



# A proposed mechanism for the interaction between the *Candida albicans* Als3 adhesin and streptococcal cell wall proteins

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*C. albicans* binds various bacteria, including the oral commensal *Streptococcus gordonii*. Published reports documented the role of *C. albicans* Als3 and *S. gordonii* SspB in this interaction, and the importance of the Als N-terminal domain (NT-Als) in *C. albicans* adhesion. Here, we demonstrate that Als1 also binds *S. gordonii*. We also describe use of the NT-Als crystal structure to design mutations that precisely disrupt peptide-binding cavity (PBC) or amyloid-forming region (AFR) function in Als3. *C. albicans* displaying Als3 PBC mutant proteins showed significantly reduced binding to *S. gordonii*; mutation of the AFR did not affect the interaction. These observations present an enigma: the Als PBC binds free C termini of ligands, but the SspB C terminus is covalently linked to peptidoglycan and thus unavailable as a ligand. These observations and the predicted SspB elongated structure suggest that partial proteolysis of streptococcal cell wall proteins is necessary for recognition by Als adhesins.

**Keywords:** interkingdom interactions, streptococcal adhesin, SspB, Als3 adhesin, peptide-binding cavity, adhesion tethers, isopeptide bond

## INTRODUCTION

*C. albicans* binds various bacterial species, participating in polymicrobial interactions in the normally healthy host (Shirtliff et al., 2009). One of these is the oral commensal bacterium *Streptococcus gordonii* (Holmes et al., 1996). Co-aggregation between the fungal and bacterial cells is mediated by binding of the adhesive, cell-wall-anchored *S. gordonii* SspB to *C. albicans* Als3 (Silverman et al., 2010). *S. gordonii* cells attach to and accumulate around wild-type *C. albicans* hyphae, but have considerably decreased interaction with hyphae of a  $\Delta als3/\Delta als3$  strain. Heterologous production of Als3 in the normally non-adherent yeast *Saccharomyces cerevisiae* promotes *S. gordonii* binding to the fungal cells. Deletion of SspA and SspB from *S. gordonii* reduces *S. cerevisiae*/Als3 binding by more than 50%. Heterologous production of SspB in *Lactococcus lactis* promotes binding between the bacterium and the *S. cerevisiae*/Als3 cells. Although residual binding interactions are observed among the various mutant strains, the experimental evidence demonstrated convincingly that SspB and Als3 play a major role in adhesion of *S. gordonii* to *C. albicans*.

Als3 is one of eight *C. albicans* Als proteins (Als1–Als7, Als9), large cell-surface glycoproteins that primarily function in adhesive interactions (Hoyer et al., 2008). While some Als proteins may have overlapping or redundant activity, an understanding of the functional relationships within the Als family is not developed fully. Cell-biology-based inquiry provided an

extensive list of divergent binding partners for Als3 including human fibronectin, laminin, collagen, gp96, EGFR, HER2, N-cadherin, E-cadherin, fibrinogen, casein, equine ferritin, bovine serum albumin [reviewed in Lin et al. (2014)], as well as *S. gordonii* SspB (Silverman et al., 2010). The N-terminal domain of Als proteins (NT-Als; approximately 315 aa in the mature protein) is responsible for much of the inferred protein-protein interactions.

Molecular modeling was used to conclude that NT-Als3 interacts with its binding partners by surface-surface interactions (Sheppard et al., 2004; Phan et al., 2007). However, the sheer number and ever-increasing list of proposed binding partners raise the question of how NT-Als domains can adapt to the surface of so many structurally unrelated ligands to establish biologically relevant interactions. Solution of the NT-Als molecular structure (Salgado et al., 2011; Lin et al., 2014) revealed that NT-Als adhesins contain a wide and flat cavity between two immunoglobulin-like domains that can bury up to six C-terminal amino acids of peptides in an extended conformation. The side chain amine of an invariant Lys at the end of this peptide-binding cavity (PBC) establishes a salt bridge with the C-terminal carboxylic acid of the incoming peptide. Thus, NT-Als adhesins have a novel mechanism to bind the flexible C terminus of proteins. The broad specificity of this mechanism can explain Als protein function in biochemical and cell-based assays (Salgado et al., 2011).

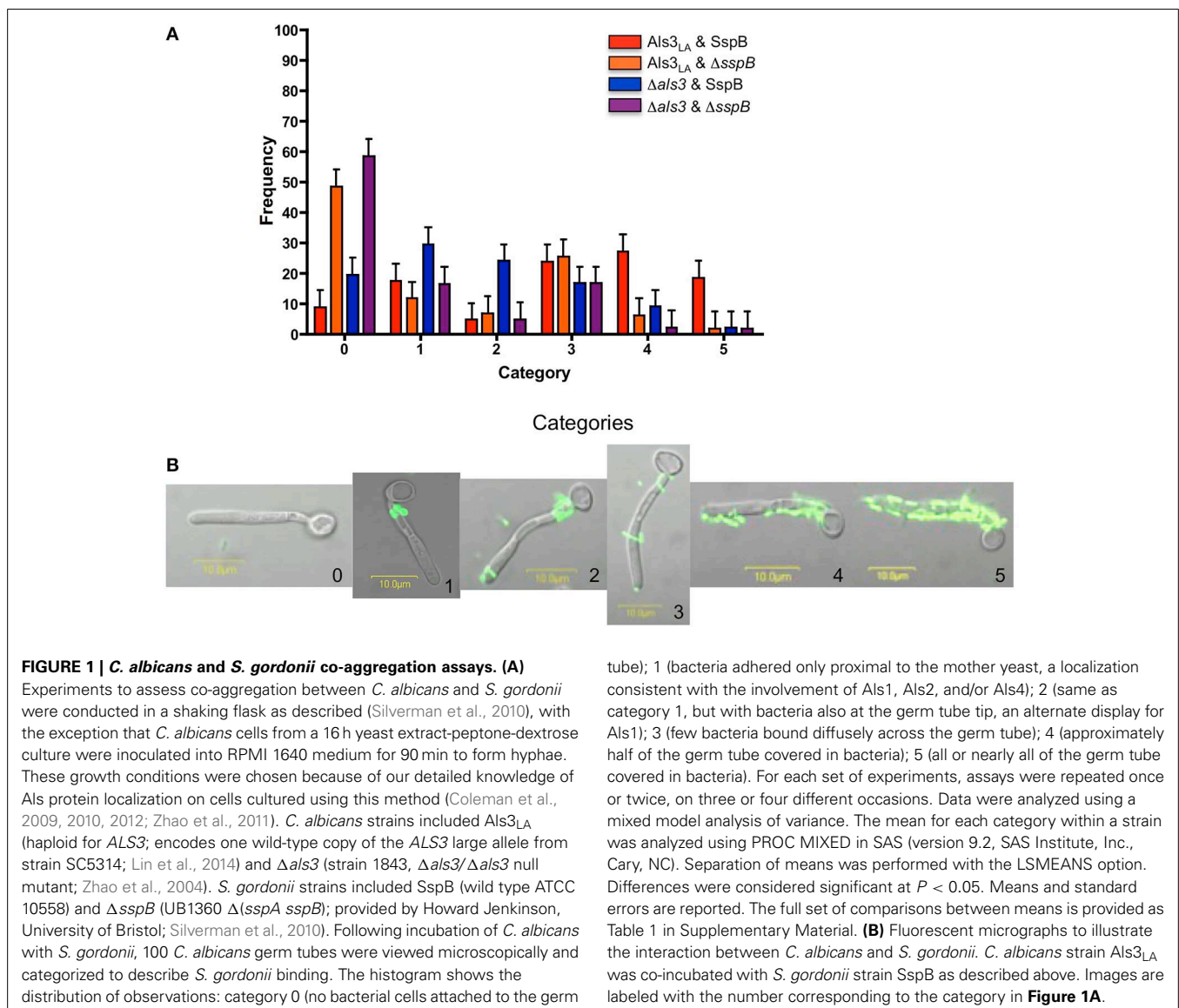
NT-Als structural data guided creation of precise site-directed mutations that disrupted function of the NT-Als3 PBC without altering any other aspect of the protein structure (Lin et al., 2014). Full-length *ALS3* genes encoding these mutations were cloned into the *ALS3* locus, resulting in display of the mutant protein on the *C. albicans* cell surface at physiological quantities and native localization (Lin et al., 2014). *C. albicans* strains with disrupted Als3 PBC function had a phenotype identical to the null  $\Delta als3/\Delta als3$  strain in assays measuring adhesion to monolayers of human pharyngeal epithelial and umbilical vein endothelial cells, and freshly collected human buccal epithelial cells in suspension.

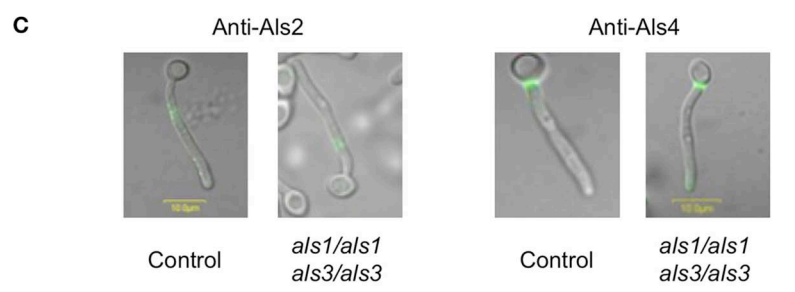
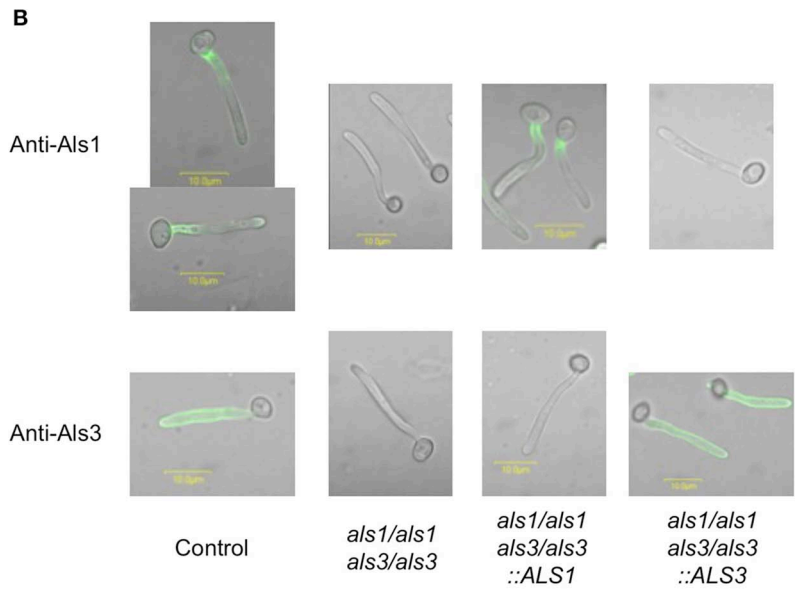
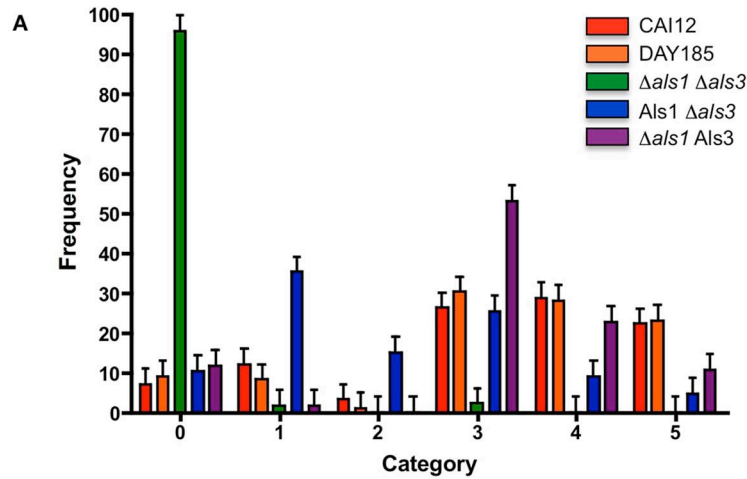
Mutations were also created in the Als amyloid-forming region (AFR), which has been suggested to be involved in *C. albicans* adhesive processes (Lipke et al., 2012). Destruction of the Als3 amyloidogenic potential had little effect on *C. albicans* adhesion to human cell types (Lin et al., 2014). These assays conclusively showed the essential and principal role of the PBC in Als3

adhesion. This system provides a powerful approach to probe Als3 binding functions in its interactions with other proteins. With these reagents and others, we began our effort to understand the interaction between *C. albicans* and *S. gordonii* in greater detail.

### A ROLE FOR ALS PROTEINS, IN ADDITION TO ALS3, IN BINDING OF *S. GORDONII* TO *C. ALBICANS*

Initial experiments evaluated binding between wild-type and mutant *C. albicans* and *S. gordonii* strains. The interactions were quantified in categories based on the location and abundance of bacteria binding to germ tubes (Figure 1). Co-incubation of control *C. albicans* (Als3<sub>LA</sub>) and *S. gordonii* (SspB) strains showed significantly more *C. albicans* cells with high levels of bacterial adhesion (categories 4 and 5) than when either Als3 or SspB, or both, were absent (compare red bars to all other colors in Figure 1A in categories 4 and 5;  $P < 0.05$ ). Similarly, co-incubation of Als3<sub>LA</sub> and SspB strains showed fewer category 0 cells than some of the other strain combinations ( $P < 0.0001$





**FIGURE 2 | *S. gordonii* co-aggregation with *C. albicans* strains lacking Als1, Als3 or both proteins. (A)** The co-aggregation assay was conducted and analyzed as described above. William Fonzi, Georgetown University, provided *C. albicans* control strain CAI12 (*ALS1/ALS1 ALS3/ALS3*; Porta et al., 1999). Aaron Mitchell, Carnegie Mellon University, provided strains DAY185 (*ALS1/ALS1 ALS3/ALS3*; Nobile et al., 2008),  $\Delta als1 \Delta als3$  (CJN1348; *als1/als1 als3/als3*; Nobile et al., 2008), Als1  $\Delta als3$  (CJN1352; *als1/als1::ALS1 als3/als3*; Nobile et al., 2008), and  $\Delta als1 Als3$  (CJN1356; *als1/als1 als3/als3::ALS3*; Nobile et al., 2008). All assays used *S. gordonii* strain SspB. The full set of

comparisons between means is provided as Table 2 in Supplementary Material. **(B)** *C. albicans* hyphae were grown for 90 min, then immunolabeled with a monoclonal antibody that recognizes either Als1 (Coleman et al., 2010) or Als3 (antibody 3-A5; Coleman et al., 2009). Genotypes of each strain are shown below the images. **(C)** *C. albicans* hyphae were grown for 90 min and immunolabeled with a monoclonal antibody that recognizes either Als2 or Als4 (Coleman et al., 2012). Methods for immunolabeling of *C. albicans* germ tubes and for fluorescence microscopy and image processing were published previously (Coleman et al., 2009).

compared to  $\text{Als3}_{\text{LA}}$  &  $\Delta\text{sspB}$  and  $\Delta\text{als3}$  &  $\Delta\text{sspB}$ ). Interestingly, there was no significant difference in category 0 cells for the combinations of  $\text{Als3}_{\text{LA}}$  & SspB and  $\Delta\text{als3}$  & SspB ( $P = 0.2$ ), despite the lack of Als3 in the latter pair. Rather than occupying category 0, cells from the  $\Delta\text{als3}$  & SspB combination tended to populate categories 1 and 2, which reflected *S. gordonii* binding to regions of the *C. albicans* germ tube with high abundance of other Als proteins including Als1, Als2, and Als4 (Coleman et al., 2010, 2012; **Figure 2**). Together, these data confirm the importance of Als3 and SspB in binding of *S. gordonii* to *C. albicans*, and also suggest the involvement of other Als proteins in the interaction.

### C. ALBICANS Als1 BINDS S. GORDONII

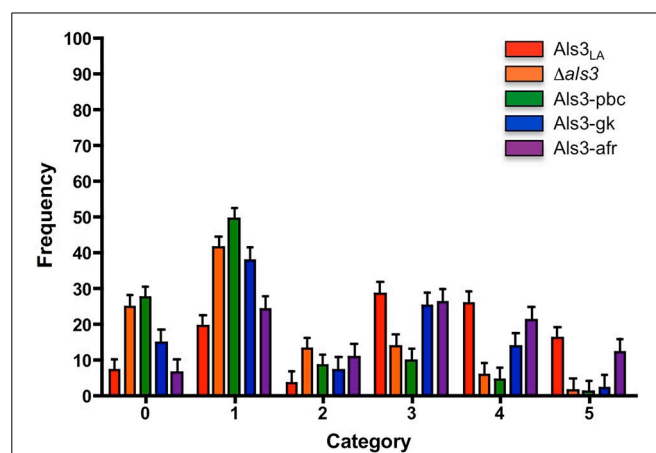
Wild-type *S. gordonii* was incubated with *C. albicans* strains lacking either Als1, Als3, or both proteins (**Figure 2A**). Als protein localization and abundance on these *C. albicans* strains are shown in **Figure 2B**. Results for the two control strains (CAI12 and DAY185; wild-type for *ALS1* and *ALS3*) statistically were indistinguishable in each category ( $P > 0.05$ ). Deleting both *ALS3* and *ALS1* (strain  $\Delta\text{als1} \Delta\text{als3}$ ) resulted in significantly more observations in category 0, and concomitantly, fewer in categories 3, 4 or 5 ( $P < 0.0001$  for all comparisons). Only approximately 4% of *C. albicans* cells of the  $\Delta\text{als1} \Delta\text{als3}$  strain bound any *S. gordonii*, with observations divided evenly between categories 1 and 3. These results suggested that other Als proteins localized to the *C. albicans* germ tube played an almost undetectable role in the *C. albicans*/*S. gordonii* interaction. Immunolabeling of the control and double-mutant strains confirmed the presence of Als2 and Als4 in these locations (**Figure 2C**).

Reintegration of *ALS1* into the  $\Delta\text{als1} \Delta\text{als3}$  strain (to produce strain  $\text{Als1} \Delta\text{als3}$ ) significantly decreased the number of adhesion-negative *C. albicans* cells (**Figure 2A**, category 0, compare green and blue bars;  $P < 0.0001$ ) and significantly increased the number of *C. albicans* cells in category 1 ( $P < 0.0001$ ) and category 2 ( $P = 0.01$ ). These results supported the conclusion that Als1 functions in adhesion of *S. gordonii* to *C. albicans*. Reintegration of *ALS3* into the  $\Delta\text{als1} \Delta\text{als3}$  strain significantly decreased the number of adhesion-negative *C. albicans* cells (**Figure 2A**, category 0, compare green and purple bars;  $P < 0.0001$ ). The *ALS3* reintegrant strain ( $\Delta\text{als1} \text{Als3}$ ) showed significant increases in cells assigned to categories 3, 4, and 5 compared to the  $\Delta\text{als1} \Delta\text{als3}$  strain; these categories reflected locations on the germ tube where Als3 is found (**Figure 2B**). There were no differences in categories 1 and 2 when comparing the  $\Delta\text{als1} \Delta\text{als3}$  strain to the *ALS3* reintegrant ( $P > 0.05$ ). Comparison between results for the *ALS1* and *ALS3* reintegrant strains ( $\text{Als1} \Delta\text{als3}$  vs.  $\Delta\text{als1} \text{Als3}$ ) showed no significant difference in category 0, but significant differences between strains in categories that emphasized the effects of protein localization. Overall, these results demonstrated that both Als3 and Als1 participated in adhesion of *S. gordonii* to *C. albicans*, with little contribution from Als2 or Als4, indicating that a common feature of Als proteins, not only present in Als3, is involved in the mechanism of association with SspB.

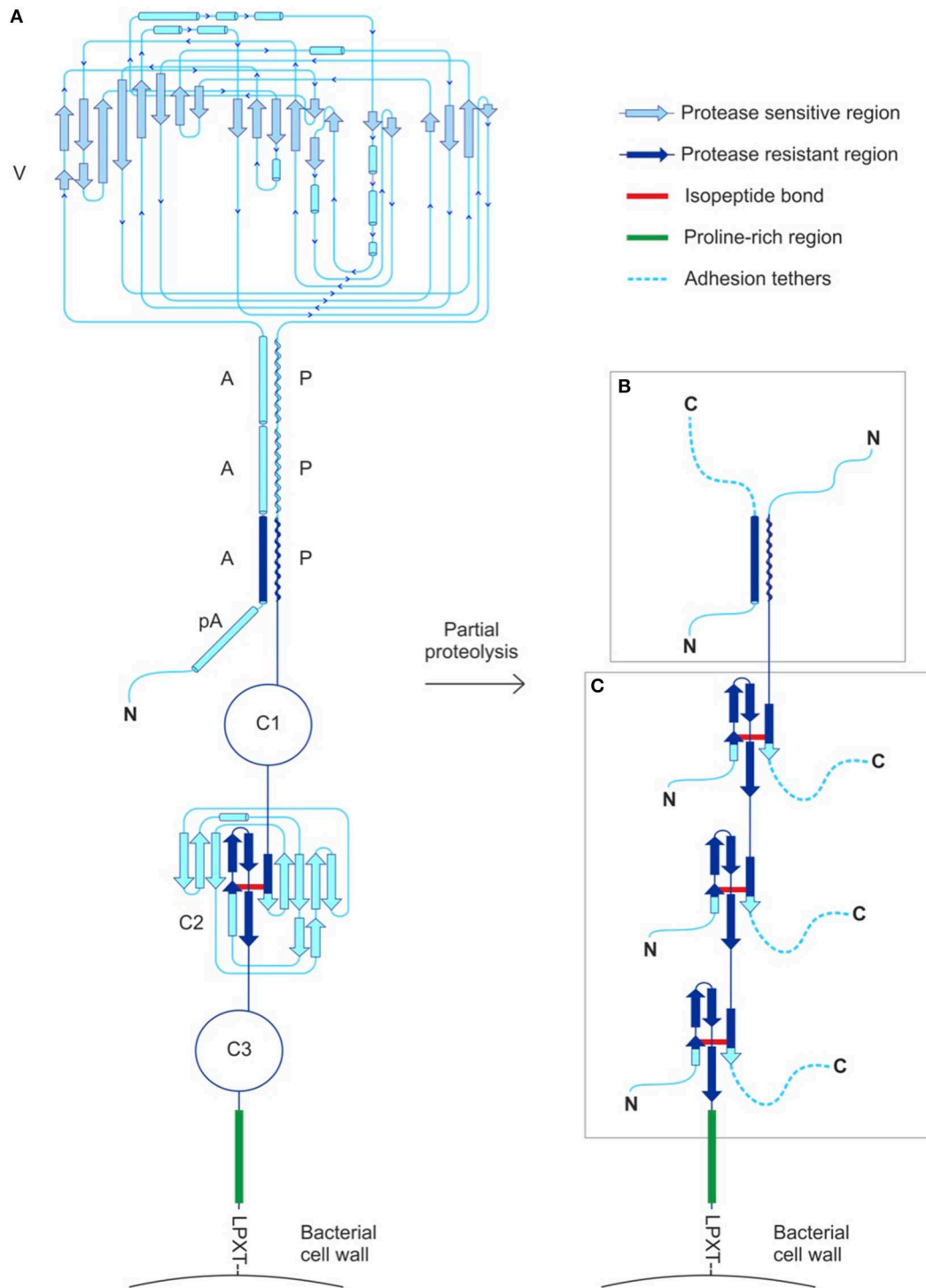
### THE Als3 PBC MEDIATES INTERACTION BETWEEN C. ALBICANS AND S. GORDONII WITHOUT CONTRIBUTION FROM THE AFR

*C. albicans* strains with precise, site-directed Als3 mutations were co-incubated with wild-type *S. gordonii* (SspB) to assess the effect of the PBC and AFR on the cross-kingdom microbial interaction (**Figure 3**). A control *C. albicans* strain ( $\text{Als3}_{\text{LA}}$ ) and the  $\Delta\text{als3}$  null mutant were included for comparison. Results for the null mutant were similar to those described above: decreased numbers of *C. albicans* cells with abundant *S. gordonii* binding ( $P = 0.0001$  for category 4,  $P = 0.004$  for category 5), an increased frequency of *C. albicans* cells without any bound *S. gordonii* (category 0;  $P = 0.0005$ ) and increased frequency of *C. albicans* with *S. gordonii* bound only in regions rich in Als1 ( $P < 0.0001$  for category 1;  $P = 0.05$  for category 2).

The *Als3*-pbc strain displays a mutant Als3 that mimics the “bound” form of the protein (K59M, A116V, Y301F; Lin et al., 2014). *Als3*-pbc lacks PBC function, while maintaining the surface properties of the wild-type protein. *S. gordonii* binding by strain *Als3*-pbc was indistinguishable from the null mutant in all categories, emphasizing that *Als3*-pbc has the same activity as a strain without any Als3. *Als3*-pbc was significantly different from the control strain in all categories except category 2, a result attributable to the low number of category 2 observations for both isolates. *Als3*-gk has a “gatekeeper” mutation in Als3 that blocks entry of a peptide ligand to the PBC (Lin et al., 2014). Relative to the control, strain *Als3*-gk (S170Y; Lin et al., 2014) was enriched for cells in lower category numbers and depleted for cells in higher category numbers, just like *Als3*-pbc. However, the degree of depletion was not as severe for *Als3*-gk as for *Als3*-pbc. *Als3* mutations in strain *Als3*-afr (I311S, I313S; Lin et al.,



**FIGURE 3 | *S. gordonii* co-aggregation with *C. albicans* strains encoding site-directed mutant Als3 alleles.** The co-aggregation assay was conducted and analyzed as described above. *C. albicans* control strains included  $\text{Als3}_{\text{LA}}$  and null  $\Delta\text{als3}$ . Experimental strains produced a mutant Als3 protein on the *C. albicans* surface. These included mutations in the PBC (*Als3*-pbc: K59M, A116V, Y301F; and *Als3*-gk: S170Y; Lin et al., 2014) and in the AFR (*Als3*-afr: I311S, I313S; Lin et al., 2014). All assays used *S. gordonii* strain SspB. The full set of comparisons between means is provided as Table 3 in Supplementary Material.



**FIGURE 4 | SspB structural features and proposed mode of interaction with Als proteins. (A)** SspB includes a “pseudo” alpha-helical repeat (pA), three alpha-helical repeats (A), a variable domain (V) and three polyproline-helix repeats (P), followed by three Ig-like domains (C1, C2, and C3), a Pro-rich region and a C-terminal LPXTG motif for sortase-mediated anchoring to the cell wall (Demuth et al., 1990; Forsgren et al., 2010). Structures were solved for two of the three Ig-like domains (C2 and C3), revealing isopeptide bonds formed by residues K1082-N1232 and K1259-N1393, respectively (Forsgren et al., 2010). A topology diagram of C2 is shown as representative of the C

domain structure. Structure of the C1 domain was predicted by homology modeling (Forsgren et al., 2010) and shows the potential to form an isopeptide bond between residues K925-N1041. The isopeptide bonds flank large cyclized regions proposed to be substrates for partial proteolysis. **(B)** Adhesion tethers resulting from partial proteolysis of the V domain remain anchored to the streptococcal cell wall by association to the proteolytically resistant AP stalk. **(C)** Partial proteolysis of C domains can also generate adhesion tethers. The proline-rich region immediately N-terminal to the LPXTG motif is likely to

(Continued)

**FIGURE 4 | Continued**

be protease-resistant, providing the means to anchor SspB fragments and its numerous potential adhesion tethers to the streptococcal cell wall. Minimally,

small remnants of C domains with an isopeptide bond (segments larger than approximately 50 amino acids, shown in dark blue) contain free C termini that provide abundant opportunities for binding *C. albicans* via the Als PBC.

2014) destroy the amyloidogenic potential of the protein. Als3-*af*r was indistinguishable from the Als3<sub>LA</sub> control strain in all categories, suggesting little contribution of the AFR to binding between *C. albicans* and *S. gordonii*.

### HYPOTHESIS AND PERSPECTIVES: HOW TO GENERATE FREE, FLEXIBLE SspB C TERMINI FOR INTERACTION WITH THE PBC OF ALS PROTEINS?

Data presented above demonstrate the primary role of the PBC in mediating interaction between *C. albicans* Als3 and *S. gordonii* SspB. The PBC functions by burying up to six amino acids from flexible C termini of polypeptide ligands (Salgado et al., 2011; Lin et al., 2014). For interactions with host surfaces, it is easy to envision PBC binding to ligands such as extracellular matrix proteins. Less evident, however, is a mechanism for PBC binding to bacterial cell surface proteins such as SspB. The SspB C terminus is not accessible for Als-mediated adhesion, because sortase A cleaves the C-terminal LPxTG recognition sequence and covalently links the exposed Thr to the bacterial peptidoglycan (Nobbs et al., 2007; **Figure 4**). Furthermore, the sequence of this protein has no detectable “lipobox,” preventing insertion of a diglyceride group for membrane anchoring by the N terminus (Sutcliffe and Harrington, 2002), and the mature form lacks cysteine residues capable to form intermolecular disulfides, as alternative modes of association with the *S. gordonii* cell surface.

Nonetheless, the unusual elongated structure of SspB (157 kDa) provides clues about its potential mode of binding to Als proteins. The SspB globular variable domain (V; **Figure 4**) is flanked by two non-contiguous A (alanine-rich) and P (polyproline type II) helical regions that associate to form a stalk-like structure (Larson et al., 2010), followed by a C-terminal region containing three tandem Ig-like domains (C1, C2, and C3). Covalent isopeptide bonds between lysine and asparagine residues in the C domains create “cyclized polypeptides” spanning up to 150 amino acids. We hypothesize that selective proteolytic cleavage within the V or C domains generates stable fragments that remain anchored to the cell wall and simultaneously expose multiple C termini, acting as “adhesion tethers” for Als proteins (**Figures 4B,C**). While *C. albicans* produces an abundance of secreted degradative enzymes that could mediate these activities (Sorgo et al., 2013), proteolytic activity could be of bacterial or even host origin in environments where polymicrobial interactions occur. Although discussions here are focused on SspB, it is important to note that SspB is homologous to SspA and shares the same domain organization with the antigen I/II (Agl/II) family of streptococcal adhesins (Brady et al., 2010). The high level of sequence (Hoyer et al., 2008) and structural (Salgado et al., 2011; Lin et al., 2014) similarity between Als proteins suggests that Als3 functional properties may be extended to the remaining adhesins in the family. Although it remains to be tested directly, it is reasonable to expect that each NT-Als adhesin will have a PBC and display binding sites compatible with a

diverse set of C termini created by partial digestion of SspB. More generally, the presence of similar cell-surface proteins in a variety of streptococci provides many potential binding partners, facilitating a broad mechanism for cross-kingdom adhesive interactions.

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### SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <http://www.frontiersin.org/journal/10.3389/fmicb.2014.00564/abstract>

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