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REVIEW
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Coordinated Regulation of Rsd and RMF for Simultaneous Hibernation of Transcription Apparatus and Translation Machinery in Stationary-Phase *Escherichia coli*

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Transcription and translation in growing phase of *Escherichia coli*, the best-studied model prokaryote, are coupled and regulated in coordinate fashion. Accordingly, the growth rate-dependent control of the synthesis of RNA polymerase (RNAP) core enzyme (the core component of transcription apparatus) and ribosomes (the core component of translation machinery) is tightly coordinated to keep the relative level of transcription apparatus and translation machinery constant for effective and efficient utilization of resources and energy. Upon entry into the stationary phase, transcription apparatus is modulated by replacing RNAP core-associated sigma (promoter recognition subunit) from growth-related RpoD to stationary-phase-specific RpoS. The anti-sigma factor Rsd participates for the efficient replacement of sigma, and the unused RpoD is stored silent as Rsd–RpoD complex. On the other hand, functional 70S ribosome is transformed into inactive 100S dimer by two regulators, ribosome modulation factor (RMF) and hibernation promoting factor (HPF). In this review article, we overview how we found these factors and what we know about the molecular mechanisms for silencing transcription apparatus and translation machinery by these factors. In addition, we provide our recent findings of promoter-specific transcription factor (PS-TF) screening of the transcription factors involved in regulation of the *rsd* and *rmf* genes. Results altogether indicate the coordinated regulation of Rsd and RMF for simultaneous hibernation of transcription apparatus and translation machinery.

Keywords: RNA polymerase sigma factor, anti-sigma factor (Rsd), ribosome, ribosome modulation factor, hibernation, stationary phase, *Escherichia coli* K-12

INTRODUCTION

Batch cultures under optimal laboratory conditions of the well-characterized model bacterium *Escherichia coli* in rich media at an optimum temperature (usually at 37°C, the temperature of host animals for enterobacterium *E. coli*) under sufficient supply of oxygen exhibit a progression of constant steady-state growth as measured by either counting of the viable cells or measuring the cell turbidity. Traditionally, the cell growth has been classified into three phases: non-replicative lag phase; replicative exponential phase; and stationary phase of replication cessation. The

growing-phase *E. coli* has long been used as a model organism relying on the belief that its laboratory culture is homogenous in cell populations. Most of our knowledge of modern molecular genetics such as the mechanisms and regulation of gene expression was established using such apparently homogenous planktonic cell cultures.

In contrast to the laboratory culture conditions, the conditions that allow steady-state bacterial growth are seldom found in nature. Instead, the lack of nutrients, accumulation of toxic waste compounds, and the influence of harsh environmental conditions such as lack of oxygen and pH change threaten the survival of *E. coli*. A variety of protection systems against such hazardous environments are induced for survival by changing the cell organization at both the molecular and cellular levels (Foster, 1999; Raivio, 2005; Battesti et al., 2011; Jin et al., 2012; Mehta et al., 2015). Under such a background, the focus in *E. coli* research is being shifted toward understanding the survival strategy of *E. coli* after growth cessation. Facing this research stage, *E. coli* is again recognized as a suitable model organism because of huge amounts of accumulated knowledge of *E. coli* such as the functions and regulation of the whole set of genes on its genome.

Upon entry into the stationary phase of laboratory *E. coli* cultures, a variety of morphological and physiological changes take place in individual cells. The growth phase-coupled changes in cell characteristics are associated with a change in expression pattern of the genome: most of the growth-related genes are turned off or leveled down, and, instead, a number of the genes needed for stationary-phase survival are expressed (for reviews, see Lowen and Hengge-Aronis, 1994; Ishihama, 1997; Ishihama, 1999). Overall level of genome expression decreased down to less than 10% of the level of exponential growth. The change in genome expression is mainly attributable to the changes in activity and specificity of gene expression system, including transcription apparatus and translation machinery in parallel with the structural reorganization of genome within the nucleoid (**Figure 1**). Upon entry into the stationary phase, unused excess cellular components are generally degraded for reuse as nutrients for survival. Both transcription apparatus and translational machinery are, however, stored without being degraded, and instead, their activity and specificity are markedly modulated for expression of the stationary-phase genes (referred to as "stationary genes" in this report). The major change of transcription apparatus is the replacement of the promoter-recognition subunit sigma from RpoD to RpoS through the aid of anti-sigma factor Rsd (regulator of sigma D) (Jishage and Ishihama, 1995) (**Figure 1**). On the other hand, 70S ribosome is converted into inactive 100S dimer with the aid of ribosome modulation factor (RMF) and hibernation promoting factor (HPF) (Maki et al., 2000; Ueta et al., 2005) (**Figure 1**). We found that these factors have been involved in detailed analyses of the regulatory roles of these factors (for reviews, see Wada, 1998; Ishihama, 1999; Ishihama, 2000; Yoshida and Wada, 2014). Here, we provide an overview of the molecular basis of genome expression system after the stationary phase, focusing on the simultaneous and coordinated hibernation of the transcription apparatus and the translation machinery.

Up to the present time, a set of anti-sigma factors have been identified, each sequestering each of all seven *E. coli* K-12 sigma factors (Hughes and Mathee, 1998; Helmann, 1999; Trevino-Quintanilla et al., 2013; Paget, 2015). Similar systems of the functional modulation of RNA polymerase (RNAP) are also known in bacteria other than *E. coli*, but the knowledge of regulatory functions of the whole set of sigma and anti-sigma factors is best known for *E. coli* (for details, see *Hibernation of the Transcription Apparatus*). Likewise, the factors for ribosome silencing differ between *E. coli* and other bacteria. For instance, non-gamma proteobacteria form 100S ribosome but lack RMF and contain long HPF homologues (Ueta et al., 2008; Yoshida and Wada, 2014) (for details see *Hibernation of the Translation Machinery*). As to the silencing of transcriptional apparatus and translational machinery, we focus on the well-characterized *E. coli* K-12 systems in this review.

GROWTH PHASE-COUPLED CHANGES IN CELL CHARACTERISTICS

Discontinuous Change of the Cell Buoyant Density

Upon entry into the stationary phase of laboratory *Escherichia coli* cultures, a variety of morphological and physiological changes take place in individual cells, including decrease in cell size, alteration in cell shape, compaction of nucleoid, changes in cell wall organization, and alterations in cytoplasm compositions (Roszak and Colwell, 1987; Kolter et al., 1993; Huisman et al., 1996). The synchronization of cell growth is disturbed, supposedly due to difference in microenvironment, and accordingly, the stationary-phase culture includes a mixture of heterogeneous cell populations including dead cells. The level and mode of cell heterogeneity differ depending on the culture conditions or factors affecting growth retardation the (Ferenci, 2001; Stewart and Franklin, 2008; Martinez-Antonio et al., 2012; Serra and Hengge, 2014; Pletnev et al., 2015). Upon entry into the stationary phase, the cell wall becomes thicker while the cytoplasm becomes condensed. In parallel, a variety of changes have been recognized for the cell characteristics, including the increase of unsaturated fatty acids in membrane, the increase of osmoprotective solutes such as trehalose and glycine betaine in cytoplasm, the accumulation of storage compounds such as glycogen and polyphosphate, and the decrease in polyamines (Roszak and Colwell, 1987; Kolter et al., 1993; Huisman et al., 1996; Ishihama, 2000). The nucleoid becomes more compact by replacing the DNA-binding proteins, for instance, from Fis in the log-phase to Dps in the stationary phase (Talukder et al., 1999; Ishihama, 2009). The DNA superhelicity, however, decreases in the stationary phase (Jaworski et al., 1991; Kusano et al., 1996).

For physical separation of heterogeneous cell populations, we succeeded in separating *E. coli* cell populations using centrifugation through gradients of polyvinylpyrrolidone-coated silica Percoll that protects the cells from toxic effects of silica (Makinoshima et al., 2002; Makinoshima et al., 2003). Due to the low viscosity of Percoll, materials as large as marker beads and bacterial cells quickly sediment to positions characteristic

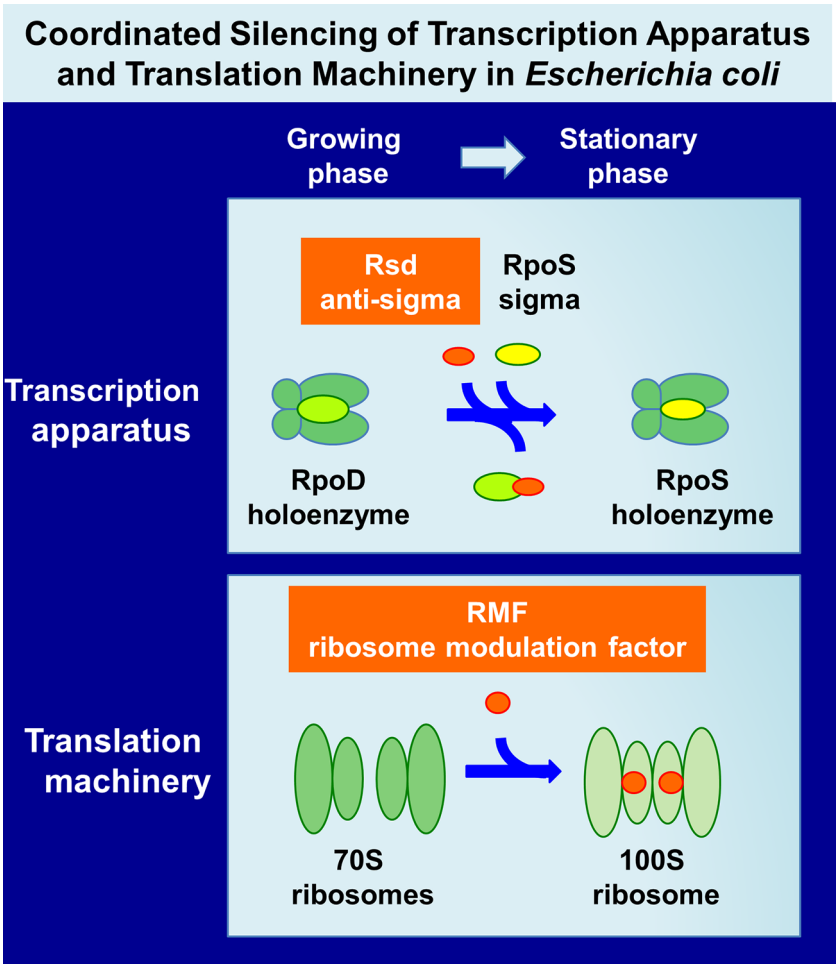

FIGURE 1 | Hibernation of transcription apparatus and translation machinery in *Escherichia coli* K-12. Upon entry of *E. coli* growth into the stationary phase, RNAP RpoD becomes silent through binding of anti-sigma factor Rsd onto the RpoD region-4 (promoter -35 recognition site) (Jishage and Ishihama, 1998; Jishage et al., 2001) while functional 70S ribosomes are converted to inactive 100S dimers through association with RMF (Wada et al., 1990; Wada, 1998) and HPF (Ueta et al., 2008; Yoshida and Wada, 2014). Here, we describe the coordinated regulation of two key regulators, Rsd and RMF, in *E. coli* K-12. The binding targets and binding sites of these two regulators on RNAP and ribosomes are described in text and also in **Figure 6**. Other factors involved in these processes are also described in text. RNAP, RNA polymerase; RMF, ribosome modulation factor; HPF, hibernation promoting factor.

of their densities. Exponential phase cultures of *E. coli* K-12 formed at least five discrete even though the density difference is within a narrow range (**Figure 2A**). This minor heterogeneity might correspond to the difference in the cycle of cell division (Kubitschek et al., 1983; Koch, 1996). In contrast, the stationary-phase cultures formed more than 10 bands, all exhibiting increased densities than the log-phase cultures (**Figure 2A**). A number of factors should influence the cell density, such as the cell volume, the chemical composition of cells, and the content of free water. One of the unexpected findings is the growth phase-coupled discontinuous transition of *E. coli* cell density. Even if the growth phase-coupled changes in molecular events are continuous, the overall cell characteristics change in discontinuous fashion as detected by the buoyant density. We concluded that the overall state of cell morphology and/or physiology of *E. coli* cells changes in discontinuous fashion during the growth transition from the log phase to the stationary phase.

A number of stationary genes have been identified by transcriptome and proteome analyses (Franchini et al., 2015; Sanchuki et al., 2017; Caglar et al., 2018). At present, however, we have only fragmentary knowledge on the expression order and the physiological roles of these stationary genes. We realized that the discontinuous change in cell buoyant density is a good marker for identification of the genes involved in each step of the cell differentiation during the transition of cell growth from exponential to stationary phase. We then subjected more than 200 single-gene-knockout mutants from the Keio collection (Baba et al., 2006; Yamamoto et al., 2009) to Percoll gradient centrifugation. Some mutants exhibited altered distribution (see **Supplemental Figure S2** for protein distribution), mostly defective in the density increase even after prolonged centrifugation. For instance, the density increase was found to be impaired at an early step for a mutant *E. coli* with the disrupted *rpoS* gene, which encodes RpoS sigma, the key player of stationary gene transcription (**Figure 2B**).

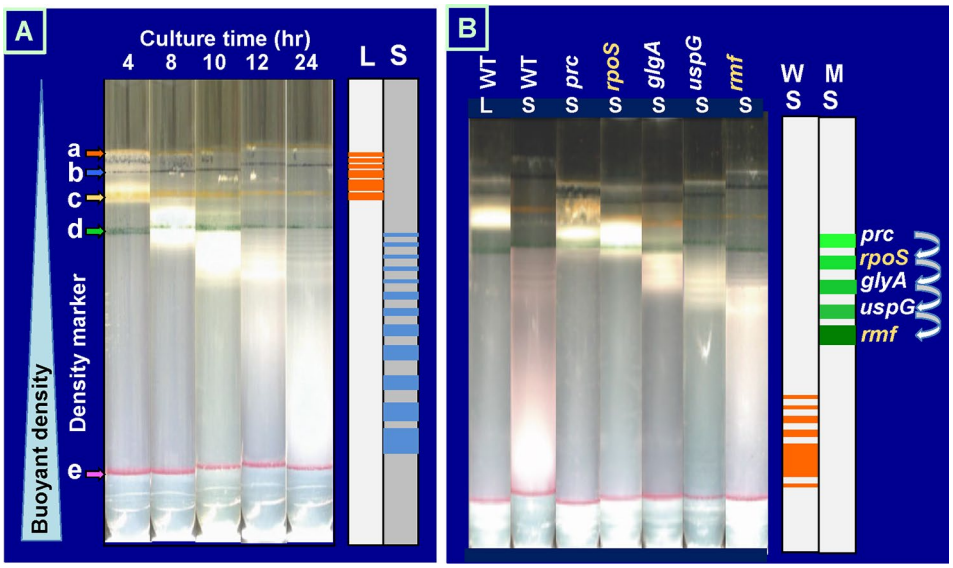

FIGURE 2 | Growth phase-dependent discontinuous increase of cell buoyant density of *Escherichia coli* K-12. **(A)** *E. coli* W3110 was grown in LB medium at 37°C with shaking. At various times, an aliquot of cell suspension was subjected to Percoll gradient centrifugation for 1 h at 20,000 rpm at 4°C in a Beckman SW40Ti rotor (Makinoshima et al., 2002; Makinoshima et al., 2003). The location of marker beads is indicated on the left: a, 1.035 g/ml; b, 1.074 g/ml; c, 1.087 g/ml; d, 1.102 g/ml; e, 1.119 g/ml. **(B)** *E. coli* wild-type BW25113 and its single-gene knockout mutants were grown in LB for 4 (L) or 24 h (S) and subjected to Percoll gradient centrifugation. The increase in cell buoyant density was interfered for these mutants, remaining at specific positions as indicated on the right. LB, lysogeny broth.

RpoS was found to be needed at the early stage of the cell density increase (for details, see next chapter). The interruption of density increase was observed for the genes not directly related to transcription. For instance, mutants defective in RpoF and RpoN exhibited essentially the same centrifugation pattern with that of wild-type *E. coli* K-12. In contrast, the density increase stopped for the mutant lacking the *rmf* gene at a step later than that for RpoS sigma, indicating that the ribosome dimerization takes place after expression of RpoS-dependent genes. Afterward, the density increase is interrupted for the mutant lacking universal stress protein (UspG) (**Figure 2B**). RMF is required for hibernation of ribosomes through conversion of functional 70S monomer to inactive 100S dimer (for details, see below) (Wada, 1998; Yoshida and Wada, 2014), while UspG is needed for cell–cell interaction in biofilm formation in the stationary phase (Nachin et al., 2005). The stop order of buoyant density increases for the *uspG* and *rmf* mutants agrees well with the order of maximum expression of UspG and RMF in wild-type *E. coli* (see **Figure 3**).

Growth-Dependent Change of the Protein Expression Pattern

As noted above, the pattern of genome expression in the stationary-phase changes for adaptation and survival as measured by genome-wide expression patterns of mRNA and protein products using the modern omics systems. In this section, we focus on the expression and degradation of the whole set of stationary proteins during the prolonged culture after the stationary phase up to 8 days. For protein separation and identification, we employed the radical-free highly reducing (RFHR) system of two-dimensional (2D) gel electrophoresis (for details, see Wada, 1986a; Wada, 1986b). The RFHR method allowed fine resolution of proteins on 2D gels, minimizing artificial spots generated through intra-molecular and inter-molecular Cys–Cys bridging under oxidation circumstances. The level of each protein on the RFHR 2D gel pattern can be determined by measuring the density of stained protein spot (**Supplemental Figure S1**). For the analysis of stationary proteins, we used *E. coli* K-12 AD202 strain lacking the *ompT* gene encoding outer membrane protease 7, which exhibits strong protein hydrolysis activity during cell lysate preparation once liberated from the outer membrane. In the experiments shown in **Figure 3**, cells were harvested at various times up to day 8. Under the culture conditions employed, the viability decreased gradually to less than 10% at day 8 (**Figure 3**, inset). The whole cell lysates were fractionated by centrifugation into CD (insoluble cell debris) and CE (cell extract supernatant fraction), which were then fractionated into CR (crude ribosome fraction) and PRS (post ribosomal supernatant fraction) (for details, see **Figure 3** legend). The nature of each protein spot on RFHR 2D gel could be determined after protein sequencing and/or mass spectroscopy. After repeating RFHR analysis thoroughly, a total of more than 650 protein spots were identified, of which a total of 65 appeared or markedly increased after the stationary phase. These proteins were detected in three cellular fractions: 31 in RPS, 30 in CD, and 4 in CR (**Supplemental Table S1**). Up to the present time, a total of 48 spots have been identified, but 17 remained unidentified.

The RFHR system is in particular useful for analysis of small proteins, allowing the identification of these small-sized ribosome-associated proteins. The CR (crude ribosomal) fraction contained the newly identified 50S proteins, L35 (RpmI)

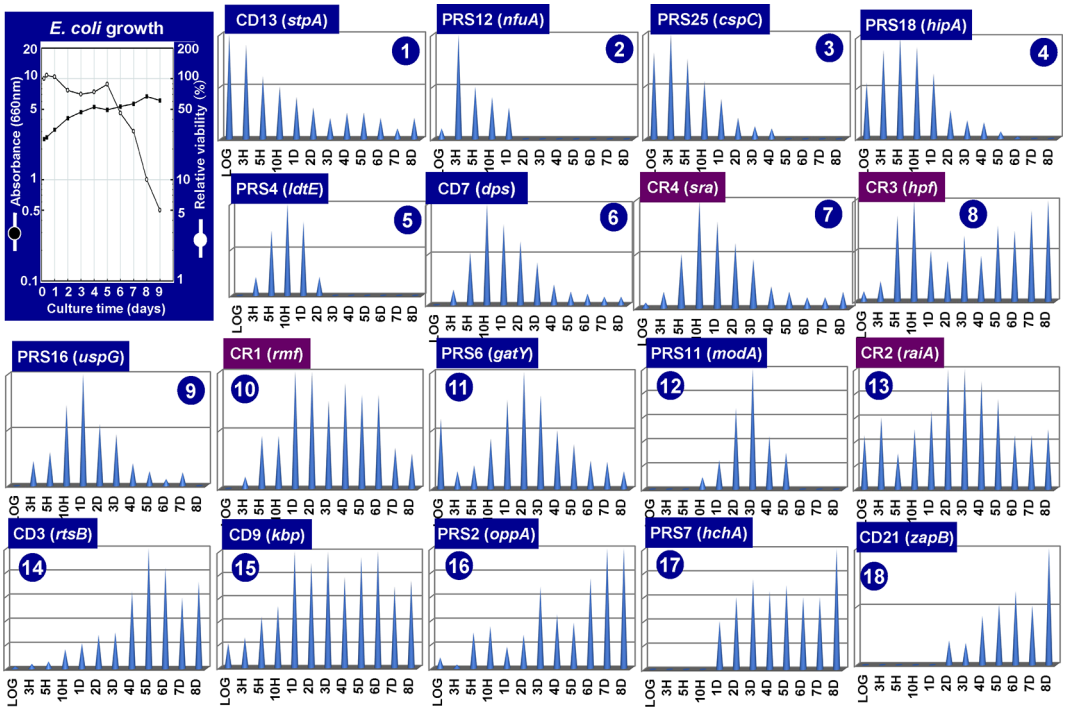

FIGURE 3 | Growth phase-dependent synthesis of 18 representative stationary proteins in *Escherichia coli* K-12. *E. coli* K-12 AD202 was grown in minimal medium E (Vogel and Bonner, 1956) containing 2% peptone at 37°C. The cell growth was monitored for 10 days by measuring the turbidity at 660 nm and by counting viable cells as shown in the inset. Aliquots of the culture were harvested at the indicated time (X-axis), and the cell lysates were fractionated into CD (insoluble cell debris), CE (cell extract supernatant), CR (crude ribosome), and PRS (post ribosomal supernatant) fractions. All these fractions prepared at each time point was subjected to RFHR 2D gel system, and the stained protein spots were measured by densitometry. The relative levels (Y-axis) are shown at each culture time (X-axis) for a total of 18 representative stationary proteins. The proteins shown under purple background indicate those involved in the hibernation of ribosomes.

and L36 (RpmJ) (Wada and Sako, 1987), and 30S protein S22 (Sra or RpsV) (Izutsu et al., 2001), leading to make the complete list of 54 r-proteins in *E. coli* K-12. Besides, some ribosome-related proteins were included in the CR fraction such as RMF, RaiA (renamed YfiA), and HPF (renamed YhbH), which all are involved in ribosome hibernation; for details, see *Hibernation of the Translation Machinery*.

The CD fraction recovered in the pellet fraction after low-speed centrifugation includes a total of 30 proteins tightly associated with cell wall and membrane. Stationary-phase-specific nucleoid proteins Dps and StpA were recovered in this CD fraction in agreement with the tight association of stationary-phase nucleoid with the cell membrane (Ishihama, 2009). Most of stress-response gene products in this CD fraction such as SlyD (chaperone with peptidyl-prolyl *cis-trans* isomerase activity) and StpA (H-NS-like nucleoid protein with RNA chaperone function), and two of six *E. coli* UspGs, UspD and UspG. All these proteins are involved in repair and refolding of RNAs and proteins (see **Supplemental Table S1**). The PRS fraction includes a total of 31 soluble stationary proteins, which all migrated in neutral to acidic regions on 2D (see **Supplemental Figure S1**). Most of these soluble proteins are involved in stationary-phase-specific metabolism, supposedly for redirection of metabolic circuits after prolonged culture in the absence of sufficient nutrients.

The level of stationary-phase proteins was measured throughout the culture up to day 8 (**Figure 3**), and the relative distribution is aligned in the order of appearance time throughout the 8-day culture (**Figure 4**). About half of the stationary-phase proteins appeared at specific time and soon disappeared, exhibiting a relatively narrow pattern of appearance in the stationary phase, but some other stationary proteins distributed in rather wide range of the stationary phase even though the distribution pattern between three subcellular fractions change. It should be noted that some stationary-phase proteins are detected in more than two fractions and exhibited culture time-dependent shift of distribution such as RPS-to-CD for GatY, RbsB, SlyD, UspD, ZapB, YdcH, and YibJ (see **Table 1**). The final deposition of these soluble proteins could be in the cell membrane and cell wall after prolonged culture. One exceptional distribution pattern was observed for RaiA, which showed a culture time-dependent alteration of distribution among all three fractions, CR, PRS, and CD (see **Table 1**), supposedly reflecting to its role in ribosome hibernation (see below).

Furthermore, it is interesting to note that even in the last day 8, expressions of some stationary-phase proteins are synthesized, including HchA (protein/nucleic acid deglycase), Mdh (malate dehydrogenase), GuaB (inosine 5′-monophosphate dehydrogenase), and ZapB (cell division factor). HchA is involved in repair of glyoxal- and methylglyoxal-glycated proteins (Mihoub

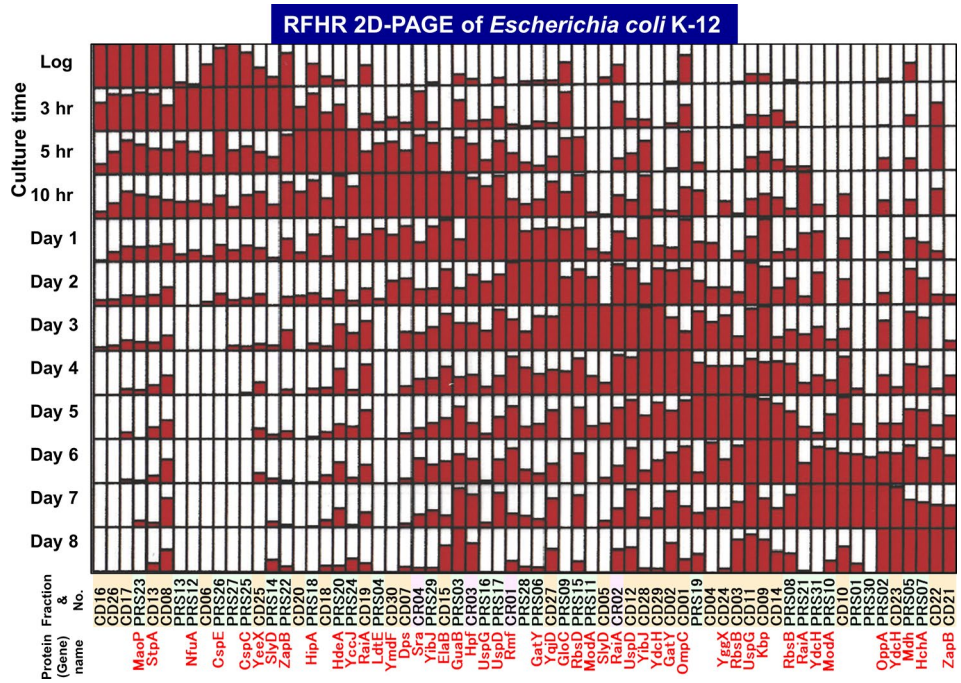

FIGURE 4 | Growth phase-dependent expression patterns of a total 65 stationary proteins in *Escherichia coli* K-12. The growth phase-dependent synthesis was measured for a total 65 stationary proteins. The relative level of synthesis from log phase (3-h culture) to day 8 is shown for all 65 proteins. The maximum level is shown by filling the day column with full red color. Spot numbers listed in **Table 1** are shown on the horizontal axis, with colors indicating fraction type (green: PRS, orange: CD, and magenta: CR). The protein products so far identified are shown in red below the corresponding spot numbers.

et al., 2015) and nucleic acids (Richarme et al., 2017). The *mdh* gene is also organized a network of genes, which facilitate stress-induced mutagenesis (Al Mamun et al., 2012). ZapB plays, together with ZapA, a role in organization and dynamics of the repaired genome in resting cells and independent of the Min system (Bailey et al., 2014; Mannik et al., 2016). Under stressful conditions unfavorable for *E. coli* growth, mutation rate increases for adaption and survival (Foster, 1999; Zinser and Kolter, 2004; Saint-Ruf et al., 2007). These 8-day proteins might be involved in repair of the genome and damaged proteins.

Both the sequential increase in cell buoyant density and the sequential synthesis of stationary-phase proteins are apparently under a single pathway, but it should be noted that the pathway for entry into the stationary phase is multiple. During the prolonged culture, the heterogeneity in the cell population should also be amplified due to generation of various types of cells on different pathways, such as persister cells, mutant cells, and dead cells (Roszak and Colwell, 1987; Kolter et al., 1993; Huisman et al., 1996; Ishihama, 1999).

GROWTH PHASE-COUPLED ALTERATIONS IN GENE EXPRESSION APPARATUS

Hibernation of the Transcription Apparatus

Upon entry into the stationary phase, the level of transcription decreases to less than 10% of that in the log phase (Ishihama, 2000). For this marked reduction in transcription pattern, the modulation of the promoter selectivity of RNAP is the major mechanism through the replacement of sigma subunit (the promoter recognition factor). In *Escherichia coli* K-12, seven different species of the sigma subunit exist, each recognizing a specific set of promoters (Ishihama, 1988; Ishihama, 2010). Transcription of the genes highly expressed in exponential growth phase is carried out by the RNAP holoenzyme containing RpoD, while RpoS is a key factor in the change in genome expression during growth transition from the exponential growth phase to the stationary phase (Lowen and Hengge-Aronis, 1994; Ishihama, 2010; Ishihama, 2012). We have measured the intracellular level of each sigma subunit at various phases of cell growth (**Figure 5A**). In exponentially growing cells of *E. coli* K-12, a significant level was detected only for three sigma factors, RpoD for growth-related genes, RpoN for nitrogen-assimilation genes, and RpoF for flagella-chemotaxis genes (Ishihama et al., 1976; Kawakami et al., 1979; Jishage and Ishihama, 1995). The concentration of RpoD is maintained at a constant level of 500–700 molecules per genome from log to stationary phase. The log-phase cells contain 1,500 to 2,000 molecules of RNAP core enzyme per genome, but about two-third are involved in transcription cycle (Ishihama and Fukuda, 1980; Ishihama, 2000). After transcription initiation, RpoD sigma is released, and the majority of free RNAP core might be associated with RpoD sigma, forming the RpoD holoenzyme.

TABLE 1 | Proteins Expressed During Prolonged Culture of *Escherichia coli* K-12.

PRS		CD		CR						
2D spot	Max stage	2D spot	Max stage	2D spot	Max stage	Gene		Map	pI/Size (aa)	Function
PRS16	Day 1	CD11	Log			*uspG*	*ybdQ,yzzU*	13.79	6.03/142	universal stress protein G
RPS26	Late-log (3 h)					*cspE*	*msmC*	14.16	8.09/69	transcription antiterminator/RNA stability regulator CspE
PRS10/11	Day-3 Day-7					*modA*		17.12	7.81/257	periplasmic molybdate transporter protein
		CD07	10 h			*dps*	*pexB,vtm*	18.27	5.70/167	stationary-phase nucleoid protein/Fe-binding storage protein
PRS09	Day 3					*gloC*	*ycbL*	21.19	4.95/215	hydroxyacylglutathione hydrolase;methylglyoxal degradation
				CR01	Day 1 and 2	*rmf*		21.87	10.86/55	ribosome modulation factor
PRS24	Late-log (5 h)					*yccJ*		22.97	4.70/75	PF13993 family protein YccJ
		CD30	10 h			*ymdF*		23.00	9.87/57	stress-induced acidphilic repreak motifs-containing protein
RPS02	Day 7 and 8					*oppA*		24.04	6.05/543	periplasmic oligopeptide transporter protein
PRS31	Day 2	CD23	Day 7 and 8			*ydcH*		32.29	9.30/74	uncharacterized protein
PRS18	Late-log (5 h)					*hipA*		34.28	8.26/440	serine/threonine kinase HipA; regulator with hipB
				CR04	10 h	*sra*	*rpsV*	35.52	11.04/45	30S ribosomal protein S22
PRS04	10 h					*ldtE*	*ynhG*	37.87	9.42/334	L,D-transpeptidase
PRS25	Late-log (3 h)					*cspC*	*msmB*	41.08	6.54/69	cold-shock stress protein CspC
PRS07	Day 8					*hchA*	*yedU,yzzC*	43.86	5.63/283	protein/nucleic acid deglycase; Hsp32 moleccular chaperone
		CD25	Late-log (3 h)			*yeeX*		44.79	9.30/109	DUF496 domain-containing protein
PRS06	Day 2	CD02	Day 4			*gatY*	*yegF*	46.91	5.87/284	tagarose-1,6-dibphosphate aldolase
		CD01	Day 4			*ompC*	*meoA,par*	49.82	4.58/367	outer membrane protein C pore for passive difusion
		CD15	10 h and Day 1			*elaB*	*yfbD*	51.34	5.35/101	tail-anchored inner membrane protein
PRS03	Day 7					*guaB*		56.60	6.02/486	Inosine 5'-monophosphate dehydrogenase; GMP symthesis GMP symthesis
PRS21	Day 7	CD19	10 h	CR02	Day 2 and 3	*raiA*	*yfiA*	58.88	6.19/113	stationary-phase translation inhibitor/ribosome stability factor
		CD13	Log			*stpA*	*hnsB,rsv*	60.19	7.95/134	nucleoid protein StpA with RNA chaperone activiry
		CD09	Day 6			*kbp*	*ygaU,yzzM*	60.24	5.67/149	K+ binding protein
		CD24	Day 5			*yggX*		66.78	5.91/91	Fe2+-tracking protein; oxidative damage protect Fe-S protein
		CD27	Day 2			*yqjD*		69.91	9.06/101	ribosome- and membrane-associated DUF-domain protein
				CR03	10 h	*hpf*	*yhbH*	72.01	6.50/95	ribosome hibernation-promoting factor; RpoN modulation protein
RPS05	Day 8					*mdh*		72.81	5.61/312	malate dehydrogenase
PRS22	Late-log (3 and 5 h)	CD21	Day 8			*zapB*	*yiiU*	75.71	4.69/81	cell division factor ZapB
RPS17	Day 1	CD12	Day 3 and 7			*uspD*	*yiiT*	75.82	6.37/142	universal stress protein D
RPS08	Day 6	CD03	Day 5			*rbsB*	*priB,rbsP*	79.62	6.85/296	periplasmic ribose transperter protein
RPS15	Late-log (3 h)					*rbsD*	*rbsP*	79.70	5.93/139	D-ribose pyranase; sugar-binding protein
RPS29	10 h	CD28	Day 3			*yibJ*		83.35	5.00/?	RHA domain-containing protein YibJ
RPS23	Log					*maoP*	*yifE*	85.06	6.09/112	macrodomain Ori protein
RPS20	Late-log (5 and 6 h)					*hdeA*	*yhhC,yhiB*	85.74	5.06/110	periplasmic acid stress chaperone HdeA
PRS12	Late-log (3 h)					*nfuA*	*gntY,yhbI*	88.12	4.52/191	iron-sulfur cluster carrier protein; gluconate transporter
PRS14	Late-log (3 h)	CD05	Day 3			*slyD*		89.57	4.86/196	FKBP-type pepridyl-prolyl cis-trans isomerase
PRS01	Day 7					*X*				
PRS13	Late-log (3 h)					*X*				

(Continued)

TABLE 1 | Continued

PRS		CD		CR					
2D spot	Max stage	2D spot	Max stage	2D spot	Max stage	Gene	Map	pI/Size (aa)	Function
PRS19	Day 5					X			
PRS27	Late-log (2 h)					X			
PRS28	Day 2					X			
RPS30	Day 7					X			
		CD04	Day 5			X			
		CD06	Late-log (3 h)			X			
		CD08	Log			X			
		CD10	Day 5 and 7			X			
		CD14	Day 6			X			
		CD16	Log			X			
		CD17	Log			X			
		CD18	Late-log (5 h)			X			
		CD20	Late-log (5 hr)			X			
		CD22	Day 8			X			
		CD26	Log			X			

(green: PRS, orange: CD, and magenta: CR; see legends of **Figure 3** *and* **4***).*

RpoS sigma is needed for transcription of stationary-phase genes. The level of RpoS starts to increase after the mid-log phase and reaches to the maximum level of about the half the level of RpoD in the stationary phase (**Figure 5B**) (Jishage and Ishihama, 1995; Jishage et al.,1996). The level of core enzyme is under the autogenous control, thereby keeping the constant level of about 2,000 molecules per genome throughout cell growth (Ishihama, 2000). In contrast, the combined level of all seven sigma factors is about two folds the level of the core enzyme, and we then proposed the "sigma competition" model (Jishage and Ishihama, 1998; Maeda et al., 2000). Since the level of RpoD was always higher than RpoS even after prolonged culture, we doubted whether RpoD is still functional in the stationary phase. As an attempt to examine this possibility, we analyzed proteins associated with RpoD at various phases of cell growth and discovered the association of a novel protein Rsd (regulator of sigma D) (Jishage and Ishihama, 1998; Jishage and Ishihama, 1999), which forms a complex with RpoD for interfering with its sigma function. The level of Rsd starts to increase upon entry into the stationary phase, finally reaching to the level of 60 to 80% of RpoD (**Figure 5B**), implying that most of RpoD stays non-functional in the stationary phase through formation of RpoD-Rsd complex. As a result, the core enzyme becomes available for association of the stationary-specific RpoS sigma (Jishage and Ishihama, 1998; Mitchell et al., 2007). The anti-sigma factor Rsd binds to the RpoD domain-4 that is involved in recognition of the promoter -35 signal (Dove and Hochschild, 2001; Jishage et al., 2001; Mitchell et al., 2007) (**Figure 5C**). Crystal structure of Rsd–RpoD complex supports this conclusion (Patikoglou et al., 2007). The affinity of Rsd to free RpoD is high, and in the presence of high concentrations of Rsd, it also binds to the core-associated RpoD (Ilag et al., 2004; Westblade et al., 2004). After sequestering RpoD into Rsd–RpoD complex, the free core enzyme could be used for formation of RpoS holoenzyme, thereby allowing transcription of stationary genes.

Based on these findings, we proposed the "sigma competition" model, in which the anti-sigma factor plays a regulator in replacement of RNAP-associated sigma for an efficient switching of its promoter selectivity (Jishage and Ishihama, 1999; Maeda et al., 2000; Mitchell et al., 2007). Along this line, it should be noted that the anti-sigma factors have been identified for all seven sigma factors of *E. coli* K-12 and widely in other bacteria (Hughes and Mathee, 1998; Helmann, 1999; Trevino-Quintanilla et al., 2013; Paget, 2015). To confirm the "sigma competition" model for control of the promoter selectivity of RNAP, we further compared the binding affinity *in vitro* of all seven sigma factors to the same core enzyme (Maeda et al., 2000). In the presence of a fixed amount of RpoD, the level of RpoD holoenzyme formation increased linearly with the increase in core enzyme level. Mixed reconstitution experiments in the presence of a fixed amount of the core enzyme and increasing concentrations of an equimolar mixture of all seven sigma subunits indicated that the core binding is the strongest for RpoD sigma, followed by RpoN, RpoF, RpoE, FecI, and RpoS in decreasing order. The order of core binding activity was also confirmed by measuring the replacement of one core-associated sigma by another sigma subunit. Since the intracellular level of core enzyme is virtually constant, the model of sigma replacement relies solely on changes in the intracellular concentrations of seven sigma subunits (Ishihama 2000; Ishihama 2010).

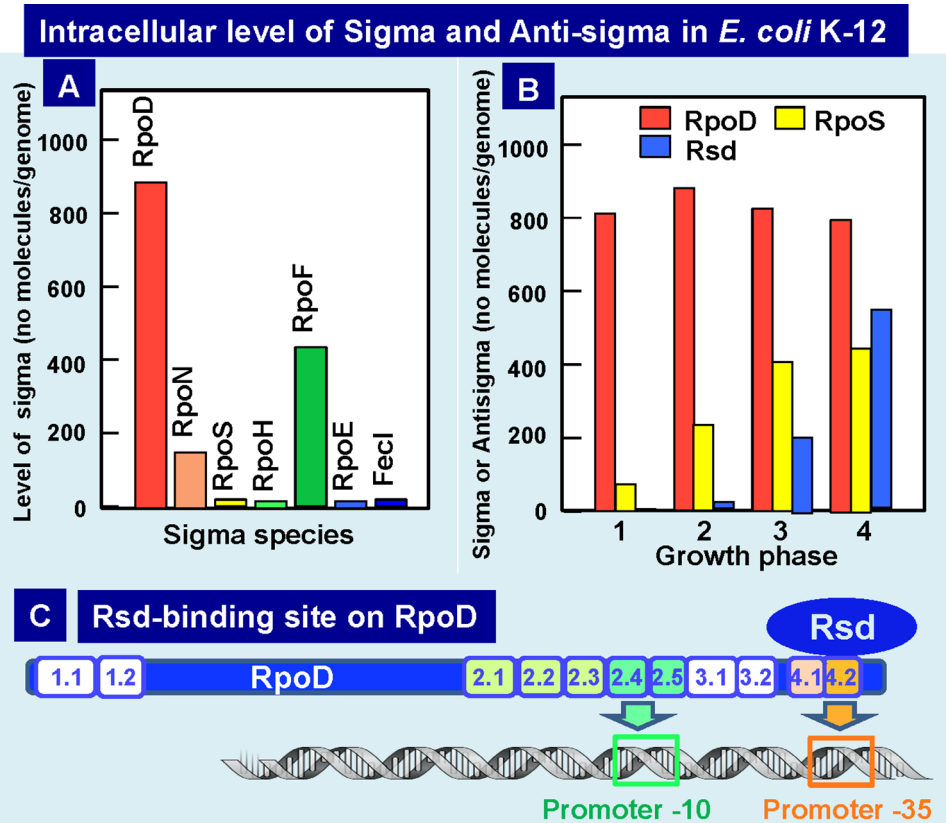

FIGURE 5 | Intracellular levels of sigma factors and anti-RpoD sigma (Rsd). **(A)** Intracellular levels of all seven sigma factors in exponential phase *E. coli* K-12 was determined by Western blot analysis with use of specific antibodies (Jishage and Ishihama, 1995; Jishage et al., 1996). **(B)** Intracellular levels of growth-related RpoD sigma, stationary-phase-specific RpoS sigma, and anti-RpoD sigma Rsd were determined at various growth phases of *E. coli* K-12 (Jishage and Ishihama, 1998; Jishage and Ishihama, 1999). **(C)** The contact site of anti-sigma factor Rsd on the growth-related RpoD sigma was determined to be located within RpoD region-4 (promoter -35 recognition site) by using the contact-dependent cleavage sites by Rsd-tethered iron-*p*-bromoacetamidobenzyl EDTA by analysis of the complex formation between Ala-substituted σ^{70} and Rsd (Jishage and Ishihama, 2001). Rsd-binding to RpoD region-3 leads to silencing RpoD function.

Besides RpoD sigma, Rsd was found to interact with HPr, a phosphocarrier component of PEP-dependent sugar-transporting phosphotransferase system (PTS), thereby interfering with anti-sigma activity (Park et al., 2013). Recently Rsd was also found to interact with SpoT and stimulates its hydrolysis activity of magic spot (p)ppGpp (Lee et al., 2018). The SpoT activity is, however, antagonized by dephosphorylated HPr, which generally interacts with a large number proteins and regulate wide varieties of carbon and energy metabolism (Rodionova et al., 2017). These observations altogether indicate the presence of a protein–protein interacting network between Rsd, HPr, and SpoT for interconnection between transcription and metabolism during the stationary phase.

Here, we propose the hibernation of growth-phase RNAP holoenzyme through conversion of RpoD sigma by Rsd anti-sigma factor. The RNAP core enzyme can then be used for assembly of RpoS holoenzyme for transcription of stationary-phase genes. It should be noted that excess free core enzyme, if present, should form transcriptionally inactive dimers or oligomers (Ishihama, 1990; Harris et al., 1995) for storage as in the case of yeast RNAP I (Fernandez-Tornero, 2018). The conversion of RpoD into the inactive RpoD-Rsd complex and the self-assembly of free core enzyme together contribute for silencing of the transcription apparatus during the stationary phase.

Hibernation of the Translation Machinery

Bacterial ribosomes are universally conserved ribonucleoprotein complexes, generally consisting of two asymmetric subparticles. In *E. coli* K-21, large (50S) and small (30S) subparticles associate with each other to form the functional 70S ribosomes. The 50S subparticle is composed of two species of rRNA (23S and 5S) and a total of 33 species of the ribosomal protein, referred to r-protein (L1 to L36), whereas the 30S subparticle is composed of 16S rRNA and a total of 21 species of r-proteins (S1 to S21) (Wada and Sako, 1987; Izutsu et al., 2001; Kaczanowska and Ryden-Aulin, 2007; Shajani et al., 2011). Under optimal laboratory culture conditions, *E. coli* grows exponentially with heavy consumption of energy and resources.

During this exponential phase, the ribosome profile detected by sucrose density gradient centrifugation (SDGC) includes 70S ribosomes as the major component and in addition, small amounts of 30S and 50S subparticles, and polysomes (**Supplemental Figure S3A**). These ribosomes are involved in the canonical ribosome cycle (initiation, elongation, termination, and recycling) of protein

synthesis (**Figure 6A**). Protein synthesis is the most energy demanding cellular process. The majority of metabolic energy is used for the formation of ribosomes (Maaloe and Kjeldgaard, 1966). Upon entry into the stationary phase, overall level of transcription decreases to less than 10% the level of log phase, yielding the superfluous translation machinery. The unused excess ribosomes are then converted into non-functional 100S ribosome dimers, the inactive stored form of ribosomes (**Supplemental Figure S3B** and **Figure 6B**) (Wada et al., 1990; Yoshida and Wada, 2014). The ribosome profile measured by SDGC includes a peak of 100S ribosomes besides the peak of 30S, 50S, and 70S ribosome (**Supplemental Figure S3B** and **Figure 6B**). The 100S ribosome is a dimer of 70S ribosomes, and inactive in translation (Wada et al., 1990; Wada et al., 1995). We then designated this stage of ribosome cycle, in which the ribosomes stay in inactive forms, for "Hibernation" (Yoshida et al., 2002).

The 100S ribosome of *E. coli* is formed by the binding of two factors, the RMF (Wada et al., 1990) and the HPF (Ueta et al., 2013). RMF alone leads only to the formation of 90S particle, which is an immature form of the 100S ribosome, suggesting that HPF is needed to convert this premature 90S particle to mature 100S ribosome (Ueta et al., 2005; Ueta et al., 2008; Ueta et al., 2013). The third protein associated with the stationary-phase ribosomes is RaiA (renamed YfiA), which interferes with the 100S dimer formation through competition with HPF binding (Maki et al., 2000; Ueta et al., 2005). Thus, two factors, HPF and RaiA, share the same binding site on the 100S ribosome and thus compete each other, thereby controlling the formation of 100S ribosomes. The binding sites of RMF and HPF investigated by several methods indicate the conformational changes of 30S subunits, thereby controlling the ribosome dimerization indirectly (Yoshida et al., 2002; Ueta et al., 2005; Yoshida and Wada, 2014; Beckert et al., 2018) (see **Figure 6**, right panel). Inactivation of the *rmf* gene leads to loss of viability in the stationary phase (Yamagishi et al., 1993), under acidic conditions (El-Sharoud and Niven, 2007) and upon exposure to heat shock (Niven, 2004). When the stationary-phase *E. coli* was transferred to nutrient-rich media, the disassembly of 100S ribosomes is rapid within 1 min (Aiso et al., 2005) for restart of protein synthesis (Yoshida and Wada, 2014). The

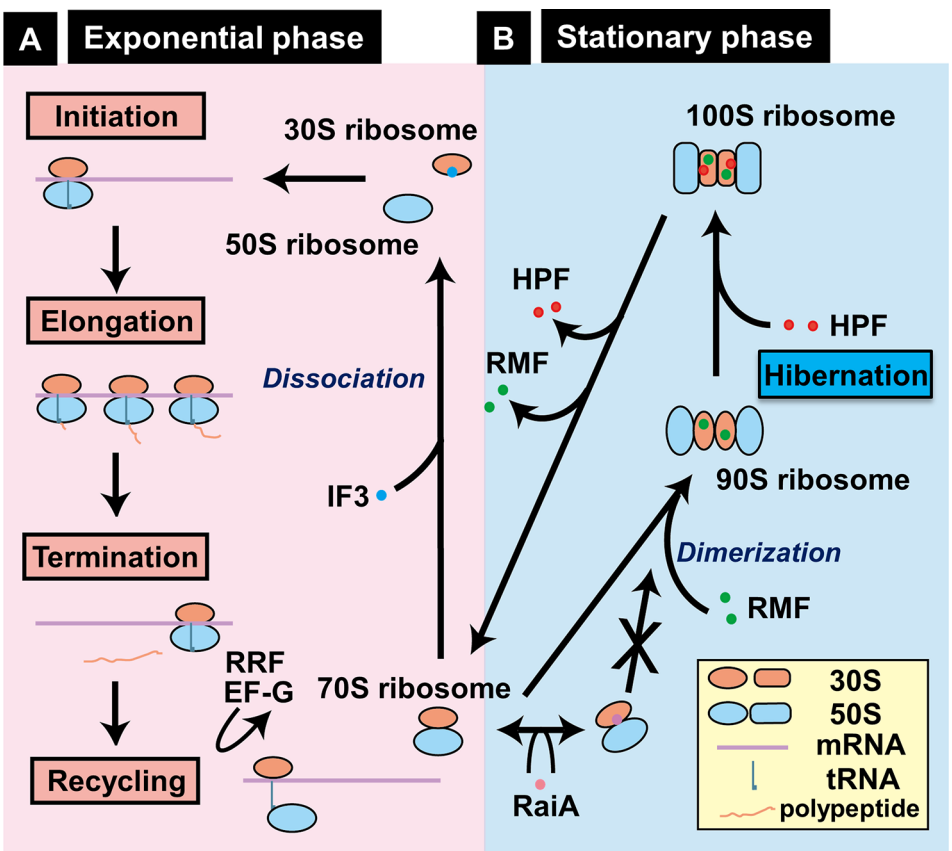

FIGURE 6 | Growth phase-coupled alteration of ribosomes in *Escherichia coli* K-12. **(A)** In exponentially growing bacterial cells, most ribosomes are involved in the functional cycle of protein synthesis, consisting of initiation, elongation, termination, and recycling. For initiation, 30S and 50S ribosomes bind to mRNA, forming functional 70S ribosomes on mRNA and ultimately leading to form polysomes. After termination, 70S ribosomes are dissociated into 30S and 50S subparticles for reutilization. **(B)** Upon entry into stationary phase, unused ribosomes are converted into functionally inactive 100S dimeric ribosomes by sequential binding of RMF and HPF in *E. coli* K-12, one of Gram-negative bacteria (Wada, 1998; Yoshida and Wada, 2014). We designated this process as "hibernation." Formation of 100S dimers is interfered by RaiA (renamed YfiA) (Ueta et al., 2005). The location of RMF on 30S ribosome is based on the recent cryo-electron micrography structure of 100S ribosome dimer (Beckert et al., 2018). By biochemical analyses, however, RMF was also indicated to bind 23S rRNA (Yoshida et al., 2004) and the peptidyl transferase center (Yoshida et al., 2002).

mechanism how RMF and HPF are removed from 100S ribosomes remains to be solved.

The ribosome hibernation is widespread but the factors involved in this process are different between bacteria (Ueta et al., 2008; Yoshida and Wada, 2014; Prossliner et al., 2018). *E. coli* and some γ-proteobacteria carry both the *rmf* and *hpf* genes, but many other bacteria have only the *hpf* gene or its homologue devoid of the *rmf* gene (Ueta et al., 2008). In bacteria carrying a long-type HPF homologue, the ribosome dimerization takes place in the absence of RMF (Ueta et al., 2013; Akanuma et al., 2016). *E. coli* forms 100S ribosomes only in their stationary growth phase, but in Gram-positive bacteria such as *Bacillus subtilis*, 100S ribosomal dimers are formed throughout entire growth phases (Ueta et al., 2013; Puri et al., 2014; Akanuma et al., 2016), implying that the factors or conditions for ribosome dimerization are different between bacterial species.

In the case of the bacterial group having long HPF, several structures have been proposed for the ribosome dimer (For instance, Matzov et al., 2019). Accordingly, the 70S–70S interface within ribosome dimers appeared different from that of *E. coli* (Kato et al., 2010; Beckert et al., 2018). Nevertheless, N-terminal domain of long HPF is predicted to bind to the site overlapping with the tRNA-binding site as in the case of HPF in *E. coli*, suggesting that common mechanism of translational silencing exists between bacteria carrying long and short HPFs.

COORDINATED HIBERNATION OF TRANSCRIPTION APPARATUS AND TRANSLATION MACHINERY

The formation of transcriptional apparatus and translational machinery are tightly coupled and coordinated, showing the growth rate-dependent synthesis of RNAP core enzyme (Ishihama and Fukuda, 1980; Ishihama, 1988) and ribosomes (Nomura et al., 1984; Zengel and Lindahl, 1994), thereby keeping the ratio of 5~10 ribosomes per RNAP core to match effective translation of mRNA through formation of polysomes. For this purpose, multiple layers of regulation are involved such as the organization of genes for RNAP subunits and ribosomal proteins into single and same operons, and the autogenous regulation of synthesis of RNAP subunits and ribosomal proteins by excess and unused products. We then examined the possible coordination in the hibernation process between transcription apparatus and translation machinery. During

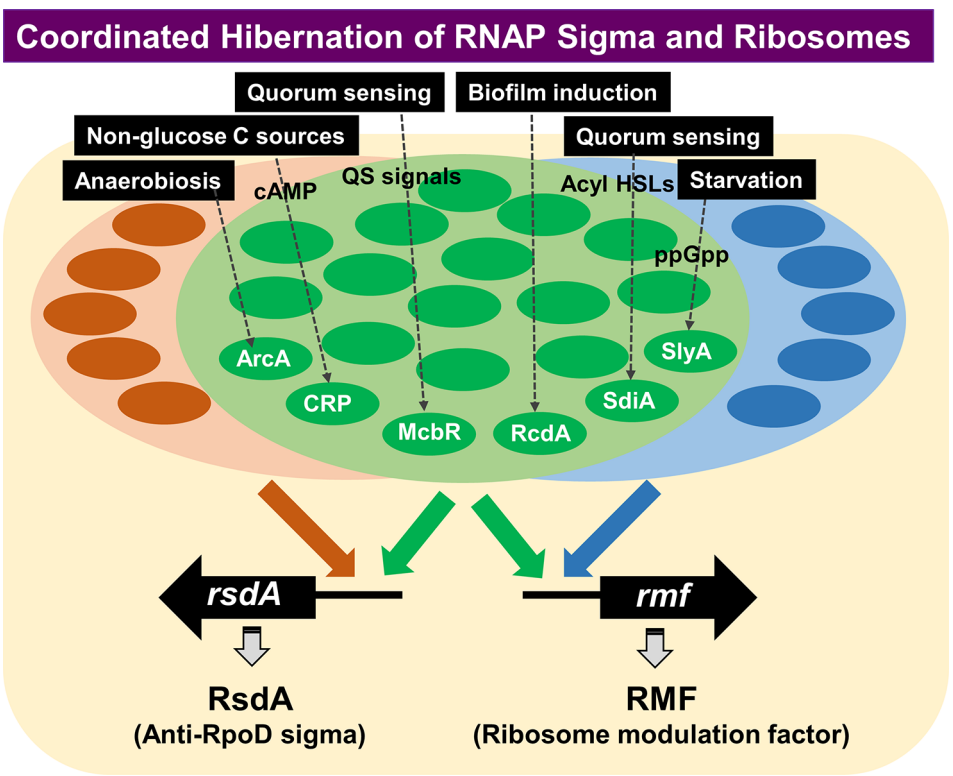

FIGURE 7 | PS-TF screening was performed for search of TFs involved in regulation of the *rsd* and *rmf* genes. A total of 74 TF species were found to bind to both the *rsd* and *rmf* promoter probes, although the binding affinity appeared different between these TFs (Yoshida et al., 2018). Besides these 74 TFs, some other TFs have been identified to bind only the *rsd* gene or the *rmf* gene, indicating independent regulation of the two genes under as yet unidentified conditions. Detailed analysis of the regulatory roles *in vitro* and *in vivo* was performed for the five representative stress-response TFs (ArcA, McbR, RcdA, SdiA, and SlyA) (Yoshida et al., 2018). ArcA was indicated to repress transcription of both *rsd* and *rmf* genes, while other four were suggested to activate both genes. gSELEX indicated that all these TFs regulate not only the *rsd* and *rmf* genes but also regulate a number of genes supposedly required for survival under stressful conditions. PS-TF, promoter-specific transcription factor.

the growth transition of *Escherichia coli* from log to stationary phase, the level of genome expression is reduced less than 10% the log-phase level and the pattern of genome expression (the species of expressed genes) is also markedly modulated. For this alteration, the transcription apparatus is altered by binding of anti-sigma factor Rsd to the RpoD sigma for sigma replacement with stationary-phase-specific RpoS (see above) while the translation machinery is modulated by binding of RMF and HPF to 70S ribosome to form the inactive 100S ribosome dimer (see above). Until recently, however, little was known how the expression of factors involved in hibernation of transcription apparatus and translation machinery is regulated. We have then performed a systematic search for TFs involved in regulation of the promoters of two key regulators, Rsd for hibernation of RNAP and RMF for hibernation of ribosomes, by using the newly developed promoter-specific transcription factor (PS-TF) screening system (Shimada et al., 2013; Yoshida et al., 2018).

Using *rsd* and *rmf* promoter probes and a total of about 200 purified TFs from *E. coli* K-12 W3110, we performed PS-TF screening (Yoshida et al., 2018). A total of 74 TF species (55 group A TFs and 19 group B TFs) were found to bind to both the *rsd* and *rmf* probes, although the binding affinity was different between these TFs (Yoshida et al., 2018), suggesting that both the *rmf* and *rsd* genes are under the control of multi-factor promoters (Ishihama et al., 2016). After repetition of PS-TF, we succeeded to focus on a total of 19 TFs, of which 9 (ArcA, CRP, CueR, McbR, NhaR, RcdA, SdiA, SlyA, and ZntR) have been experimentally confirmed to be involved in regulation *in vitro* and *in vivo* of both the *rsd* and *rmf* genes (Yoshida et al., 2018) (**Figure 7**). The synthesis of RMF is also under the control of ppGpp (Izutsu et al., 2001). Results altogether indicated the involvement of a common set of TFs, each sensing a specific but different environmental condition, in coordinated hibernation of the transcriptional apparatus and translational machinery for adaptation and survival under stressful conditions. Translation of RMF is stimulated by polyamines (Terui et al., 2010), which accumulates in the stationary phase (Igarashi and Kashiwagi, 2018).

Besides the large set of TFs with binding activity to both *rsd* and *rmf* probes, a small number of TFs bound only to either the *rsd* or *rmf* probe (**Figure 7**). This finding indicates the two key players for hibernation of transcription apparatus and translational machinery are regulated independently under certain specific conditions. These *rsd*- or *rmf*-specific TFs might be involved in independent regulation of either transcriptional apparatus or translational machinery under as yet unidentified specific environmental conditions. This review proves the initial stage of molecular basis of the hibernation of *E. coli*, focusing on the transcription apparatus and the translation machinery. The whole set of TFs involved in the regulation of *rsd* and *rmf* genes will be described elsewhere.

AUTHOR CONTRIBUTIONS

HY: data collection, writing, and figure preparation in Hibernation of the Translation Machinery and Coordinated Hibernation of Transcription Apparatus and Translation Machinery sections. TS: data collection and figure preparation in Discontinuous Change of the Cell Buoyant Density and Coordinated Hibernation of Transcription Apparatus and Translation Machinery. AW and YM: data collection, writing, and figure preparation in Growth-Dependent Change of the Protein Expression Pattern section. AI: design of this review article, data collection, writing, and figure preparation in Introduction, Discontinuous Change of the Cell Buoyant Density, Hibernation of the Transcription Apparatus, and Coordinated Hibernation of Transcription Apparatus and Translation Machinery. All authors read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2019.01153/full#supplementary-material

SUPPLEMENTAL FIGURE S1 | RFHR 2D gel patterns of *E. coli* proteins. *E. coli* K-12 AD202 was grown at 37 °C in minimal medium E containing 2% peptone. Cell lysates were prepared as described in text, and fractionated by centrifugation into CD (Insoluble cell debris), CE (supernatant cell extract), CR (crude ribosome), and PRS (post ribosomal supernatant) fractions. Soluble proteins of the CR [A], PRS [B], basic CD [C] and acidic CD [C] were subjected to RFHR (radical free and highly reducing) method of 2D gel analysis (Wada 1986a; Wada, 1986b). Gels were stained with CBB.

SUPPLEMENTAL FIGURE S2 | Contents of some growth-related proteins in cells fractionated by Percoll centrifugation. *E. coli* K-12 was grown at 37°C in LB medium for 12 hrs. Cell suspension was directly subjected to Percoll gradient centrifugation under the standard procedure (Makinoshima et al., 2002; Makinoshima et al., 2003). The gradient was fractionated and the content of some representative growth-related proteins in each fraction was determined by Western blot analysis with use of specific antibodies (Ishihama et al., 2014).

SUPPLEMENTAL FIGURE S3 | Ribosomes were subjected to sucrose density gradient centrifugation (SDGC) (Wada et al., 1990). **(A)** The pattern of ribosomes from exponential phase includes 70S ribosome as the major component and in addition, small amounts of 30S and 50S subparticles, and polysomes. **(B)** Ribosomes from stationary phase showed 100S dimeric ribosomes in addition to 30S, 50S and 70S ribosomes.

SUPPLEMENTAL TABLE S1 | Proteins Expressed During Prolonged Culture of Escherichia coli K-12 PRS (Post Ribosomal Supernatant) fraction

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