PadR, and TetR families, sigma and anti-sigma factors, or one- and two-component system proteins. Examination of the genomic region around each of these regulators revealed a number of potential carbohydrate-related genes, corroborating a role in the global cell response toward polysaccharide utilization (**Figure 4**). Half of the up-regulated regulators (17/35) responded specifically to one of the tested polysaccharides and likely participate to trigger the expression of substrate-specific pathways. On the other hand, some regulatory genes responded to different polysaccharides (**Figure 4**). These genes might be involved more generally in the adaptation of cells toward interaction with algal biomass. A striking example is the gene ZGAL_1768, encoding a putative PadR-type transcriptional regulator that was strongly up-regulated with all six polysaccharides tested ($\log_2$FC $>$ 3), together with the downstream gene of unknown function ZGAL_1769 (Supplementary Figure 6). Both genes were found as part of a transcriptional unit in the coexpression network analysis (Supplementary Table 5). By contrast, the upstream gene *paaE* (ZGAL_1767), encoding a putative phenylacetic acid (PAA) degradation NADH oxidoreductase, was down-regulated with all six polysaccharides tested and negatively correlated with the expression of the ZGAL_1768 PadR-type regulator (Supplementary Figure 6). This is reminiscent of the role of some members of the large and diverse PadR-like family (PFAM accession PF03551) for the response to phenolic acids, including the prototypical PadR phenolic acid decarboxylation repressor that inhibits the expression of an inducible phenolic acid decarboxylase in gram-positive bacteria (Barthelmebs et al., 2000) and the VanR repressor controlling the vanillate utilization operon in *Corynebacterium glutamicum* (Heravi et al., 2015). This suggests that ZGAL_1768 could represent a new member of the PadR-like family repressing PAA degradation in *Z. galactanivorans*. PAA is known as a natural growth stimulator for green, red, and brown macroalgae (Fries and Iwasaki, 1976; Fries, 1977; Fries and Āberg, 1978). The up-regulation of ZGAL_1768 in response to algal polysaccharides might therefore participate to the adaptation of *Z. galactanivorans* as an alga-associated bacterium by promoting the repression of PAA degradation in the presence of macroalgae.

Growth on polysaccharides also triggered the expression of genes and operon-like structures related to carbohydrate catabolism in *Z. galactanivorans*. Laminarin induced the expression of the transcriptional unit ZGAL_209 to ZGAL_214, which encodes two TonB-dependent receptors (TBDR) with their associated surface glycan-binding protein (SGBP) of the SusD-like family and a CBM4-containing hypothetical protein localized in the outer membrane (**Figure 5**). Tandems of TBDRs and SusD-like SGBPs are considered a hallmark of PULs in *Bacteroidetes* genomes (Grondin et al., 2017). To date, binding of CBM4 modules has been demonstrated with β-1,3-glucan, β-1,3-1,4-glucan, β-1,6-glucan, xylan, and amorphous cellulose (CAZY database, http://www.cazy.org/). Therefore, this operon-like structure could be involved in the binding of laminarin to the cell surface. The three genes ZGAL_587, ZGAL_588, and ZGAL_589 were also detected as a transcriptional unit and were significantly up-regulated when cells were grown on laminarin compared to glucose (**Figure 5**). The first of these genes encodes a periplasmic gluconolactonase, predicted to hydrolyze the laminarin degradation product gluconolactone to gluconate that in turn can be imported to the cytoplasm by the gluconate transporter GntT1 encoded by ZGAL_588. The gene ZGAL_589 is annotated as a cytoplasmic galactonate dehydratase *dgoD*. However, its induction by laminarin and its proximity with gluconate-related genes suggest that it rather converts gluconate to 2-dehydro-3-deoxy-D-gluconate. Laminarin further induced ($\log_2$FC $=$ 2.4) the expression of ZGAL_3183, a member of the polysaccharide lyase family PL9, subfamily 4. This protein shares 32% identity with DssA from *Paenibacillus koleovorans*, which catalyzes the endolytic eliminative cleavage of (1➔4)-α-galactosaminic bonds found in the sheath polysaccharide of *Sphaerotilus natans* (Kondo et al., 2011). Laminarin from the brown algae *Cystoseira barbata* (Stackhouse) C. Agardh 1820 and *C. crinita* Duby 1830 can contain a small percentage of N-acetylhexosamine-terminated chains (Chizhov et al., 1998). Induction of ZGAL_3183 by laminarin and homology with DssA might therefore point at new substrate specificity toward these non-canonical motifs.

The expression of genes from two detected transcriptional units was significantly increased in the presence of alginate, namely ZGAL_2613–2624 and ZGAL_4130–4132 (**Figure 5**). These regions were previously shown by RT-PCR to be transcribed as genuine operons, confirming the sensitivity of the co-expression network approach (Thomas et al., 2012). They encode the main components of the alginate-utilization system in *Z. galactanivorans*, notably biochemically validated alginate lyases and downstream processing enzymes, a transcriptional regulator and a TBDR/SGBP tandem (Thomas et al., 2012). These two regions are reminiscent of a set of genes that was recently found upregulated in the *Firmicutes B. weihaiensis* Alg07 when grown with kelp powder, with the important difference that it included ATP-binding cassette (ABC) importer genes instead of a TBDR/SGBP tandem (Zhu et al., 2016). ABC importers are mainly restricted to small solutes such as, free amino acids and sugars, whereas TBDR/SGBP systems can target high molecular weight compounds. Differences in substrate binding and import mechanisms might therefore point at contrasting ecological strategies for the degradation of brown algal biomass, with *Z. galactanivorans* performing initial attack on complex polysaccharides and *B. weihaiensis* preferentially using soluble degradation products. Such niche speciation between flavobacteria and other marine bacteria has already been proposed regarding the degradation of phytoplankton-derived organic matter (Teeling et al., 2012; Williams et al., 2013). In addition, the genes ZGAL_2990 and ZGAL_2991, encoding, respectively, glycosyltransferases of family GT4 and GT2, were up-regulated by both laminarin and alginate together with adjacent genes of unknown function (**Figure 5**). Similarly, the expression of the detected transcriptional unit ZGAL_631-636, encoding proteins of unknown function, was significantly enhanced with alginate or laminarin. The

Gene	Annotation	Alginate	Laminarin	Agar	Porphyran	κ-carrageenan	ι-carrageenan	Potential carbohydrate-related neighbor genes
ZGAL_920	AraC-type transcriptional regulator	●	●	●			●	tagatose epimerase (ZGAL_919), SusCD-like (ZGAL_922-923)
ZGAL_4664	AraC-type transcriptional regulator	●		●	●	●	●	GH117 (ZGAL_4663)
ZGAL_4436	AsnC/Lrp-type transcriptional regulator		●					-
ZGAL_2286	BlaI-type transcriptional regulator				●			SusCD-like (ZGAL_2291-2292)
ZGAL_2269	BlaI-type transcriptional repressor		●					-
ZGAL_4473	HxlR-type transcriptional regulator				●			-
ZGAL_4236	LysR-type transcriptional regulator					●		agarase D (ZGAL_4243)
ZGAL_95	MarR-type transcriptional regulator		●					GH15 (ZGAL_100)
ZGAL_4224	MarR-type transcriptional regulator		●	●	●			-
ZGAL_1768	PadR-type transcriptional regulator	●	●	●	●	●	●	-
ZGAL_235	TetR-type transcriptional regulator					●		κ-carrageenase (ZGAL_236)
ZGAL_4212	TetR-type transcriptional regulator				●			-
ZGAL_358	anti-sigma factor						●	GH97 (ZGAL_355), SusCD-like (ZGAL_356-357)
ZGAL_3986	anti-sigma factor			●	●	●		SusCD-like (ZGAL_3987-3988)
ZGAL_52	RNA polymerase ECF-type sigma factor			●		●	●	-
ZGAL_331	RNA polymerase ECF-type sigma factor	●		●	●	●	●	sulfatase S1-11 (ZGAL_332)
ZGAL_511	RNA polymerase ECF-type sigma factor			●	●	●	●	-
ZGAL_937	RNA polymerase ECF-type sigma factor			●			●	-
ZGAL_3528	RNA polymerase ECF-type sigma factor			●			●	sulfatase S1-20 (ZGAL_3527), SusCD-like (ZGAL_3531-3532), GH2 (ZGAL_3533)
ZGAL_3932	RNA polymerase ECF-type sigma factor					●		SusCD-like (ZGAL_3934-3935), GH95 (ZGAL_3936), GH127 (ZGAL_3937)
ZGAL_4502	RNA polymerase ECF-type sigma factor	●	●		●			-
ZGAL_3636	One-component system sensor protein						●	sulfatase S1-28 (ZGAL_3635), SusCD-like (ZGAL_3637-3638), porphyranase E (ZGAL_3640)
ZGAL_117	Two-component system - Response regulator			●			●	-
ZGAL_686	Two-component system - Response regulator	●	●					-
ZGAL_1894	Two-component system - Response regulator			●			●	-
ZGAL_2978	Two-component system - Response regulator				●		●	-
ZGAL_3666	Two-component system - Response regulator			●				-
ZGAL_4134	Two-component system - Response regulator			●				alginate lyases (ZGAL_4130, 4131, 4132)
ZGAL_120	Two-component system - Sensor histidine kinase						●	-
ZGAL_1127	Two-component system - Sensor histidine kinase						●	-
ZGAL_1876	Two-component system - Sensor histidine kinase			●			●	-
ZGAL_1893	Two-component system - Sensor histidine kinase						●	-
ZGAL_4003	Two-component system - Sensor histidine kinase	●						CE14 (ZGAL_4002)
ZGAL_4133	Two-component system - Sensor histidine kinase			●			●	alginate lyases (ZGAL_4130, 4131 4132)
ZGAL_4295	Two-component system - Sensor histidine kinase		●					-

FIGURE 4 | Genes involved in transcriptional regulation and induced with at least one polysaccharide (FWER < 0.05; $\log_2$FC > 2). A colored circle indicates that the gene was induced by a given substrate. For each regulator, genes potentially involved in carbohydrate catabolism found in the same genomic region are reported.

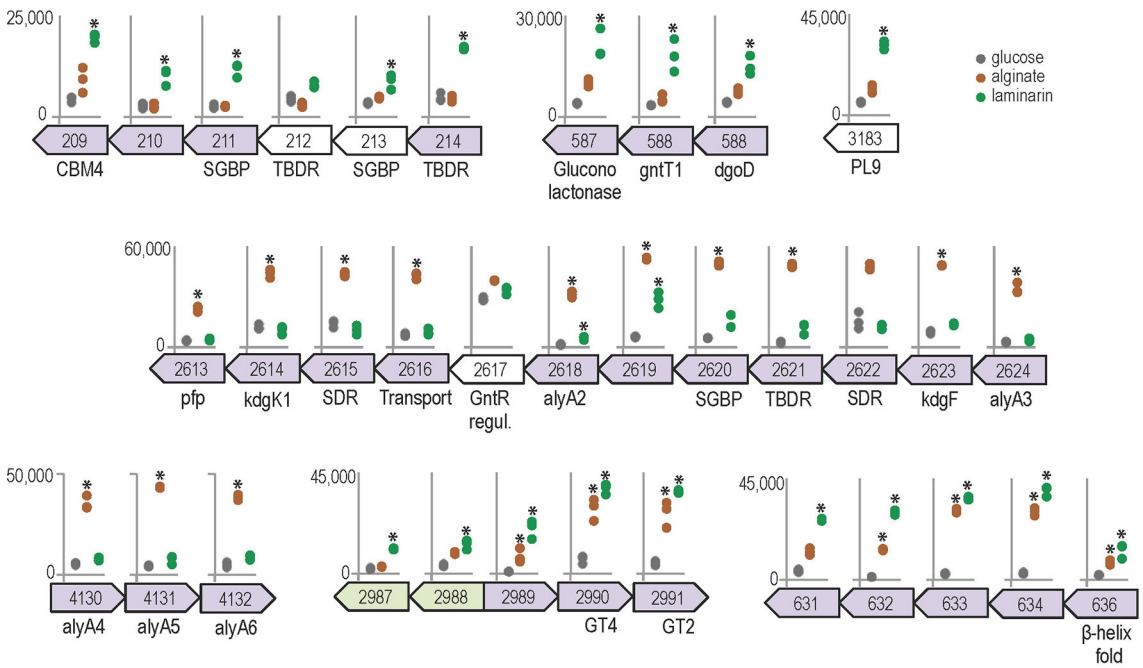

FIGURE 5 | Genomic context and expression values of selected genes induced by alginate (brown) and/or laminarin (green) compared to glucose condition (gray). Asterisks denote significant up-regulation compared to glucose (FWER < 0.05). The y-axis scale reports normalized expression values and is conserved for each genomic region. Genes from the same genomic region and shaded with the same color were found to belong to the same transcription unit by the network approach.

presence of Thrombospondin type 3 repeats (IPR028974, four in ZGAL_631, one in ZGAL_633) and Calx-beta domains (PF03160, one in ZGAL_631, two in ZGAL_636) suggests a role in calcium binding. Furthermore, ZGAL_636 contains a domain of the CUB family, some members of which are believed to function in protein/carbohydrate interactions (Töpfer-Petersen et al., 2008), and a C-terminal β-helix fold domain resembling that of PL and GH28 families. Therefore, ZGAL_636 might represent a new CAZyme family of unknown specificity.

Agar induced the expression of the four β-agarases AgaA-D (**Figure 6A**), which have complementary roles in the complex *Z. galactanivorans* agarolytic system. AgaA and AgaD are secreted enzymes, thought to be specialized in the initial attack of solid-phase agars (Jam et al., 2005; Hehemann et al., 2012). AgaA expression was also induced by porphyran, corroborating its tolerance for sulfated moieties as shown previously (Hehemann et al., 2012). A gene of unknown function ZGAL_4202 localized next to *agaA* was highly expressed with agar and thus might play a yet unclear role for agar catabolism. The soluble oligosaccharides produced by AgaA and/or AgaD can be further processed by the outer membrane-bound AgaB (Jam et al., 2005). *agaB* is part of a detected transcriptional unit with genes encoding a TBDR, a SusD-like SGBP and a CBM22-containing lipoprotein. The expression of the latter two genes was induced with agar (**Figure 6A**). The paralogous gene cluster encompassing ZGAL_2296 (42% similarity with ZGAL_3572), ZGAL_2297 (48% similarity with ZGAL_3571), and ZGAL_2298 (62% similarity with ZGAL_3570) was also strongly expressed with agar. This organization is reminiscent of a PUL organization, suggesting a role for the binding and import of agaro-oligosaccharides into the periplasm. Furthermore, a large cluster ZGAL_4657 to ZGAL_4669 was significantly induced in the presence of agar and to a lesser extent of porphyran. It contains the *ahgA* gene coding for an exolytic 3,6 anhydro-α-L-galactosidase of the GH117 family, which releases 3,6-anhydro-L-galactose (L-AnG) from agaro-oligosaccharides (Rebuffet et al., 2011). Other genes from the cluster show strong sequence identities (Supplementary Table 6) with genes involved in L-AnG catabolism in *Pseudoalteromonas atlantica* T6c and *Vibrio natriegens* EJY3 (Lee S. B. et al., 2014; Yun et al., 2015). This cluster also encodes a TBDR/SGBP tandem, two transcriptional regulators and a sulfatase of the S1-19 family (Barbeyron et al., 2016a). Although not induced by agars in our experiments, the gene ZGAL_4655 next to the L-AnG catabolism cluster has 48% sequence identity with the β-galactosidase VEJY3_09170 from *V. natriegens* EJY3 (Supplementary Table 6), which releases galactose residues from the non-reducing end of agaro-oligosaccharides (Lee C. H. et al., 2014). Therefore, we discovered a substrate-inducible PUL for agaro-oligosaccharides in *Z. galactanivorans* that complements the action of the above-mentioned agarases. Two additional sulfatases are good candidates to desulfate agars, namely ZGAL_3527 (S1-20 family, expression induced 12-fold with agar compared to glucose) and ZGAL_3509 (S1-16 family), which is located next to a predicted SGBP induced with porphyran (**Figure 6A**). Finally, results point at agar-responsive genes for which a link with agar catabolism is still unclear, including ZGAL_1272 and the detected transcriptional unit ZGAL_4688 to ZGAL_4690. ZGAL_1272 encodes a putative glycoside hydrolase from the GH114 family, in which only one member was characterized as an endo-α-1,4-polygalactosaminidase (Tamura et al., 1995). However, the two sequences only share 25% identity (data not shown), suggesting different substrate specificities. ZGAL_4688 encodes a protein that likely adopts a beta-propeller fold (InterProScan domain IPR011042), which might be reminiscent of the structure found in several known GH families.

Both κ- and ι-carrageenan induced the expression of ZGAL_3150, annotated as a glycoside hydrolase of family GH127 (**Figure 6B**). The only characterized activities in the GH127 family are the hydrolysis of β-L-arabinofuranose from plant extensins (Fujita et al., 2014) and of 3-C-Carboxy-5-deoxy-L-xylofuranose from pectin (Ndeh et al., 2017). These sugars have not been found in red algae, suggesting a new substrate specifity on carrageenan motifs for ZGAL_3150. Both carrageenans also strongly induced the expression of a SusD-like SGBP (ZGAL_3580, $\log_2$FC $>$ 3) adjacent to a TBDR gene, suggesting a role in binding of carrageenan to the cell surface. κ-carrageenan, but not ι-carrageenan, further induced the expression of another TBDR/SGBP pair (ZGAL_3987/ZGAL_3988) and one TBDR (ZG_2305), which might have concerted roles for substrate binding. In addition, the two adjacent genes ZGAL_234 and ZGAL_235 were up-regulated during growth with κ-carrageenan (**Figure 6B**). These two genes are adjacent to ZGAL_236, which encodes the characterized κ-carrageenase CgkA (Barbeyron et al., 1998). ZGAL_235 encodes a putative transcriptional regulator of the TetR family. ZGAL_234 encodes a protein with an alpha/beta hydrolase-fold containing an N-terminal haloalkane dehalogenase domain that shares 40% sequence identity with that of the characterized enzyme DbjA from *Bradyrhizobium japonicum* 3I1B110 (Sato et al., 2005). The up-regulation of ZGAL_234 by carrageenan might therefore help the bacteria when degrading cell walls, to cope with halogenated compounds that are released by red algae under stress conditions (Cosse et al., 2007). Finally, the expression of the locus ZGAL_2985–2988 was induced by ι-carrageenan, but not by κ-carrageenan (**Figure 6B**). It encodes three proteins of unknown function and a glycoside hydrolase of family 5, subfamily 42 (ZGAL_2986). GH5 is one of the largest of all CAZy families, encompassing a variety of activities. To date, GH5_42 counts 54 members in the CAZy database (http://www.cazy.org/GH5_42_all.html) but their substrate specificity remains unknown since all of them lack experimental characterization (Aspeborg et al., 2012). Our results could therefore guide future activity tests on ι-carrageenan related substrates.

In summary, this study provided an unprecedented view of genome-wide expression changes in an alga-associated flavobacterium during polysaccharide degradation. This integrative approach succeeded in detecting substrate-induced regulation of the expression of several characterized

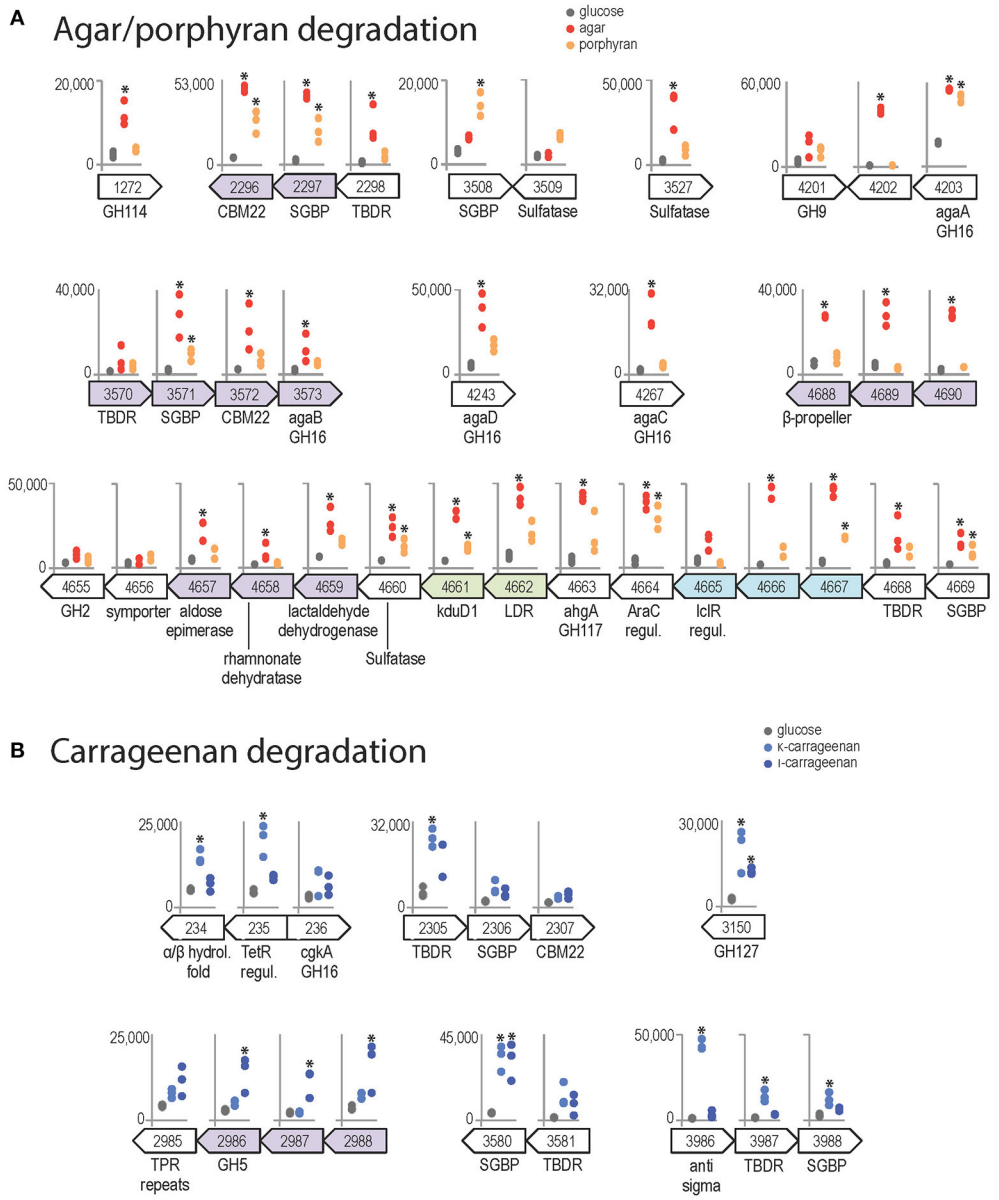

FIGURE 6 | Genomic context and expression values of selected genes induced by red algal polysaccharides (FWER < 0.05). Asterisks denote significant up-regulation compared to glucose (FWER < 0.05). The y-axis scale reports normalized expression values and is conserved for each genomic region. Genes from the same genomic region and shaded with the same color were found to belong to the same transcription unit by the network approach. **(A)** Genes induced by agar (red) and/or porphyran (orange) compared to glucose condition (gray). **(B)** Genes induced by κ-carrageenan (light blue) and/or ι-carrageenan (dark blue) compared to glucose condition.

enzymes acting on algal polymers, such as, a 3,6-anhydro-L-galactosidase, agarases, and alginate lyases. It also revealed a set of candidate genes potentially representing new substrate specificities, and will guide future biochemical characterization attempts. In addition, transcriptomes shared common features when growing on chemically divergent polysaccharides from the same algal phylum. Together with the induction of numerous transcription factors, this hints at complex regulation events that fine-tune the cell behavior during interactions with algal biomass in the marine environment.

AUTHOR CONTRIBUTIONS

FT and GM conceived and designed the experiments. FT carried out the experiments. PB and DE developed the script to detect transcription units. FT, PB, and DE analyzed the results.

All authors discussed the results and assisted in writing the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fmicb.2017.01808/full#supplementary-material

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