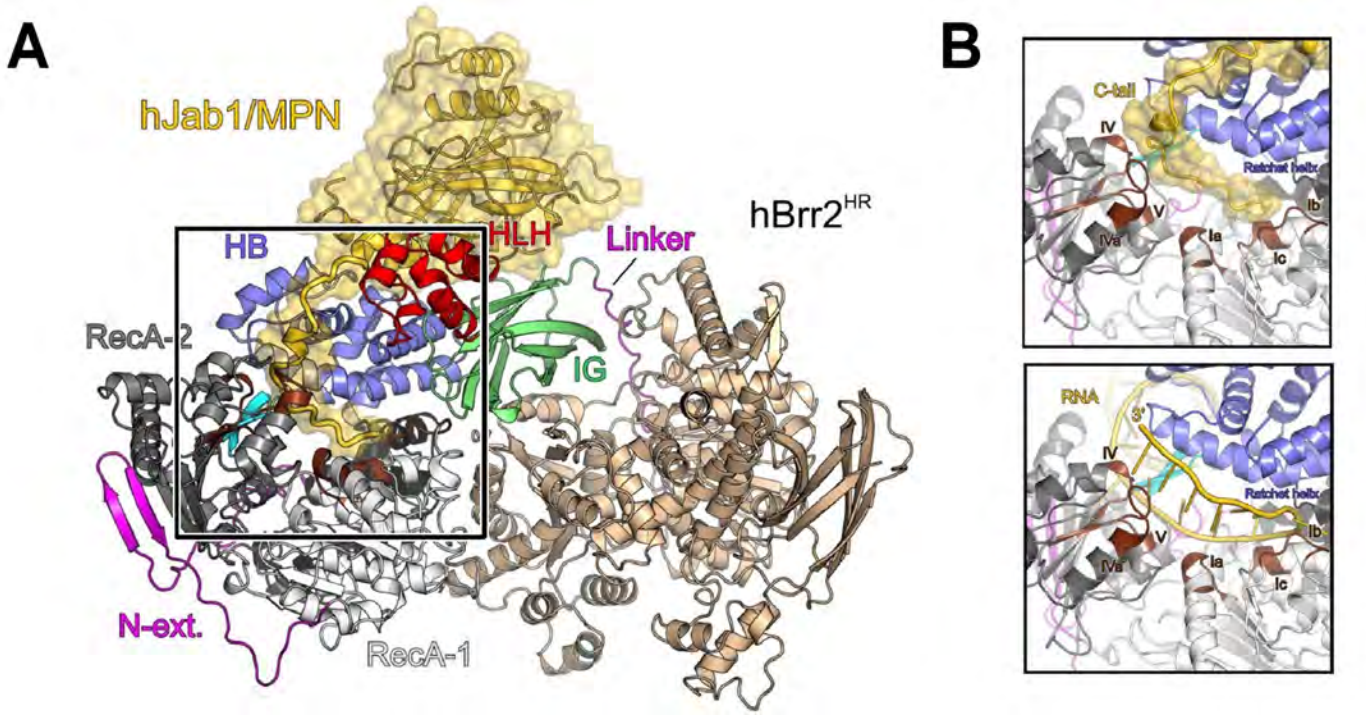

Fig. 3. Crystal structure of the spliceosomal helicase Brr2 complexed with the Jab1 domain of the Prp8 protein. **(A)** Structural overview of the human Brr2-Prp8 Jab1 complex with the Jab1 domain highlighted in gold and various domains of the N-terminal helicase cassette colored as follows: the helical bundle (HB), blue; the helix-loop-helix, red; the immunoglobulin-like (IG), green; the RecA RNA binding motifs, grey; the separator loop, cyan. The C-terminal helicase domain of Brr2 is colored beige. **(B)** Insertion of the C-terminal tail of the Jab1 domain of Prp8 into the RNA binding channel of Brr2 inhibits Brr2 interaction with its RNA substrate. Upper panel, the C-terminal tail of the hPrp8 Jab1 domain runs across all of the canonical RNA binding motifs of the N-terminal RecA-1 (motifs 1a, 1b, and 1c) and RecA-2 (motifs IV, IVa and V) domains. Lower panel, model of an RNA bound in the central RNA binding tunnel of the N-terminal helicase cassette of Brr2.

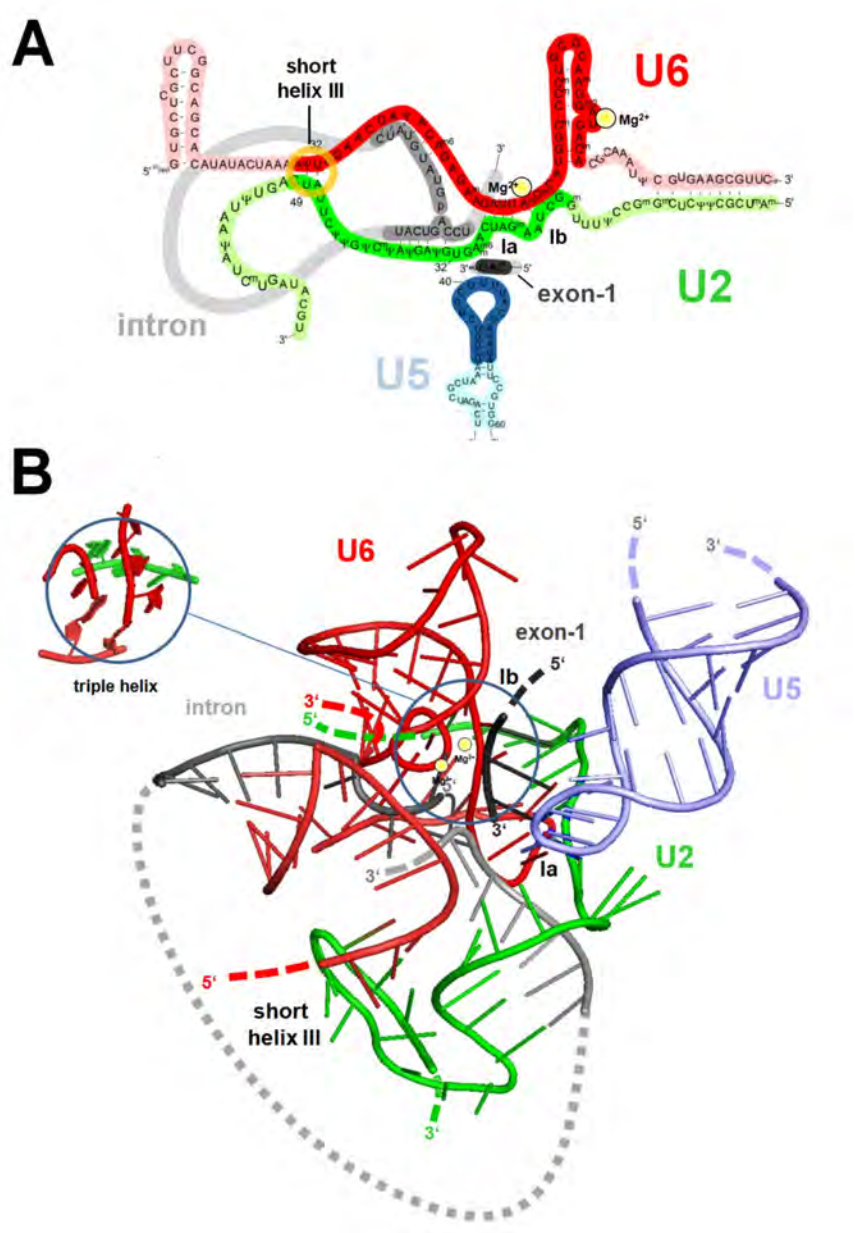

Fig. 4. 3D model of the catalytic RNA network in the spliceosomal C complex. **(A)** Schematic of RNA-RNA interactions at the core of the catalytically active spliceosome. Regions of the pre-mRNA and the U2, U5, and U6 snRNAs modeled in panel B are highlighted in bold. **(B)** 3D model of RNA-RNA interactions at the catalytic core of the step I spliceosome.

snRNA duplex present in the precatalytic B complex, which is a prerequisite for spliceosome activation[3]. Brr2 is an integral component of the U4/U6.U5 tri-snRNP and the spliceosome, and thus its activity must be tightly regulated to prevent premature U4/U6 unwinding. We have recently provided novel insights into the structure, function, and regulation of Brr2 by performing X-ray crystallography (Fig. 3) and biochemical assays, in collaboration with the group of Markus Wahl (FU Berlin). These studies showed that the C-terminal helicase cassette of Brr2, which is inactive on its own, acts as an intra-molecular cofactor that stimulates the activity of its N-terminal RNA helicase cassette[8]. They also revealed the molecular mechanisms by which the C-terminal RNase H-like (RH) domain and the Jab1 domain of the spliceosomal protein Prp8 regulate Brr2 helicase function during the spliceosome activation step. Specifically, we showed that the Prp8 RH domain binds the U4/U6 snRNAs and thereby competes with Brr2 for loading onto its substrate RNA duplex[9]. In addition, our studies revealed that the Prp8 Jab1 domain can insert its C-terminal tail into Brr2's RNA binding tunnel, thereby intermittently blocking Brr2 RNA binding, ATPase, and U4/U6 unwinding activities[10] (Fig. 3). These studies provided novel insights into the complex regulation of Brr2 during splicing and reveal unique mechanisms whereby the activity of RNA helicases can be inhibited prior to their activation.

Molecular interactions in the catalytic core of the spliceosome

Due to the lack of a high resolution structure of the spliceosome, information about the RNA-RNA and RNP networks formed at its core is currently limited. Biochemical information about interacting partners and the spatial arrangement of individual proteins and RNAs within the spliceosome provides insight into the molecular dynamics of the splicing machinery, and will be instrumental in interpreting moderate resolution 3D electron microscopy maps and ultimately solving the structure of the spliceosome at atomic resolution.

In active spliceosomes the pre-mRNA intron and U2, U6, and U5 snRNAs form an RNA network at the center of the catalytic core whose higher order structure is only poorly understood (Fig. 4). By performing chemical RNA structure probing and psoralen crosslinking with purified human B^{act} and C complexes, we obtained novel insights into the secondary and tertiary structure of the spliceosomal RNA network and its dynamics during splicing[11]. Given the evolutionary conservation between nuclear and self-splicing group II intron splicing, we constructed an experimentally-constrained homology model of the spliceosomal RNA network after step 1 based on the recently published crystal structure of a group II intron[12] (Fig. 4). The model is clashfree, allows predictions of RNA rearrangements during the step 1 to 2 transition, and provides an important basis for interpreting moderate resolution structures of the spliceosome obtained by EM or crystallography.

Pre-mRNA splicing and the splicing of group II introns share many similarities including identical chemistry of the first and second step reactions. However, in contrast to group II self-splicing introns, which assemble on their own into a catalytically active conformation, the catalytically active RNA-RNA network

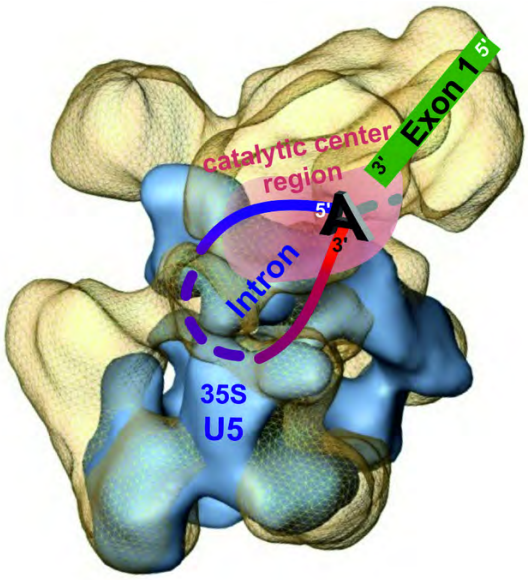

Fig. 5. 3D cryo-EM structure of the human spliceosomal C complex. The proposed area of the catalytic center (pink) and the likely path of the pre-mRNA splicing intermediates is superimposed on the C complex 3D structure (yellow). The fitted 3D EM map of the 35S U5 snRNP is shown in blue.

of the spliceosome requires numerous proteins for its assembly and for maintaining its structure. Recent studies in our lab suggest that the function of RNA elements of group II introns are carried out in the spliceosome by proteins. That is, by performing UV-crosslinking and RNA structure probing with purified spliceosomes, we could show that the yeast Cwc2 protein contacts catalytically important RNA elements, such as the U6 snRNA internal stem-loop, and U6 and pre-mRNA intron nucleotides near the 5′ splice site, placing Cwc2 at/near the spliceosome's active center[13]. Determination of the crystal structure of Cwc2, carried out in collaboration with Vlad Pena and Jana Schmitzová (PG *Macromolecular Crystallography*), revealed a novel architecture consistent with it acting as a multipartite RNA-binding protein[14]. Our data suggest that Cwc2 induces an active conformation of the spliceosome's catalytic RNAs and may functionally replace structurally important RNA tertiary interactions of self-splicing group II introns that are required for the catalytically active conformation of the latter.

Structural investigation of the spliceosome by electron microscopy

Due to the very complex and, above all, highly dynamic nature of the spliceosome, together with the relatively low amounts of a given spliceosomal complex that can be purified, crystallization of the spliceosome remains a highly challenging undertaking. Thus, the current method of choice for studying the molecular architecture of the splicing machinery is electron cryomicroscopy. In collaboration with Holger Stark's group (*3D Electron Cryo-Microscopy*) we have recently been able to generate a 3D structure of a catalytically active human spliceosome[15] at a resolution of 20-30 Å. In addition, we have localized the positions of functionally important proteins and the pre-mRNA's exons and intron via immuno-EM studies[16,17]. By determining the 3D EM structures of isolated snRNPs and other sub-complexes of the spliceosome and fitting these into the 3D maps of the various spliceosomal complexes, we have obtained important information about the molecular organization of the spliceosome. In this way, it was possible to map the position of the catalytic core within the spliceosomal C complex and the probable pathway of the pre-mRNA[15,17] (Fig. 5). With the aim of stabilizing the structure of spliceosomes, we have recently made improvements in the protocols for spliceosome purification, sample handling, and EM imaging, which has paved the way for obtaining significantly higher resolution structures of the spliceosome.

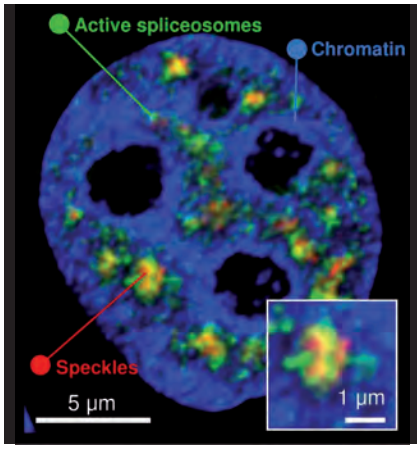

Fig. 6. Localization of active spliceosomes within and surrounding nuclear speckles via immunofluorescence studies in HeLa cells using antibodies against phosphorylated SF3b155. Active spliceosomes are green, nuclear speckles are red and an overlap of both signals is yellow.

Posttranscriptional spliceosomes remain in nuclear speckles until splicing completion

Many splicing events occur co-transcriptionally – that is, introns are removed and the neighboring exons are spliced together while a nascent transcript is still being transcribed by RNA polymerase II. There is little quantitative information regarding how much splicing occurs co-transcriptionally in higher eukaryotes, and it remains unclear where precisely splicing occurs in the nucleus. To determine the global extent of co- and post-transcriptional splicing in mammalian cells and their respective subnuclear locations, we generated antibodies that specifically recognize the phosphorylated form of the spliceosomal protein SF3b155, which is found only in catalytically activated/active spliceosomes[18]. These antibodies have allowed us to visualize active spliceosomes in the cell by immunofluorescence microscopy, which showed that active spliceosomes are found in situ in regions of decompacted

chromatin, at the periphery of or within nuclear speckles[18] (Fig. 6). Our studies revealed that >80% of pre-mRNA splicing occurs co-transcriptionally. Immunofluorescence microscopy with anti-P-SF3b155 antibodies, coupled with transcription inhibition and a block in splicing after SF3b155 phosphorylation, indicates that post-transcriptional splicing occurs in nuclear speckles and that release of post-transcriptionally spliced mRNA from speckles is coupled to the nuclear mRNA export pathway. Our data thus provide new insights into when and where splicing occurs in cells.

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Zusammenfassung

Die Synthese von Proteinen in Zellen höherer Lebewesen ist ein komplexer, mehrstufiger Vorgang. Zunächst wird die genetische Information für ein Protein von der DNA in eine Arbeitskopie, die Precursor-Boten-RNA (Prä-mRNA), umgeschrieben. Diese RNA-Kopien können jedoch erst dann für die Proteinherstellung verwendet werden, wenn durch präzisen Zuschnitt die nicht benötigten internen Bereiche, sogenannte Introns, entfernt und die informationsrelevanten Bereiche, die Exons, neu verknüpft worden sind. Dieser Reifungsprozess wird als mRNA-Spleißen bezeichnet. Die mRNA-Spleißreaktion erfolgt in zwei Schritten über Phosphoester-Transferreaktionen und wird im Zellkern durch die molekulare Maschine des Spleißosoms bewerkstelligt. Spleißosomen setzen sich aus weit über 100 Proteinen und fünf kleinen RNA-Molekülen (den snRNAs U1, U2, U4, U5 und U6) zusammen und sind damit gigantische, sehr proteinreiche Nanomaschinen. Viele dieser Bausteine sind in stabilen Subkomplexen organisiert. So lagern sich zum Beispiel zirka 50 spleißosomale Proteine mit den snRNAs zu RNA-Proteinpartikeln, den snRNPs (*small nuclear ribonucleoproteins*) U1, U2 und dem U4/U6.U5 tri-snRNP zusammen.

Spleißosomen existieren im Zellkern nicht als vorgefertigte Maschinen, sondern werden auf jedem zu spleißenden Intron jeweils von Neuem aus ihren Bausteinen aufgebaut und nach Abschluss der Spleißreaktion wieder

getrennt. Während eines einzigen Funktionszyklus wird das Spleißosom kontinuierlich in seiner Zusammensetzung und Struktur verändert, wobei die entscheidenden Strukturumwandlungen von insgesamt acht evolutionär konservierten sogenannten RNA-Helikasen aus der Familie der DEAD/H-Box-ATPasen katalysiert werden. Ein Schwerpunkt unserer Forschung lag in den letzten Jahren darin, die strukturelle Dynamik des Spleißosoms zu verstehen und die Funktion und Regulation bestimmter RNA-Helikasen des Spleißosoms zu untersuchen.

Durch eine partielle Komplementationsstrategie im Hefesystem gelang es uns erstmals, die gesamte katalytische Phase mit gereinigten Komponenten *in vitro* zu rekonstituieren. Mit diesem System konnten die Einzelschritte der katalytischen Aktivierung des Spleißosoms analysiert und die Funktion einzelner Proteine während der katalytischen Phase aufgeklärt werden. Dies führte auch zur Entdeckung und Funktionsbeschreibung eines neuen, für den ersten katalytischen Schritt notwendigen Proteins, Cwc25. Durch Fluoreszenz-Korrelationsspektroskopie wurde die Dynamik der Proteine während der katalytischen Phase des Spleißosoms quantitativ und zeitaufgelöst erfasst. Weiterhin gelang es uns, die Endphase des Spleißzyklus, das heißt die Abtrennung des gereinigten Intronlariat-Spleißosoms in seine Einzelteile, *in vitro* nachzuvollziehen. Durch Kombination von biochemischen Untersuchungen und Röntgen-Kristallstrukturuntersuchungen zeigten wir neue Regulationsprinzipien der RNA-Helikase Brr2, die die katalytische Aktivierung des Spleißosoms einleitet.

In einem weiteren Schwerpunkt erstellten wir auf der Basis biochemischer Strukturuntersuchungen des RNA-RNA-Netzwerkes in einem isolierten katalytisch aktiven Spleißosom ein Homologie-Modell des spleißosomalen katalytischen RNA-Zentrums.

Das Spleißosom und selbstspleißende Gruppe II-Introns haben ähnliche katalytische Strategien: Während in einem Gruppe II selbstspleißenden Intron der Hauptteil der intronischen RNA dazu da ist, die katalytisch aktive Konformation des katalytischen RNA-Zentrums aufrechtzuerhalten, muss im Spleißosom diese Funktion durch Proteine übernommen werden.

Wir konnten zeigen, dass unter anderem das Protein Cwc2 diese Aufgabe sowohl im Hefe-Spleißosom als auch im humanen Spleißosom in evolutionär konservierter Weise durch Wechselwirkung mit katalytisch wichtigen RNA-Regionen übernimmt.

Die Kristallstruktur des Cwc2-Proteins weist eine neuartige kompakte Kombination von drei RNA-Bindungsdomänen auf. Dies ist konsistent mit der Funktion des Proteins, verschiedene RNA-Regionen des katalytischen RNA-Zentrums des Spleißosoms in einer aktiven Konformation zu halten.

Einblicke in die strukturelle Organisation der molekularen Maschine

Außerdem konnten wir durch Elektronen-Kryomikroskopie eine 3D-Struktur des katalytisch aktiven humanen C-Komplex-Spleißosoms rekonstruieren. Wir passten unabhängig erzeugte 3D-Strukturen der im C-Komplex enthaltenen snRNP-Komplexe in die 3D-Struktur des C-Komplexes ein. In Kombination mit direkten Immunlokalisierungs-Experimenten gelang es, die annähernde Position des katalytischen Zentrums und die Lage bestimmter Prä-mRNA-Segmente im Spleißosom zu kartieren. Somit erhielten wir neue Einblicke in die strukturelle Organisation dieser molekularen Maschine.

Schließlich haben wir neue Antikörper gegen post-translationale Modifikationen spleißosomaler Proteine erzeugt, die es erlauben, aktive Spleißosomen im Zellkern mikroskopisch zu visualisieren. Mit diesen Werkzeugen konnten wir unter anderem zeigen, dass zirka 15 Prozent der Prä-mRNA-Transkripte post-transkriptional gespleißt werden und dieses Spleißen in der Nähe spleißfaktorreicher Orte im Zellkern, den sogenannten *speckles*, stattfindet.

Thomas Jovin mit *Gregorio Weber Award* geehrt

Thomas Jovin, Emeritusdirektor des Labors für *Zelluläre Dynamik* am MPIbpc, hat den *Gregorio Weber Award for Excellence in Fluorescence Theory and Applications 2014* beim diesjährigen *Annual Meeting of the Biophysical Society* erhalten.

Er wurde damit für seine Verdienste in der Weiterentwicklung von Fluoreszenztechniken geehrt. Der Preis wird von der Firma ISS gesponsert.

Thomas Jovin
promovierte 1964 an der Johns Hopkins University (USA). Seit 1969 forschte als Direktor und Leiter der Abteilung *Molekulare Biologie* am MPIbpc. Nach seiner Emeritierung 2007 führt er seine Forschung als Leiter der Emeritusgruppe *Labor für Zelluläre Dynamik* und des *Laboratorio Max Planck de Dinámica Celular*, Universität von Buenos Aires (Argentinien), fort.

Herbert Jäckle auf dem „Platz des Himmlischen Friedens".

Hohe chinesische Auszeichnung für Herbert Jäckle

Die Volksrepublik China hat Herbert Jäckle den *Preis für internationale wissenschaftlich-technische Zusammenarbeit 2013* verliehen. In einer feierlichen Zeremonie am 10. Januar dieses Jahres wurde ihm der Preis in der *Großen Halle des Volkes* in Peking in Anwesenheit der chinesischen Staatsführung überreicht. Mit ihm wurden sieben weitere Wissenschaftler und Ingenieure aus aller Welt ausgezeichnet.

Mit dieser höchsten Auszeichnung für ausländische Personen oder Organisationen im Bereich Wissenschaft und Technik wird Herbert Jäckle für seine bedeutenden Beiträge zur Entwicklung Chinas geehrt.

Herbert Jäckle hat die Kooperationen zwischen der Max-Planck-Gesellschaft (MPG) und der Chinesischen Akademie der Wissenschaften (CAS) nachhaltig gefördert. Seit 2002 setzt Herbert Jäckle als Vizepräsident der Max-Planck-Gesellschaft mit kreativen Ideen wichtige Impulse in der deutschen und chinesischen Wissenschaftslandschaft sowie in der internationalen Zusammenarbeit. Auf seine Initiative entstand im Jahr 2005 das von der MPG und der CAS gemeinsam getragene Partnerinstitut für Computergestützte Biologie in Shanghai (China). Nicht zuletzt entwickelte Herbert Jäckle ein neues sehr erfolgreiches Konzept zur Nachwuchsförderung innerhalb der MPG. Dieses wird auch am Partnerinstitut in Shanghai umgesetzt, um dort junge talentierte Forscherinnen und Forscher früh in ihrer Karriere zu unterstützen.

„Ich fühle mich sehr geehrt, dass mir die Volksrepublik China diesen hochkarätigen Preis verliehen hat. Es ist nicht nur eine große Freude für mich, sondern auch für die Max-Planck-Gesellschaft. Der tiefe gegenseitige Respekt und das Vertrauen, das sich zwischen den Kooperationspartnern in Deutschland und China entwickelt hat, ist für mich neben den wissenschaftlichen Erfolgen die wohl wichtigste Errungenschaft", so der Max-Planck-Vizepräsident. Für den Göttinger Wissenschaftler ist es bereits die zweite Auszeichnung der Volksrepublik China: Im Januar 2013 hatte ihn die Chinesische Akademie der Wissenschaften mit dem *Preis für Internationale Zusammenarbeit* geehrt.

Auf seinem Forschungsgebiet der molekularen Entwicklungsbiologie hat der Direktor am MPIbpc bahnbrechende Erkenntnisse gewonnen, wie die frühe Entwicklung der Taufliege *Drosophila melanogaster* molekular reguliert wird und was den Energiestoffwechsel des kleinen Insekts im Gleichgewicht hält. Mit seinen Kollegen hat er eine Reihe von Schaltergenen und molekularen Regelmechanismen identifiziert, die auch beim Menschen bei der Bildung von Organen und bei der Kontrolle des Energiestoffwechsels eine wichtige Rolle spielen. Seine Arbeiten eröffnen den Weg für neue und innovative Therapieansätze, die zur körpereigenen Wiederherstellung defekter Organstrukturen und -funktionen – wie etwa bei Diabetes oder Fettleibigkeit – eingesetzt werden könnten. In der gemeinsam mit dem amtierenden Max-Planck-Präsidenten Peter Gruss gegründeten Göttinger Biotech-Firma *DeveloGen AG* (heute *Evotech International GmbH*) wird daran gearbeitet, diese Erkenntnisse aus der Grundlagenforschung in die Anwendung zu überführen. Für sein Engagement als Wissenschaftsmanager und für seine Erfolge als Forscher wurde der Entwicklungsbiologe vielfach ausgezeichnet. (cr)

Prestigious Chinese award for Herbert Jäckle

The People's Republic of China has given its *2013 International Science and Technology Cooperation Award* to Herbert Jäckle. The prize was awarded in a solemn ceremony held on January 10th, 2014 in the *Great Hall of the People* in Beijing in the presence of Chinese Government representatives.

About the prize

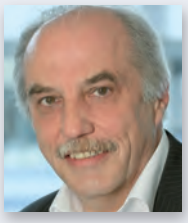
The *International Science and Technology Cooperation Award* of the People's Republic of China is a national science and technology award established by the State Council. It is given to foreign scientists, engineers, experts, or organizations, which have made important contributions to China's development through bilateral or multilateral scientific and technological cooperation. Eight international scientists and engineers have received the *2013 International Science and Technology Cooperation Award*: Jan Eduard Harff (Germany), Jun Ni, Zhong Lin Wang, Hse Chung-Yun (all USA), Arun S. Mujumdar (Canada), Fabio Rocca (Italy), G.A. Zherebtsov (Russia).

This, the highest prize for foreign individuals or organizations in the field of science and technology honors the significant contributions the awardee has made to China's social and economic development. In addition to Herbert Jäckle seven scientists and engineers from all over the world received the prestigious prize.

Awardee Herbert Jäckle has strongly promoted cooperation between the Max Planck Society and the Chinese Academy of Sciences. Herbert Jäckle, who was appointed Vice President of the Max Planck Society in 2002, has provided creative ideas which have altered both the Chinese and the German scientific landscape and strengthened international cooperation. The Partner Institute for Computational Biology in Shanghai (China) – jointly supported by the Max Planck Society and the Chinese Academy of Sciences – was established in 2005 on his initiative. Herbert Jäckle has further developed a new and very successful concept for promotion of junior scientists within the Max Planck Society. This concept was also implemented at the Partner Institute in Shanghai to support talented young researchers early in their scientific careers.

"I feel deeply honored and humbled by the recognition the People's Republic of China has bestowed on me. I do think, however, that this award honors not so much me as a person but the Max Planck Society. The deep mutual respect and trust that has developed between the cooperation partners in Germany and China, besides the scientific successes, is the most important achievement for me," the Max Planck Vice President said. For the Göttingen scientist, it is already the second prize he has received from the People's Republic of China within one year: In January 2013, the Chinese Academy of Sciences honored him with its *Award for International Scientific Cooperation*.

Herbert Jäckle also heads the successful and internationally highly regarded Department of *Molecular Developmental Biology* at the MPIbpc. His pioneering work has provided important insights into how the early development of the fruit fly *Drosophila melanogaster* is regulated on the molecular level and which control mechanisms keep the insect's energy metabolism in balance. He and his colleagues have identified a number of genes and molecular regulatory mechanisms which are also essential for organ formation and energy homeostasis in humans. His work has important implications for human diseases including obesity and diabetes. The aim of the Göttingen biotech company *DeveloGen AG* (now *Evotech International GmbH*) founded by Max Planck President Peter Gruss and by Herbert Jäckle is to use these research findings to discover and develop new medical and pharmaceutical products. Recognizing his commitment as a science manager and his achievements as a scientist, the developmental biologist has received numerous prizes and awards. (cr)



Herbert Jäckle

received his PhD in biology from the University of Freiburg in 1977. He subsequently worked at the University of Texas in Austin (USA), the European Molecular Biology Laboratory in Heidelberg, and the Max Planck Institute of Developmental Biology in Tübingen. In 1987, he became a university professor for genetics at the Ludwig Maximilians University in Munich.
He has headed the Department of *Molecular Developmental Biology* at the MPIbpc since 1991. He has taught as an honorary professor at the University of Göttingen since 1993. In 2002, he was appointed Vice President of the Max Planck Society. Herbert Jäckle has received numerous prizes and awards including the *Gottfried Wilhelm Leibniz Prize* (1986), the *Feldberg Prize* (1990), the *Otto Bayer Prize* (1992), the *Louis Jeantet Prize for Medicine* (1999), the *German Future Prize* (1999) and the *Chinese Academy of Sciences Award for International Scientific Cooperation* (2013). In 2010, he was given the *Order of Merit of the Federal Republic of Germany*. The Weizmann Institute of Science in Rehovot (Israel) awarded him an honorary doctorate in 2007.

Argentinien würdigt Christian Griesinger

Der Präsident der argentinischen Nationalversammlung hat Christian Griesinger mit einer Medaille und einer Urkunde für seine Beiträge zum Fortschritt der Wissenschaft in Argentinien geehrt. Er nahm die Auszeichnung bei einem für ihn veranstalteten Festakt im Parlament in Buenos Aires entgegen. Ferner verlieh ihm die Nationale Universität Rosario die Ehrendoktorwürde.

Christian Griesinger (links) mit Claudio Fernández.
(Bild / image: Universidad Nacional de Rosario)

Christian Griesinger, Abteilungsleiter für *NMR-basierte Strukturbiologie* am MPIbpc, arbeitet bereits seit dem Jahr 2003 gemeinsam mit argentinischen Wissenschaftlern an der Erforschung molekularer Grundlagen von neurodegenerativen Erkrankungen wie Alzheimer und Parkinson. In ihrer Laudatio im Parlament betonten die Vorsitzende des Wissenschaftsausschusses, Graciela Maria Giannettasio, und der stellvertretende Vorsitzende, Omar Perotti, die Verdienste Christian Griesingers um die Entwicklung der Kernspinresonanz in Argentinien. Weiterhin lobten sie sein Engagement beim Aufbau des *Max-Planck-Labors für Strukturbiologie und biophysikalische Chemie* an der Nationalen Universität in Rosario, das aus diesen Kooperationen hervorging. Dort wird unter der Leitung von Claudio Fernández, eines ehemaligen Mitarbeiters von Thomas Jovin und Christian Griesinger am MPIbpc, an der Entwicklung von Wirkstoffen gegen neurodegenerative Erkrankungen geforscht.

Zusammen mit Claudio Fernández initiierte Christian Griesinger im vergangenen Jahr außerdem die Einrichtung eines gemeinsamen Promotionsprogramms der Nationalen Universität Rosario und der Universität Göttingen. Das internationale Deutsch-Argentinische Promotionsprogramm *Molecular Biosciences and Biomedicine* ermöglicht es Doktoranden, an der Partneruniversität zu forschen und so bereits während der Promotion wichtige Auslandserfahrung zu sammeln. Mit diesem Promotionsprogramm erweitert der *Göttingen Research Campus* seine bereits intensive Zusammenarbeit mit argentinischen Wissenschaftseinrichtungen. (fk)

Argentina honors Christian Griesinger

The President of the National Assembly of Argentina has awarded a medal and a commemorative certificate to Christian Griesinger for his contributions to the scientific development in Argentina. The Max Planck scientist received the award on a ceremony in his honor in the parliament in Buenos Aires. Two days later, the National University of Rosario granted him an honorary doctorate.

Christian Griesinger, head of the Department for *NMR-based Structural Biology* at the MPIbpc, has been investigating the molecular basis of neurodegenerative diseases like Alzheimer's or Parkinson's together with Argentinian colleagues since 2003. In their laudatory speeches in the parliament, chair of the science committee Graciela Maria Giannettasio, and deputy chair Omar Perotti emphasized Christian Griesinger's services to the development of nuclear magnetic resonance in Argentina. They furthermore praised his commitment to the foundation of the *Max Planck Laboratory for Structural Biology and Biophysical Chemistry* at the National University of Rosario, resulting from these collaborations. There, a research team headed by Claudio Fernández, a former co-worker of Thomas Jovin and Christian Griesinger at the MPIbpc, works on the development of drugs to treat neurodegenerative diseases.

Together with Claudio Fernández, Christian Griesinger also initiated a joined PhD program of the universities of Rosario and Göttingen last year. The international German-Argentine PhD Program *Molecular Biosciences and Biomedicine* provides PhD students with the opportunity to conduct research at the partner university, thus allowing them to gain important experience abroad already during their PhD. This PhD program extends the strong collaboration of the *Göttingen Research Campus* with scientific institutions in Argentina. (fk)

Jan Zelmer wurde Erster Kammersieger im Beruf Feinwerkmechanik in Südniedersachsen.

Handwerkliche Top-Leistungen ausgezeichnet

Qualität setzt sich durch – das haben die Auszubildenden des MPIbpc schon häufiger bewiesen und in den vergangenen Jahren mehrfach Preise für ihre herausragenden Prüfungsergebnisse erhalten. Der Jahrgang 2013 ist da keine Ausnahme: Zwei Auszubildende des MPIbpc waren beim *Leistungswettbewerb des Deutschen Handwerks – Profis leisten was* erfolgreich.

Jan Zelmer wurde Erster Kammersieger im Beruf Feinwerkmechaniker und Julia Eilers Zweite Kammersiegerin im Beruf Tischlerin der Handwerkskammer Hildesheim-Südniedersachsen. Beide hatten sich als Innungssieger für den Kammerwettbewerb qualifiziert. Das Institut erhält somit zwei weitere Urkunden für seine hervorragende Ausbildung. Julia Eilers war zuvor schon mehrfach für ihre Leistungen ausgezeichnet worden, unter anderem mit dem Azubipreis 2013 der Max-Planck-Gesellschaft.

Der Leistungswettbewerb des Deutschen Handwerks wird von den Handwerkskammern und dem Zentralverband des deutschen Handwerks ausgetragen. Er kürt jährlich die besten Handwerkerinnen und Handwerker der verschiedenen Ausbildungsberufe, die ihre Gesellenprüfung im vorangegangenen Ausbildungsjahr abgelegt haben. Bewertet werden die schriftliche Gesellenprüfung, das Gesellenstück und Arbeitsproben. Die Ersten Kammersieger ermitteln anschließend unter sich die Landes- und Bundessieger.

Julia Eilers und Jan Zelmer nahmen ihre Preise am Samstag, den 25. Januar 2014, bei einem Festakt im Berufsbildungszentrum Hildesheim von der Handwerkskammer Hildesheim-Südniedersachsen entgegen. Die Auszeichnung eröffnet den beiden auch die Möglichkeit, sich nun um Fördergelder von bis zu 6000 Euro für berufsbezogene Weiterbildungen zu bewerben. Ihre Ausbilder Bernd Henkner und Peter Böttcher gratulieren zu diesem tollen Ergebnis!

Julia Eilers wurde Zweite Kammersiegerin im Beruf Tischlerin in Südniedersachsen.

Für kommende Wettbewerbe und den weiteren Berufsweg wünschen wir beiden viel Erfolg! (fk)

IMPRESSUM

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