The role of chromatin remodeling complexes in Schwann cell development

Franziska Fröb | Michael Wegner

Institut für Biochemie, Emil-Fischer-Zentrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

Correspondence
Michael Wegner, Institut für Biochemie, Emil-Fischer-Zentrum, FAU Erlangen-Nürnberg, Fahrstrasse 17, Erlangen 91054, Germany. Email: michael.wegner@fau.de

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Abstract
Schwann cells develop from neural crest cells in an ordered series of events and give rise to myelinating and nonmyelinating subtypes. In their mature state, myelinating Schwann cells produce myelin sheaths that provide trophic support to axons and allow saltatory conduction in the vertebrate peripheral nervous system. Each step of Schwann cell development requires defined changes in chromatin structure that are catalyzed by chromatin remodeling complexes. Over the last years, all major types of chromatin remodeling complexes have been detected in Schwann cells and several have been functionally analyzed. SWI/SNF-type, CHD-type, and INO80/SWR-type chromatin remodelers in particular have been shown to interact with multiple cell-type specific transcription factors and histone modifiers and to be important regulators of Schwann cell development. As a result of different recruitment strategies, each chromatin remodeler targets defined genomic areas and impacts unique mechanisms at specific stages of Schwann cell development. Chromatin remodeling complexes undoubtedly constitute essential components of the Schwann cell regulatory network.

KEYWORDS
BAF, developmental epigenetics, Ep400, glia, myelin, NuRD

1 | INTRODUCTION

Schwann cells of the peripheral nervous system are one of several cell types derived from the neural crest in vertebrates (Le Douarin & Kalchheim, 1999). Their specification occurs after migratory neural crest cells have established contact with peripheral axons. Further development follows a defined path from Schwann cell precursor to immature Schwann cell (Jessen & Minsky, 2005; Moni, Feltl, & Tavaglia, 2015). Immature Schwann cells are in contact with large bundles of differently sized axons, which they invade with their processes to sort out large caliber axons. As a result of this radial sorting process, some Schwann cells stay in contact with several small caliber axons, give rise to Remak bundles and convert into nonmyelinating Schwann cells. Others establish a 1:1 relationship with large caliber axons and convert via promyelinating Schwann cells into myelinating Schwann cells. Each myelinating Schwann cell forms a single multilamellar myelin sheath that provides trophic support and electrical insulation to a single axonal segment (Nave, 2010). It also contributes to formation of a node of Ranvier between adjacent myelinated segments as a precondition to saltatory conduction along peripheral nerves (Rasband & Peles, 2015). In case of nerve injury, mature Schwann cells have the capacity to convert into repair Schwann cells, proliferate, promote the regeneration process, and eventually undergo again differentiation (Jessen & Arthur-Farraj, 2019). Each of these stages in the Schwann cell life cycle is characterized by a particular pattern of gene expression, to which changes in chromatin contribute as much as the activity of specific transcription factors (Ma & Svaren, 2018).

Chromatin changes involve alterations at the level of the single nucleosome as its main building block and affect histones as well as
DNA. Histones are the target of a plethora of posttranslational modifications including acetylations, methylations, phosphorylations, ubiquitinations, sumoylations, and ADP-ribosylations, and these histone marks have a substantial impact on chromatin accessibility and compaction. The DNA itself can also be modified at single base positions, such as in the case of cytosine methylation.

In addition to changes at the nucleosome level, the number of nucleosomes on a particular stretch of DNA can be varied. Other alterations include changes in nucleosomal positions or exchange of nucleosomes with canonical histones against nucleosomes with non-canonical isoforms such as histone 2A.Z (H2A.Z) and histone 3.3 (H3.3). A higher density of nucleosomes in a genomic region is usually inversely correlated to its accessibility and the transcription rates of genes within the region. A nucleosome positioned over an important regulatory region or the transcriptional start site may interfere with expression of the associated gene, and nucleosomes with non-canonical histones often mark active enhancer or promoter regions. Removal, addition, repositioning, or exchange of nucleosomes require energy. These ATP-dependent processes are referred to as chromatin remodeling and catalyzed by so-called chromatin remodelers, which often represent large multisubunit protein complexes (Hota & Bruneau, 2016). Common to all these chromatin remodeling complexes is the presence of an ATPase subunit that generates the required energy, belongs to the Snf2 family of DNA helicases and is grouped into one of four subtypes according to the exact sequence of its ATPase domain. The ATPase subunit also serves to classify the chromatin remodeling complex as a member of the SWI/SNF (switch/ sucrose non-fermentable), ISWI (imitation of SWI), CHD (chromodomain helicase DNA-binding), or INO80/SWR (inositol requiring protein 80/SWI2 related) family (Figure 1). Other subunits are constitutively or variably present in the complex, modify the ATPase activity or direct the complex to specific regions in the genome. Chromatin remodelers of the SWI/SNF, ISWI, and CHD families usually affect presence or position of nucleosomes, whereas INO80/SWR-type remodelers change the type of nucleosome. Their influence can be activating as well as repressing.

Despite their obvious relevance and proven importance in many other developmental systems (Hota & Bruneau, 2016), the impact of chromatin remodelers in Schwann cells has only recently begun to be addressed. These efforts have provided convincing evidence for a role of SWI/SNF-, CHD-, and INO80/SWR-type remodelers in lineage progression and differentiation of Schwann cells and will be the focus of this review.

2 | DIFFERENTIAL EXPRESSION OF CHROMATIN REMODELING COMPLEXES AND THEIR COMPONENTS IN SCHWANN CELLS

A survey of publicly available RNA-Seq data from primary Schwann cells cultured under proliferative or differentiating conditions confirms that at least one central ATPase subunit for each of the four types of chromatin remodeling complexes is expressed at medium to high levels (Figure 1). In contrast, expression of other subunits from chromatin remodeling complexes is more variable. In fact, several subunits, such as Smarcb1 (also known as Baf47) in case of the SWI/SNF-type BAF (Brg1/Brm-associated factor) remodeling complex, appear not to be expressed. Among isoforms for a particular subunit, some are expressed at substantially higher levels than others, such as Bcl11b relative to Bcl11a or Bcl7a and Bcl7c relative to Bcl7b in case of the BAF complex (Figure 1). These observations argue that at least some of the chromatin remodeling complexes will have a Schwann-cell specific composition. Such cell-type specific compositions have previously been shown to exist for instance for the SWI/SNF-type BAF complex and to be functionally relevant in embryonic stem cells, neuronal cells, and cardiac mesoderms (Ho et al., 2009; Lessard et al., 2007; Lickert et al., 2004).

Intriguingly, our survey shows that there are also differences in expression levels between Schwann cells kept either under proliferating or differentiating culture conditions. In case of the BAF complex, some of the Baf45 isoforms (i.e., Dpf3/Baf45c and Phf10/Baf45a) are for instance downregulated under differentiating conditions, whereas others (i.e., Dpf1/Baf45b) are upregulated (Figure 1). Thus, it is likely that a switch of subunit composition may occur in chromatin remodeling complexes during Schwann cell differentiation. Considering that such switches have been shown to be essential for development and differentiation of neurons (Lessard et al., 2007), they may also be relevant for Schwann cell development. In summary, these findings demonstrate the presence of all major types of chromatin remodeling complexes in Schwann cells and point to subunit composition as a possible determinant of cell-type- or stage-specific complex activity.

3 | SWI/SNF-TYPE CHROMATIN REMODELERS IN SCHWANN CELL DEVELOPMENT

The standard approach to study the role of chromatin remodeling complexes in vivo is the cell-type specific deletion or inactivation of the gene coding for the central ATPase thereby rendering the complex enzymatically inactive.

In vertebrates, the main SWI/SNF-type chromatin remodeler is the BAF complex, which contains at least 15 different subunits. Either Brm (also known as Brahma, Smarca2) or Brg1 (also known as Brahma-related gene 1, Smarca4) can be the central ATPase. When Brg1 is present, the BAF complex can exist as standard BAF complex or as polybromo-associated BAF complex (PBAF) in which there is additional association of the BAF remodeler with a complex containing Baf200, Baf180, and Brd7 (Yan et al., 2008). In contrast, PBAF formation is not possible with Brm as ATPase subunit.

Considering this, as well as Schwann cell expression levels of Brg1 and Brm (Figure 1), cell-type specific deletion of Brg1 will strongly reduce activity of the standard BAF complex and inactivate the PBAF complex completely. Two studies chose this approach and deleted Brg1 in the late Schwann cell precursor to immature Schwann
cell stage using Dhh::Cre, which together with P0::Cre represents the earliest available Schwann cell-specific Cre driver line (Limpert et al., 2013; Weider et al., 2012). As a consequence of the deletion, Schwann cell development was predominantly stalled at the immature Schwann cell stage as evident from the persistence of Schwann cell-surrounded mixed axon bundles and a lack of radial sorting. Few Schwann cells ever reached a 1:1 relationship with large caliber axons as promyelinating Schwann cells and signs of myelination were virtually absent. The block in differentiation was also reflected by a failure to extinguish Sox2 as a marker of the immature stage and the inability to activate Oct6 (also known as Pou3f1) and Egr2 (also known as Krox20) as markers and regulators of the promyelinating and myelinating stage, respectively (Sock & Wegner, 2019). After a month, mice showed signs of severe paralysis and substantially increased mortality.

Phenotypic defects in Brg1-deficient Schwann cells were furthermore highly reminiscent of (though less severe than) those in mice with Sox10-deficient Schwann cells (Finzsch et al., 2010), and a genetic interaction between Brg1 and Sox10 was detected in vivo (Weider et al., 2012). Sox10 is a transcription factor that is expressed throughout Schwann cell development and required at all stages (Bremer et al., 2011; Finzsch et al., 2010; Fröb et al., 2012). As molecular mode of action, two mechanisms were proposed. One of the studies found evidence for a physical interaction between the NFκB

FIGURE 1 Components of chromatin remodeling complexes: expression and regulation in Schwann cells. For each remodeling complex, components are listed by gene symbol and frequently used alternative name. Mean expression levels are categorized as nonexistent (−), low (l), medium (m), or high (h) according to GSE101153. Additionally listed are significant changes of expression during Schwann cell differentiation (p ≤ .05) and the presence of Sox10 and Egr2 binding sites in the vicinity of coding genes according to GSE64703 and GSE35132. Central ATPase subunits for each remodeling complex are highlighted in red. Subunits with occurrence in several complexes are only mentioned once. (1) Occurs also in Ep400/Tip60 complex; (2) occurs also in INO80, SRCAP, and Ep400/Tip60 complexes; (3) occurs also in NURF complex; (4) occurs also in SRCAP and Ep400/Tip60 complexes; (5) occurs also in WICH, RSF, and NoRC complexes.
p65 subunit and Brg1-containing complexes and suggested that upon Neuregulin-dependent induction, NFκB recruits Brg1-containing complexes to Sox10 and other target genes, increases Sox10 expression and promotes Schwann cell differentiation (Limpert et al., 2013; Figure 2a). However, it has since been shown that NFκB signaling has only minor effects on Schwann cell development and myelination in vivo (Morton et al., 2013). Therefore the NFκB-mediated and Brg1-dependent upregulation of Sox10 is probably not the decisive mechanism whose disruption is responsible for the observed phenotypic defects.

The second study detected a physical interaction between Brg1-containing complexes and Sox10 itself and showed that Sox10-dependent activation of Oct6 and Egr2 in differentiating Schwann cells can only occur in the presence of Brg1 (Weider et al., 2012). Activation furthermore required Brg1 recruitment to the corresponding regulatory regions of the Oct6 and Egr2 genes, which

**FIGURE 2** Chromatin remodeling complexes: mode of action in Schwann cells. (a) NFκB- and Sox10-dependent recruitment of Brg1-containing BAF complexes to regulatory regions (prom, promoter; SCE, Schwann-cell specific enhancer; MSE, myelinating Schwann cell enhancer) of Sox10, Oct6, Egr2, and myelin genes (Mbp, Mpz) results in target gene activation. (b) Zeb2- and Egr2/Nab-dependent recruitment of Chd4-containing NuRD complexes represses early regulators of Schwann cell development (Hey2, Sox2, Id2, Oct6) and activates myelin genes. (c) Recruitment of Ep400-containing Tip60/Ep400 complexes leads to a local exchange of histone 2A (H2A) against histone 2A.Z (H2A.Z) and shuts off expression of early neural regulators such as Tfp2a, Pax3, and Sox2
was only observed in the presence of Sox10 (Figure 2a). Absence or strongly reduced expression of Oct6 and Egr2 would prevent Schwann cell differentiation and could explain the arrest in the immature state.

There is ample evidence that many terminal differentiation and myelin genes are under joint control of Sox10 and Egr2 (Bondurand et al., 2001; Jones et al., 2007; Leblanc et al., 2005). Considering the physical and functional interaction between Sox10 and Brg1-containing complexes, it would therefore be expected that Brg1 also has an influence on the expression of myelin genes such as Mbp and Mpz. This has indeed been shown (Marathe et al., 2013) and argues that Brg1-containing complexes may have additional roles during the terminal differentiation process (Figure 2a).

In summary, these studies provide convincing evidence that Brg1-containing chromatin remodeling complexes have essential functions in Schwann cell development from the immature Schwann cell stage onwards and identify physical interactions with Schwann cell transcription factors such as Sox10 and recruitment to regulatory regions as relevant mechanisms. Considering the activity of Brg1-containing complexes, recruitment likely leads to local changes in chromatin that increase the accessibility of regulatory regions and associated genes with relevance for differentiation. Simultaneously, Brg1-containing complexes may also decrease accessibility of genes that need to be shut off as development progresses. However, Brg1-dependent chromatin changes have not yet been studied directly in Schwann cells.

Several other limitations should be kept in mind. For one, the published data do not allow a distinction between the activity of standard BAF and PBAF complexes as both are affected by Brg1 deletion. Furthermore, Brm is still present in Brg1-deficient Schwann cells and should permit residual SWI/SNF-type remodeling activity. Whether Brg1- and Brm-containing complexes are functionally interchangeable in Schwann cells is not clear. Finally, co-immunoprecipitation of two proteins from whole cell extracts generally does not allow a clear distinction between direct and indirect interactions. Thus, it is not clear whether the detected interaction between Brg1 and Sox10 or NFκB is direct or mediated by other subunits of the Brg1-containing complex. It may well be that interactions between remodeling complex and transcription factor with in vivo relevance have to occur via multiple subunits. In this context, it is worth mentioning that a direct protein–protein interaction has been detected between Sox10 and Baf660a (also known as Smarcd1) using bacterially expressed proteins (Weider et al., 2012; Figure 2a). Intriguingly, this interaction is confined to Baf660a and was not observed with its paralogs Baf660b (also known as Smarcd2) and Baf660c (also known as Smarcd3). Considering that Baf660 subunits define specific subsets of BAF complexes, such a finding raises the possibility that the interaction of Schwann cell transcription factors may occur with a subgroup of BAF complexes that subserve specific functions.

Interestingly, ChIP-Seq data indicate that Schwann cell transcription factors such as Sox10 and Egr2 also bind in the vicinity of many genes that code for subunits of chromatin remodeling complexes including subunits of the BAF complex (Figure 1). As binding of a transcription factor in the vicinity of a gene often correlates with an impact on its expression, this finding highlights an additional aspect of the tight and complex interplay between transcription factors and chromatin remodelers in the Schwann cell regulatory network.

4 | CHD-TYPE CHROMATIN REMODELERS IN SCHWANN CELL DEVELOPMENT

Nine CHD-type ATPases (Chd1–Chd9) exist. Whereas some of them act alone, Chd3 and Chd4 are usually active in multi-subunit NuRD (nucleosome remodeling deacetylase) complexes. The role of NuRD complexes has been studied in Schwann cells by deleting Chd4 using P0:Cre (Hung, Kohnken, & Svaren, 2012). Again, it has to be kept in mind that Chd3 is still present and may allow for residual NuRD activity in the absence of Chd4.

The resulting conditional knockout mice showed abnormalities in Schwann cell development. This included radial sorting defects, prolonged persistence in the promyelinating state and myelination defects. In contrast to mice with Schwann cell-specific Brg1 deletion, defects were less severe and mostly transient. At 1 month of age, myelin sheaths were still thinner in peripheral nerves, but other ultrastructural features had largely normalized. However, Chd4-deficient Schwann cells still showed reduced expression of myelin genes despite the fact that amounts of Egr2 and Sox10 as the main regulators of the myelination program were essentially unaltered. Only earlier transcriptional regulators of Schwann cell development such as Id2, c-Jun, Sox2, and Oct6 showed increased expression. Importantly, Chd4 had previously been shown to interact with Nab proteins (Srinivasan, Mager, Ward, Mayer, & Svaren, 2006), which represent transcriptional coregulators that are constitutively required for Egr2 function in Schwann cells (Le et al., 2005).

Therefore it is plausible to assume that Nab proteins mediate contact between Egr2 and the NuRD complex and allow recruitment of the chromatin remodeler to Egr2 target genes (Figure 2b). As already mentioned, these target genes include many of the genes induced during terminal differentiation and myelination. In addition to activation of these genes, Egr2 has also been shown to act as a repressor, for instance of earlier transcriptional regulators of Schwann cell development such as Id2, c-Jun, Sox2, and Oct6 (Decker et al., 2006; Mager et al., 2008; Srinivasan et al., 2006). The presence of Chd4 and Mta2 as another subunit of the NuRD complex on these Egr2 target genes supports the assumption that the NuRD complex is involved in both Egr2-dependent gene activation and repression (Hung et al., 2012). These Egr2-associated functions explain the late defects observed in mice with Chd4-deficient Schwann cells.

What this mechanism cannot explain is the earlier radial sorting delay. In this context, a recent publication offered an interesting explanation by showing that Schwann cell-specific deletion of Zeb2 (also known as Sip1, Zfhx1b) led to a severe radial sorting and differentiation defect (Wu et al., 2016). The study furthermore showed that Zeb2 repressed Notch signaling in immature Schwann cells by recruiting the NuRD complex to the gene coding for the Notch effector.
Hey2 and inhibiting its expression (Figure 2b). In line with such a mechanism, differentiation of Zeb2-deficient Schwann cells could be rescued when Notch signaling was repressed. Thus it is plausible that Zeb2-dependent NuRD recruitment is instrumental in shutting off early Schwann cell regulators and thus permits radial sorting and line-age progression past the immature Schwann cell stage.

It is also interesting to note that histone deacetylases Hdac1 and Hdac2 are part of the NuRD complex (Figure 1). Hdac1 and Hdac2 are themselves essential for Schwann cell differentiation and closely interact with Sox10 (Jacob et al., 2011). Thus, NuRD may not only interact with Egr2 or Zeb2, but may also cooperate via Hdac1 and Hdac2 with Sox10 as another essential factor involved in the same processes. The presence of Hdac1 and Hdac2 in NuRD complexes furthermore documents how close chromatin remodeling activity is linked to histone modifications (see Duman, Martinez-Moreno, Jacob, & Tapinos, 2020).

5 | INO80/SWR-TYPE CHROMATIN REMODELERS IN SCHWANN CELL DEVELOPMENT

In contrast to other chromatin remodelers, INO80/SWR-type chromatin remodelers do not change nucleosomal localization or occupancy. Instead, they exchange canonical histones such as histone 2A (H2A) against noncanonical variants such as H2A.Z within nucleosomes, or standard nucleosomes against variant histone-containing nucleosomes (Venkatesh & Workman, 2015). Among the three INO80/SWR-type complexes, only the Tip60/Ep400 complex has been analyzed. No data are yet available for the INO80 and the SRCAP complexes. All three complexes have several subunits in common. Among the subunits of the Tip60/Ep400 complex both Tip60 and Ep400 are specific and code for a histone acetylase in case of Tip60 and the central ATPase in case of Ep400 (Hota & Bruneau, 2016; Venkatesh & Workman, 2015). The presence of a histone acetylase within the complex again supports the close link between histone modification and chromatin remodeling activity.

To analyze the role of the Tip60/Ep400 complex in Schwann cells, Ep400 was conditionally deleted using Dhh::Cre (Fröb et al., 2019). The resulting mice exhibited a severe defect in Schwann cell development. Radial sorting defects were minor. Instead there was a pronounced arrest at the promyelinating stage that eventually resolved so that many ultrastructural features of mutant nerves appeared normal at 2 months of age. However, myelin sheaths remained thinner and expression of most myelin genes was substantially reduced. Abnormal myelin structures and myelin debris were frequently found. Additionally, Remak bundles were altered arguing that nonmyelinating and myelinating Schwann cells were both affected. The most dramatic changes in Schwann cell expression concerned a set of developmental regulators that are usually active at earlier phases of Schwann cell development and turned off in mature Schwann cells such as Tfap2a, Pax3, Sox2, Oct6, or paralogous factors. Many of the corresponding genes furthermore showed substantial enrichment of H2A.Z around their transcriptional start sites, whereas H2A.Z occupancy was largely unaltered for Sox10, Egr2, and tested myelin genes (Figure 2c). The presence of H2A.Z at promoters or enhancers often correlates with higher rates of transcription. Considering that the Tip60/Ep400 complex is involved in the exchange of H2A and H2A.Z, it appears likely that the observed alterations at the start of Tfap2a, Pax3, Sox2, Oct6, and related genes are causal to the observed Schwann cell defect. Their persistent expression likely interferes with myelin gene expression directly or indirectly by inhibition of Egr2 activity and expression (Doddrell et al., 2012; Le et al., 2005; Roberts et al., 2017). In line with such an assumption, additional deletion of Tfap2a in Ep400-deficient Schwann cells led to a substantial rescue of the Schwann cell defect in vivo (Fröb et al., 2019). In case of the Ep400/Tip60 complex, recruitment to its target genes has not been studied. Studies in oligodendroglial cells suggest that Sox10 and Ep400 can physically interact (Elsesser et al., 2019). The relevance of this finding for Schwann cells is not known so far.

6 | CONCLUSIONS

Until now, only few studies exist on chromatin remodeling complexes in Schwann cells. However, even the few provide ample evidence that chromatin remodeling complexes have important functions in Schwann cell development. Considering the differences in the observed defects it is furthermore obvious that chromatin remodeling complexes have their own separate functions and do not act interchangeably during Schwann cell development. They are differently recruited and act through different molecular mechanisms in close association with histone modifications and Schwann cell transcription factors. A similar impact on Schwann cells during regeneration and remyelination is likely, but has not yet been investigated.

Analysis of chromatin remodeling complexes in Schwann cells is still in its infancy. By deleting the central ATPase and inactivating a specific chromatin remodeling complex, existing studies only scratched the surface. RNA-Seq studies clearly indicate that several subunits of chromatin remodeling complexes are differentially expressed or may change their expression during Schwann cell differentiation. Therefore it seems plausible to assume that the function of a chromatin remodeling complex depends on its exact composition, that several subtypes of a particular complex may exist and be differentially active as development proceeds. Future experiments will have to look into these possibilities as well as into the various interactions of chromatin remodeling complexes with histone modifiers and modified histones.

It also needs to be mentioned that all of the existing studies cannot exclude that residual function of the studied activities may still exist because of the existence of alternative ATPase subunits for the studied remodeling complex or alternative remodeling complexes with similar activities. Existing studies have furthermore primarily focused on changes in gene expression. However, chromatin remodeling complexes also influence other processes such as DNA repair and DNA
replication (Venkatesh & Workman, 2015). Although, little evidence has been obtained for the relevance of such functions during Schwann cell development, their existence should be kept in mind.

Finally, it is quite intriguing to compare the function of chromatin remodeling complexes in Schwann cells with those in oligodendrocytes (see Parras, Marie, & Zhao, Lu, 2020). Currently, this is only possible for Brg1- and Ep400-containing complexes. Both Brg1 and Ep400 also impact oligodendrocyte development. However, the exact function and mode of action appear very different. In oligodendrocytes, Brg1-containing complexes have the biggest impact on oligodendroglial specification and only minor effects on differentiation (Bischof, Weider, Küspert, Nave, & Wegner, 2015; Yu et al., 2013). Furthermore, in oligodendrocytes Brg1-containing complexes seem to be primarily recruited to their genomic target areas by Olig2 and not by Sox10 as in Schwann cells (Yu et al., 2013). Following Ep400 deletion in oligodendrocytes, early regulators seem to be appropriately shut off (Elsesser et al., 2019). Here, Ep400-containing complexes appear to primarily function on regulators of differentiation and myelin genes. Additionally, an altered response to DNA damage was observed in these cells. Again, it will be interesting to determine the reason for these different functions in future experiments.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT
All data described in this article have been previously published or deposited and can be freely accessed from the primary sources referenced in this article.

ORCID
Franziska Fröb https://orcid.org/0000-0002-6404-8631
Michael Wegner https://orcid.org/0000-0002-4586-3294

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