CORRESPONDENCE

Dynamics of Hepatitis C Viremia

To the Editor—The recent report of Yasui et al. [1] describing the dynamics of hepatitis C viremia following interferon-α administration contains some intriguing information regarding the ratio of core protein to hepatitis C virus (HCV) RNA. First, there are very few laboratories that can measure the concentration of HCV core protein in serum. Thus, the information provided in table 1 of [1], giving the concentration of core protein (picograms/milliliter) and the corresponding concentration of HCV RNA (kilocopies/milliliter), allow the number of core protein molecules per RNA to be calculated. This calculation is based on the predicted molecular mass of the core protein as 21 kDa and Avogadro’s constant of being the number of molecules per mole. Taking the mean values from table 1 for 12 different sera gives a ratio of RNA molecules to number of molecules per mole. As calculated above, their data suggest there are 12,240 copies of core protein per RNA molecule. This indicates that there may be many “empty” particles in the serum of HCV-infected patients. These are virions that contain capsids (or possibly free capsids) that do not contain RNA. The implications of this with regard to the mechanisms of persistence and immune evasion are obvious. With the techniques at their disposal, Yasui et al. [1] could establish whether there are indeed two populations of particles in the serum of HCV-infected patients. These particles would differ in their densities on the basis of the presence or absence of RNA.

Anthony R. Carroll
Medicines Research Centre, Department of Virology, Glaxo-Wellcome Research and Development, Stevenage, United Kingdom

References

Reply

To the Editor—We agree with Carroll [1] that the calculated ratio of hepatitis C virus (HCV) core protein to HCV RNA based on the data in table 1 of our paper [2] does not correspond with the theoretically estimated one. Nevertheless, we do not think that there are many “empty” particles that contain HCV core protein but not HCV RNA or “free” HCV core proteins in the sera of patients infected with HCV. In our recent study [3], the quantities of HCV core protein and HCV RNA in each fraction obtained from sucrose density-gradient centrifugation of the patient sera were determined. The fraction numbers of peak HCV core protein and peak HCV RNA were identical for these sera. This finding suggests that native HCV particles consist of HCV core protein and HCV RNA.

Kohichiro Yasui and Takeshi Okanoue
Third Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan

References

Reprints or correspondence: Dr. Takeshi Okanoue, Third Department of Internal Medicine, Kyoto Prefecture University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-0841, Japan (okanoue@koto.kpu-m.ac.jp).

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Adhesion of Staphylococcus aureus to Collagen Is Not a Major Virulence Determinant for Septic Arthritis, Osteomyelitis, or Endocarditis

To the Editor—We read with interest the article by Ryding et al. [1], showing that the ability to bind collagen in vitro and the possession of the gene cna, encoding a collagen adhesin, is found in ~60% of isolates of Staphylococcus aureus, regardless of their clinical source. These data contradict an earlier report that isolates from human bone and joint infections expressed collagen-binding activity, whereas only a minority of skin and soft tissue isolates did so [2]. Experiments with animal models were also supportive of a key role for cna [3], suggesting that it might be a target for novel therapeutic intervention or immunization. As such, it is important to obtain a resolution to these conflicting results.

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We have carried out a study similar to that of Ryding et al., using isolates from diverse geographic regions (Oxford, UK, and Auckland, New Zealand). We tested 159 strains of methicillin-susceptible S. aureus isolated between 1993 and 1996 from 102 patients in Oxford (septic arthritis, 14; osteomyelitis, 8; metal-associated orthopedic infection, 27; infective endocarditis, 24; nasal carriage, 29) and 57 patients in Auckland (septic arthritis, 24; osteomyelitis, 8; infective endocarditis, 10; nasal carriage, 15). We used polymerase chain reaction (PCR) to detect cna in the 102 Oxford isolates, using previously published primers specific for the whole gene, its nonrepetitive A domain and the repeat B domains [2]. We assayed adhesion to collagen for all strains with a microtiter method using human collagen IV immobilized on plastic, in contrast to Ryding et al., who used labeled fragments of collagen to bind bacteria in the liquid phase.

We found that 68 of 102 (67%; 95% confidence interval [CI], 58%–76%) Oxford isolates and 27 of 57 (44%; 95% CI, 31%–57%) Auckland isolates bound to immobilized collagen IV. The clinical source bore no relation to the proportion of isolates that bound collagen (figure 1) in either location, but the proportion of isolates able to bind to collagen did differ significantly between Oxford and Auckland ($\chi^2 = 6.9, P < .01$). PCR amplification demonstrated the presence of cna in 70 of the 102 Oxford isolates (69%; 95% CI, 60%–78%). A single isolate bound to collagen despite lacking a full-length cna gene on PCR, but this strain did possess an A domain. Three strains did not bind collagen despite the possession of cna, which we
attribute to point mutations in the gene, leading to lack of expression. We did not analyze the New Zealand isolates by PCR but noted a low frequency of collagen-binding strains in a geographic location known for a high incidence of primary septic arthritis and osteomyelitis.

Our results confirm those of Ryding et al. [1]. The reasons for the disparity between these data and earlier reports may include differing methodologies, differing geographic locations, the epidemiologic context within which the strains were isolated, and sampling error due to small numbers in early studies. The close agreement in results for the Swedish and UK isolates, despite differences in PCR and collagen adhesion assays, argues that the findings are robust and certainly generalizable within northern Europe. However, the significant difference in collagen-binding ability between strains from our two study locations argues that the bacterial population genetic structures may differ due to host population or environmental factors. Therefore, there may also be real differences between North America, where in the largest reported series, collagen binding was found in 39 of the 90 strains tested (43%; 95% CI, 33%–53%) [4], and Europe or Australasia.

None of the studies reported were prospective, and no examination of the clonal structures within these populations of S. aureus has been reported. It may be that earlier studies inadvertently examined isolates that were drawn from a very small proportion of S. aureus clones, leading to selection bias and hence a spurious association of collagen binding with isolates from bone and joint infections.

Our data and those of Ryding et al. therefore suggest that cna encodes the only significant collagen adhesin in the S. aureus genome, but that the possession of this gene is not essential in the pathogenesis of human musculoskeletal infection. We cannot exclude a role for cna in determining the severity or prognosis of disease, which would require a prospectively gathered matched series with detailed clinical documentation. On the basis of these two large studies, however, cna can at best only be considered to be one of several potential virulence factors in the pathogenesis of bone and joint sepsis.

Mark G. Thomas, Sharon Peacock, Susan Daenke, and Anthony R. Berendt
Adhesion and Infection Laboratory and Molecular Science Division, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, United Kingdom

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Reprints or correspondence (present address): Dr. Mark G. Thomas, Dept. of Molecular Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand (mg.thomas@auckland.ac.nz).

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