Novel Selective Medium for the Isolation of *Rothia aeria*, Which Is an Inhabitant of the Human Oral Cavity

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Abstract

*Rothia aeria*, *Rothia dentocariosa*, and *Rothia mucilaginosa* are isolated from the human oral cavity. Among them, *R. aeria* can cause severe systemic infection diseases (e.g., bronchitis, endocarditis, pneumonia, and sepsis). However, the veritable prevalence of this organism in the human oral cavity has not ever been known. Thus, the selective medium for the isolation and quantification of *R. aeria* is necessary to assess the prevalence of this organism, and to diagnose various *R. aeria* infection diseases.

To investigate *R. aeria* distribution in oral cavities, a novel selective medium (RAEMS) was developed for isolating and quantifying *R. aeria*. RAEMS consists of sodium gluconate, tryptone, meat extract, sodium fluoride, acriflavin neutral, fosfomycin, lincomycin, colistin, aztreonam, and agar. Polymerase chain reaction (PCR) primers were designed based on partial sequences of the 16S rDNA genes of *R. aeria*. The percentage of *R. aeria* in saliva samples collected from 20 subjects was examined. Moreover, we examined the antibiotic susceptibility of thirty isolates from six subjects.

The average growth recovery of *R. aeria* on RAEMS was 96.6% compared with that on Brain Heart Infusion supplemented with Yeast Extract (BHI-Y) agar. Growth of other representative oral bacteria, including other *Rothia* species, was remarkably inhibited on the selective medium. The PCR primers reacted to *R. aeria* and did not react to other *Rothia* species or representative oral bacteria. *R. aeria* was detected as 1.0% of the total bacteria, 5.9×10^7 CFU/ml, on BHI-Y agar in the oral cavities of all subjects. *R. aeria* isolates obtained in this study were susceptible to most antibiotics; however *R. aeria* isolates from one subject were highly resistant to erythromycin, lincomycin, and clindamycin. *R. aeria* may be a part of the normal flora in the human oral cavities. A novel selective medium, RAEMS, was useful for isolating *R. aeria*. Moreover, it was indicated that RAEMS was useful for diagnosing *R. aeria* infections.

Key words

*Rothia aeria*; Genus *Rothia*; Selective medium; Oral cavity; PCR

Introduction

The genus *Rothia* comprises 8 species ([www.bacterio.net/rothia.html](http://www.bacterio.net/rothia.html)), *Rothia aeria* [1], *Rothiaaeariaae* [2], *Rothia dentocariosa* [3], *Rothia mucilaginosa* [4], *Rothia nasmimurium* [4], *Rothia terrae* [5], *Rothia endophytica* [6], and *Rothia saerola* [7], which were isolated from an air sample, sludge of a foul water sewer, a human oral cavity, a human pharynx, the nose of a healthy mouse, subtropical fields, plant tissues, and pig barn respectively. Among the genus *Rothia*, *R. dentocariosa*, *R. mucilaginosa*, and *R. aeria* are found in the oral cavity and pharynx of humans [8-11]. Concerning *R. aeria*, it was first isolated from air and condensation water samples from the Russian space station Mir. Initially, it was known as *R. dentocariosa* genomovar I [1]. *R. aeria* is capable of causing serious systemic infections, such as sepsis, bronchitis, pneumonia, and endocarditis [12-17]. *R. aeria* is difficult to identify because of its similar morphology and colony appearance to those of *Nocardia* species. Therefore, 16S rRNA sequencing is required to distinguish *R. aeria* from *Nocardia* species [18].

*R. aeria* was detected in the mouths of healthy individuals [11,19]. We have previously reported selective media for the isolation of *R. dentocariosa* and *R. Mucilaginous*, respectively.

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[9,10]. Moreover, we have also previously reported selective media for the simultaneous isolation of three oral Rothia species (R. dentocariosa, R. mucilaginosa, and S. aeria) [11]. However, there has never been reported the selective medium for the isolation of R. aeria only. Therefore, a suitable selective medium for the isolation of R. aeria is necessary to assess the accurate prevalence of this organism in the human oral cavity.

The aim of the present study was to develop a selective medium for the isolation of R. aeria and reveal its distribution in the human oral cavity.

Materials and Methods

Bacterial strains and culture conditions

Table 1 shows all bacterial strains used in this study. All strains were subcultured on brain heart infusion (BHI, CM1135, Oxoid, UK) supplemented with 0.5% yeast extract (Oxoid, UK) and 1.5% agar (BHI-Y agar, Difco agar, BD, USA). Genus Rothia were cultivated at 37°C in the air for up to 24 hours. Representative oral bacteria strains except genus Rothia were cultivated at 37°C in 5% CO2 for up to 24 hours.

Development of the selective medium

ORSM [11] was chosen as a base medium for the selective medium. Disk susceptibility tests were used for antibiotic selection. (KB-Disk, EIKEN CHEMICAL CO., LTD., Tokyo, Japan). After choosing appropriate antibiotics, the microbroth dilution method was performed [20,21].

Recovery of representative Rothia species

The recovery of Rothia species reference strains and isolates from the human oral cavity in our previous studies [11] were calculated as colony-forming units (CFU) / mL on the selective medium compared with those on BHI-Y agar for total cultivable bacteria. Rothia species were cultivated at 37°C in the air for up to 24 hours. Rothia reference strains and isolates were suspended at three different concentrations (105, 106, and 107 CFU/mL), and then 0.1 mL Tris-HCl buffer (0.05 M, pH 7.2) of each suspension was inoculated in triplicates onto BHI and the selective medium. After the culture, CFU/mL was calculated.

Clinical samples

Clinical samples were obtained from twenty volunteers (age 22-58, male 9, female 11). Slava samples stimulated with paraffin from each volunteer were collected in sterile vials containing 0.5 mL of 0.05 M Tris-HCl buffer (pH 7.2). This study was approved by the Ethics Committee of Nihon University School of Dentistry at Matsudo, Japan (EC15-025). Samples were processed as described previously [11].

Identification of R. aeria isolated from clinical samples

Ten colonies (which appeared to be R. Erie based on colony morphology), per subject were subcultured to confirm the presence of R. aeria. Pure cultures of each isolate were identified by: (i) gram staining; and (ii) polymerase chain reaction (PCR) analyses.

Design of species-specific primers for representative Rothia species and PCR method procedure

The 16S rRNA sequences of R. aeria (accession no. AB071952) were obtained from the DNA Data Bank of Japan (DDB; Mishima, Japan). Design of species-specific primers and the procedure of PCR method were performed as described previously [11].

Antibiotics susceptibility tests of R. aeria isolates

Antimicrobial susceptibility testing of R. aeria isolates were evaluated using the microdilution method. Table 4 shows antibiotics used in this study. They are widely used in the treatment of Gram-positive infections. Because there is not Clinical and Laboratory Standards Institute (CLSI) protocols for R. aeria, the organism's drug susceptibility utilizing the 2016 CLSI criteria (M100-S27) for staphylococci was substituted in this study.

Results

Development of the selective medium

R. Dentocariosa, R. mucilaginosa, and R. aeria grew well and at similar ratios on a base medium, i.e. ORSM [11]. The minimal inhibitory concentration (MIC) of aztreonam for R. mucilaginosa and R. aeria were 100 μg/mL. R. dentocariosa was sensitive to 30 μg/mL of aztreonam. Moreover, R. aeria was more resistant to fosfomycin than R. mucilaginosa. The MIC of fosfomycin for R. aeria was 80 μg/mL. R. mucilaginosa was sensitive to 3 μg/mL of fosfomycin.

The selective medium for the isolation of R. aeria (RAESM) was composed of the following (per liter): 5 g meat extract (Sigma-Aldrich Co. LLC., Tokyo, Japan), 1 g tryptone (Sigma-Aldrich), 10 g sodium gluconate (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan), 125 mg sodium fluoride (Sigma-Aldrich), 15 g agar (Difco agar, BD, USA), 3 mg acriflavine neutral (Sigma-Aldrich), 10 mg colistin sulfate salt (Sigma-Aldrich), 0.2 mg lincomycin hydrochloride (Tokyo Chemical Industry), 3 mg fosfomycin disodium salt (Tokyo Chemical Industry), 30 mg aztreonam (Tokyo Chemical Industry). When the mixture except of the antibiotics was cooled to 50°C, colistin sulfate salt, lincomycin hydrochloride, fosfomycin disodium salt, and aztreonam were added aseptically.

PCR analyses

Table 2 shows specific primer sets covering the upstream regions of the 16S rDNA sequences of R. aeria, and the ampiclon size of this organism was 918 bp. The PCR method used to identify R. aeria produced positive bands from R. aeria (Figure 1) and did not produce any ampiclons from other Rothia species or any of the representative oral bacteria, i.e. some Streptococcus, Actinomyces, Neisseria, and Corynebacterium species.

Recovery of R. aeria on the selective medium

Table 1 shows the recovery of R. aeria and isolates on RAESM relative to BHI-Y agar. The growth recoveries of R. aeria reference strains and the isolates ranged from 95.1% to 97.7% (average 96.6%) on RAESM relative to that on BHI-Y agar. The growth of R. dentocariosa and R. mucilaginosa was markedly inhibited on the selective medium.

Clinical examination

The percentage of R. aeria in saliva from the twenty subjects on BHI-Y and RAESM is shown in Table 3. The mean number of total cultivable bacteria was 5.9 × 107 CFU/ml (range: 2.1 × 107 - 9.8 × 107). The mean number of R. aeria was 5.6 × 105 CFU/ml (range: 3.0 × 105 - 27 × 105). R. aeria accounted for 1.0% of the total cultivable bacteria number on the BHI-Y medium and was detected in all twenty subjects.

In the first isolation, R. aeria colonies on RAESM commonly exhibited a rough, dry, folded, and convex appearance (Figure 2) and

| Strain       | BHI-Y CFU/ml, × 105 | RAESM CFU/ml, × 105 | Recovery, % |
|--------------|---------------------|---------------------|-------------|
| R. aeria     |                      |                     |             |
| JCM 11412    | 1.1 ± 0.2a           | 1.0 ± 0.2           | 96.7        |
| GTC 02043    | 1.7 ± 0.1            | 1.7 ± 0.1           | 95.1        |
| NUM-Ra 7006  | 1.0 ± 0.1            | 1.0 ± 0.1           | 96.3        |
| NUM-Ra 7007  | 1.2 ± 0.2            | 1.2 ± 0.2           | 97.3        |
| NUMRa 7008   | 1.0 ± 0.2            | 1.0 ± 0.2           | 97.7        |
| R. dentocariosa |                 |                     |             |
| JCM 3067     | 1.4                  | 0.0001              | 0.01        |
| NUM-Rd 6018  | 1.9                  | 0                   | 0           |
| NUM-Rd 6020  | 1.0                  | 0                   | 0           |
| R. mucilaginosa |                   |                     |             |
| JCM 1091     | 1.0                  | 0                   | 0           |
| NUM-Rm 6504  | 2.1                  | 0                   | 0           |
| NUM-Rm 6505  | 1.6                  | 0                   | 0           |

Table 1: Recovery of representative Rothia species on BHI-Y and RAESM
Figure 1: Specificity of multiplex PCR assays. Primers are a mixture of RAF and RAR
Lanes: 1, R. aeria JCM 11412; 2, R. aeria GTC 02043; 3, R. dentocariosa JCM 3067; 4, R. mucilaginosa JCM 10910; 5, R. terrae JCM 15158; 6, R. amarae JCM 11375; 7, R. nasimurium JCM 10909; 8, R. endophytica JCM 18541; 9, Streptococcus mitis JCM 12971; 10, S. oralis JCM 12977; 11, S. gordonii JCM 12995; 12, S. sanguinis JCM 5708; 13, S. salivarius ATCC 7073; 14, S. anginosus JCM 12993; 15, S. mutans JCM 5705; 16, S. sobrinus DSM 20742; 17, Actinomyces naeslundii JCM 8349; 18, A. oris JCM 16131; 19, A. odontolyticus JCM 14871; 20, Neisseria sicca CCUG 23929; 21, Corynebacterium matruchotii JCM 9386; 22, C. durum JCM 11948.M, molecular size marker (100-bp DNA ladder).

Figure 2: Appearance of R. aeria colonies on RAESM
A: R. aeria colonies on RAESM inoculated with saliva sample.
B: Stereomicroscope image of R. aeria colony on RAESM.

Table 2: Locations and sequences of species-specific primers for the 16S rDNA of R. aeria

| Species   | Primer | Sequence                  | Product size (bp) | Position | number  |
|-----------|--------|---------------------------|-------------------|----------|---------|
| R. aeria  | RAF    | GTGCTTGCAGGTGGATAGTGG     | 918               | 28-49    | AB071952|
|           | RAR    | TGACCGGATCTAATCGATGCAAG   | 945               | 945-922  |         |

Table 3: Percentage of R. aeria in saliva samples from 20 subjects

| Subject | Total bacteria BHI-Y CFU/ml, × 10^7 | R. aeria RAESM CFU/ml, × 10^5 | Detection rate |
|---------|-------------------------------------|--------------------------------|----------------|
| A       | 3.3                                 | 2.0                            | 0.6            |
| B       | 2.7                                 | 0.3                            | 0.1            |
| C       | 2.1                                 | 0.7                            | 0.3            |
| D       | 5.8                                 | 27                             | 4.7            |
| E       | 4.5                                 | 1.0                            | 0.2            |
| F       | 6.2                                 | 4.8                            | 0.8            |
| G       | 11                                  | 6.0                            | 0.5            |
| H       | 2.3                                 | 3.2                            | 1.4            |
| I       | 4.1                                 | 1.5                            | 0.4            |
| J       | 3.8                                 | 1.5                            | 0.4            |
| K       | 6.3                                 | 4.0                            | 0.6            |
| L       | 7.2                                 | 2.5                            | 0.4            |
| M       | 11                                  | 3.3                            | 0.3            |
| N       | 3.4                                 | 1.1                            | 0.3            |
| O       | 9.8                                 | 3.0                            | 0.3            |
| P       | 6.5                                 | 5.7                            | 0.9            |
| Q       | 8.8                                 | 8.0                            | 0.9            |
| R       | 8.7                                 | 8.4                            | 1.0            |
| S       | 5.2                                 | 9.0                            | 1.7            |
| T       | 4.6                                 | 4.8                            | 1.0            |
| Average | 5.9                                 | 5.6                            | 1.0            |
Table 4: Antibiogram of *R. aeria* reference strains and clinical isolates

| Antimicrobial agent | CLSI Standards (μg/ml) | MIC (μg/ml) | Clinical isolates of *R. aeria* (No. of isolates) |
|---------------------|------------------------|-------------|-----------------------------------------------|
|                     | *R. aeria* JCM 11412   |             | | |
| Oxacillin           | S \( \leq 0.25 \) R \( \geq 0.5 \) | 0.06        | A (n=5) | B (n=5) | C (n=5) | D (n=5) | E (n=5) | F (n=5) |
| Erythromycin        | S \( \leq 0.5 \) R \( \geq 8 \) | 0.25        | 0.03-0.06 | 0.03-0.06 | 0.03-0.06 | 0.03-0.06 | 0.03-0.06 | 0.03-0.06 |
| Lincomycin          | S \( \leq 0.5 \) R \( \geq 8 \) | 2           | 0.05-0.125 | 0.05-0.125 | 0.05-0.125 | 0.125-0.5 | 0.05-0.125 |
| Clindamycin         | S \( \leq 0.5 \) R \( \geq 8 \) | 1           | 2-4        | 64-128     | 1-2       | 1-2       | 1-2       | 1-2       |
| Gentamycin          | S \( \leq 4 \) R \( \geq 16 \) | 8           | 4-8        | 4-8        | 4-8       | 4-8       | 4-8       |
| Teikoplanin         | S \( \leq 8 \) R \( \geq 32 \) | 0.5         | 1-2        | 1-2        | 0.5-2     | 0.5-1     | 1-2       | 0.5-2     |
| Vancomycin          | S \( \leq 4 \) R \( \geq 32 \) | 2           | 1-2        | 1-2        | 1-2       | 1-2       | 1-2       | 1-2       |

Adhered to the agar medium such that they were not easily scraped off. The average colony size of *R. aeria* on RAESM was 1.8 mm in diameter.

Antibiotics susceptibility tests of *R. aeria* isolates

*R. aeria* reference strains and isolates from subject A, C, D, E, and F were susceptible to most antibiotics (Table 4). On the other hand, *R. aeria* isolates from subject B were highly resistant to erythromycin, lincomycin and clindamycin.

Discussion

*R. dentocariosa*, *R. mucilaginosa*, and *R. aeria* are part of the normal flora in the human oral cavity and pharynx [8-11]. *R. aeria* was first isolated from air and condensation water samples from the Russian space station Mir [1]. *R. aeria* was originally classified as *R. dentocariosa* genovar II before the report of Li et al. [1]. *R. aeria* is capable of causing serious systemic infections, such as sepsis, bronchitis, pneumonia, and endocarditis [12-17]. However, there has never been reported the selective medium for the isolation of *R. aeria* only. Therefore, a suitable selective medium for the isolation of *R. aeria* is necessary to assess the veritable prevalence of this organism in the human oral cavity and to diagnose *R. aeria* infections rapidly. To examine the bacterium population in the oral cavity, a novel selective medium, designated RAESM, was developed for the isolation of *aeria* in this study. RAESM was highly selective for *R. aeria*.

On clinical microbiological examination, *Rothia* species can be mistaken for bacteria such as *Dermabacter hominis*, *Actinomyces viscosus*, *Propionibacterium avidum*, *Corynebacterium matruchotii*, and *Nocardia* species because many laboratories are unfamiliar with these organisms, which may be difficult to culture due to having the same gram positive rods and to their variable aero-tolerance [22-24]. Moreover, the colonies of *Nocardia* species are similar to those of *R. aeria* [18]. *R. aeria* is capable of causing serious systemic infections [15-20]. Therefore, RAESM may contribute to the correct and rapid diagnosis of the infectious diseases caused by *R. aeria*.

In this study, *R. aeria* was detected in all subjects and accounted for 1.0% of total bacteria in saliva. These results indicated that *R. aeria* is a part of the normal flora in the oral cavity of humans and is not a microorganism peculiar to a specific environment, such as the space station. In our previous studies, *R. dentocariosa* and *R. mucilaginosa* accounted for 2.6% and 3.4% of total bacteria in saliva, respectively [9,10]. Consequently, it was indicated that *R. aeria* is a part of the normal flora in the human oral cavity, and the genus *Rothia* includes three species that inhabit the human oral cavity. *aeria* can be mistaken for *Nocardia* sp due to the morphological similarities, and discrimination between *R. aeria* and *Nocardia* spp needs further analyses, such as 16S rRNA sequencing [18]. Microorganisms of the genus *Nocardia* are branching and partially acid-alcohol-fast gram-positive bacilli, and they belong to the order of *Actinomycetales*. Numerous species have been described and are being reclassified continuously thanks to the use of molecular biology techniques. Nocardiosis is caused by various species of the genus *Nocardia*. It can cause lung disease, skin disease, or systemic disorders by involving the central nervous system, but it can also colonize the airways asymptomatically. Saraya et al. [25] has reported that *R. aeria* should be considered in the differential diagnosis of *Nocardia* spp, especially in immunocompromised patients who are vulnerable to *Nocardia* infections. Selective medium for the isolation of *R. aeria*, i.e. RAESM, and the PCR analysis developed in this study may help us rapidly diagnose the infectious diseases caused by *R. aeria* or *Nocardia* spp.

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