In the Literature

Angiotensin-Converting Enzyme (ACE) and Lung Injury in Severe Acute Respiratory Syndrome (SARS)

Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature Med 2005; 11:875–9.

ACE converts angiotensin I to angiotensin II. The carboxypeptidase ACE2 negatively regulates angiotensin II production by cleaving a single residue from both angiotensin I and II, thus interfering with the renin-angiotensin cascade. This cascade has recently been demonstrated to play a role in diffuse pulmonary alveolar injury mediated by the interaction of angiotensin II with angiotensin II receptor type 1.

ACE2 has been demonstrated in vitro to be a cell-surface receptor for the surface spike protein of the SARS coronavirus. This suggests the possibility that the severe diffuse alveolar damage commonly seen in patients with SARS may be, at least in part, the consequence of the effects of angiotensin II. If so, the down-regulatory effects of ACE2 could play a protective role.

Experimental pulmonary infection with SARS coronavirus infection in mice reduced the expression of ACE2 in the lungs and, as also occurs in humans, caused diffuse lung injury. These findings were reproduced by exposure to SARS coronavirus spike protein in the absence of replicative virus. In a murine model of acute lung injury due to acid aspiration, SARS coronavirus spike protein exacerbated lung failure by down-regulation of the renin-angiotensin system. SARS coronavirus Spike protein–induced lung failure could be mitigated by inhibition with angiotensin II receptor type 1, the receptor that mediates angiotensin II–induced vascular permeability and lung injury. In a separate publication, the same investigators demonstrated that recombinant ACE2 protects mice from acid aspiration-induced lung injury [1]. The investigators also note that ACE1 polymorphisms have been associated with progression of SARS [2].

On the basis of these findings, the investigators proposed that the severe pulmonary alveolar injury seen in patients with SARS is the consequence of SARS coronavirus spike surface protein–associated down-regulation of ACE2. The decreased availability of ACE2 impairs the ability to down-regulate the renin-angiotensin system, exacerbating lung injury. The authors suggest that recombinant ACE2 protein could be a potential therapeutic agent in this and related pulmonary infections and diffuse alveolar injuries.

References

1. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005; 436:112–6.
2. Itoyama S, Keicho N, Quy T, et al. ACE1 polymorphism and progression of SARS. Biochem Biophys Res Commun 2004; 325:1124–9.

Tripartite Interaction Motif 5 (Trim5) α and the Epidemic of HIV-1 Infection

Yap MW, Nisole S, Stoye J. A single amino acid change in the SPRY domain of human Trim5α leads to HIV-1 restriction. Curr Biol 2005; 15:73–8.

Trim5 is an intracellular retroviral restriction factor that effectively binds to incoming retroviral capsids and inhibits their replication at a stage prior to or concurrent with reverse transcription. Trim5α appears to account for the resistance of Old World monkeys to HIV-1 infection. Human Trim5α, in contrast, is unable to abort intracellular HIV-1 infection, despite having 87% homology at the amino acid level with its rhesus monkey counterpart.

Stoye and colleagues explored the difference between simian and human Trim5α by constructing chimeras of human and rhesus monkey Trim5α gene sequences and mapping the regions required for HIV-1 restriction. This approach revealed that the region involved in this restriction is the SPRY domain of Trim5α and that a single amino acid substitution in the human gene product (arginine for proline at amino acid position 332) enables human cells to block HIV-1 replication.

These findings suggest that the vulnerability of the human population to HIV-1 is the consequence of mutations in Trim5α during our remote evolutionary history. Other investigators have provided evidence for positive selection within the relevant SPRY domain, presumably as a consequence of ancient exposures to retrovirus [1]. Finally, these results point to the potential therapeutic value of molecules that mimic Trim5α, as well as to the possibility of future targeted gene therapy.

Reference

1. Sawyer SL, Wu LJ, Emerman M, Malik HS. Positive selection of primate TRIM5α identifies a critical species-specific retroviral restriction domain. Proc Natl Acad Sci U S A 2005; 102:2832–7.

Golden Virulence

Liu GY, Essex A, Buchanan JT, et al. Staphylococcus aureus golden pigment impairs neutrophil killing and promotes virulence through its antioxidant activity. J Exp Med 2005; 202:209–15.

The golden pigment produced by S. aureus is compromised of a group of carotenoids. Carotenoids produced by fruits and vegetables are capable of scavenging free radicals and quenching singlet oxygen. Liu and colleagues devised a set of experiments designed to examine the hypothesis that carotenoids produced by S. aureus provide a survival advantage to the organisms by allowing them to resist the oxygen-dependent bactericidal activity of phagocytic cells.

With use of targeted mutagenesis and heterologous expression, they demon-
strated that mutant (knockout) S. aureus with impaired synthesis of carotenoids was more susceptible to killing by oxidants than was the wild-type strain. Inhibition of the neutrophil oxidative burst eliminated the relative survival advantage of wild-type S. aureus strains that were capable of normal carotenoid biosynthesis. Mutant S. aureus strains were incapable of abscess formation after subcutaneous injection in mice. Heterologous expression of S. aureus carotenoids in Streptococcus pyogenes conferred relative resistance to oxidants and killing by neutrophils, as well as increased virulence in an animal model of infection.

A mixed-function oxidase inhibitor known to inhibit pigment formation in S. aureus did so in a dose-dependent fashion that paralleled an increase in the susceptibility of the organism to killing by singlet oxygen, as well as a decreased survival rate in murine whole blood. This observation indicates that targeting the carotenoids of S. aureus may provide a fruitful approach to the development of novel therapeutic agents directed at this organism.

**Voriconazole plus Neurosurgery for CNS Aspergillosis**

Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis with voriconazole treatment. Blood 2005 [Epub ahead of print].

Schwartz and colleagues identified 81 patients with definite (n = 48) or probable (n = 33) CNS aspergillosis who had received treatment with voriconazole in either clinical trials or compassionate-use programs. All patients but 3 had received ≥1 systemic antifungal agent before receiving voriconazole. Thirty-one patients (38%) also underwent neurosurgical procedures (14 underwent craniotomy and abscess resection, and 12 underwent abscess drainage), 4 patients underwent shunting, and 1 patient had an Ommaya reservoir placed.

Thirty-two patients were recipients of hematopoietic stem cell transplants (HSCTs), all but 2 of which were allogeneic, whereas 11 had received solid organ transplants. All but 6 of the 50 isolates speciated were found to be Aspergillus fumigatus.

A complete or partial response to voriconazole was achieved in 25 patients (35%) overall but in only 16% of HSCT recipients. Thirty-one percent of patients were alive at the last follow-up visit, but only 22% of HSCT recipients and 27% of solid organ transplant recipients had survived. Multivariate analysis found that HSCT was a significant predictor of a reduced survival rate, whereas neurosurgical procedures were associated with an improved survival rate. However, patients who underwent such procedures were less likely to have multiple brain lesions. The potential role of surgical intervention was previously suggested in a review of 26 survivors of cerebral aspergillosis, 21 of whom had undergone a neurosurgical procedure [1].

As miserable as these results seem at first glance, they are quite superior to previously published data, which have indicated that responses to other therapies occur in as few as 10% of patients and that the fatality rate for CNS aspergillosis in solid organ transplant recipients approaches 100%.

Although affected by the study’s observational nature and likely selection bias, these data strongly suggest that voriconazole therapy is effective for some patients with CNS aspergillosis. Furthermore, although objections can be made with regard to the findings for neurosurgical interventions (i.e., patients were more likely to have single lesions and had to be considered capable of surviving the procedure), the availability of an aggressive neurosurgical colleague may also be invaluable in improving survival rates for this devastating infection.

**Reference**

1. Lin JJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 2001; 32:358–66.

**Salvaging Peritoneal Dialysis Catheters**

Crabtree JH, Burchette RJ. Surgical salvage of peritoneal dialysis catheters from chronic exit-site and tunnel infections. Am J Surg 2005; 190:4–8.

In patients with chronic infections involving the exit site or tunnel portion of peritoneal dialysis catheters, treatment with antibiotics and local care is often unsuccessful. In such cases, removal of the catheter is usually recommended. One less drastic method that allows salvage of the infected catheter—unroofing of the tunnel tract and removal of the superficial catheter cuff—has been used, but published evidence of benefit has been scanty.

This procedure was used by Crabtree and Burchette in 13 consecutive patients with chronic peritoneal dialysis catheter infections that had been present for a mean duration of 3.2 months, with successful results for all 13. The procedure consisted of excision, of the superficial cuff after its identification and mobilization through an incision along the course of the catheter. The exit-site skin and all inflammatory tissue were excised. The catheter and shaved tubing segment were moved out of the wound and secured to the adjacent skin surface with tincture of benzoin and sterile adhesive strips. The wound was packed open and allowed to heal. Peritoneal dialysis was allowed immediately, and antibiotics were administered orally for 2–4 weeks.

Wound healing was complete after a mean period of 1.4 months (range, 0.9–2.2 months). During a mean follow-up period of 18.2 months, 2 persons with nasal carriage of S. aureus developed infection involving the deep cuff (at months 8.9 and 33.7). Three patients subsequently had their catheters removed because of peritonitis without exit-site or tunnel infection at months 8–11.

This procedure—at least, as performed by this team—appears to be a highly effective means of catheter preservation that allows continuation of peritoneal dialysis without interruption.