though the cells of higher eukaryotic organisms generally exist in a comparatively stable environment, they still must balance the synthesis of interacting macromolecules. The tight regulation of globin synthesis by free heme is one example (*21*).

There are two ways in which the RNA and protein components of a ribonucleoprotein complex such as a snRNP could be coregulated. The absolute levels of snRNA might be regulated directly, and snRNA proteins would then be synthesized in sufficient quantity to package all the snRNA. Excess snRNP proteins would either autogenously turn off their own synthesis or simply be degraded. This model may account for the regulation of the components of the bacterial ribosome (*22*). Alternatively, one or more protein components of the snRNP might be regulated directly, and snRNA's would be synthesized until excess snRNA failed to be properly packaged. In this model, excess snRNA would autogenously regulate its own synthesis or be degraded.

The existence of proteins that are common to different snRNP species necessarily complicates any model for regulation of the protein and RNA components of the particles. For example, the Sm protein is common to distinct snRNP's containing U1, U2, U4, U5, U6, and U7; the RNP antigen is restricted to the U1 snRNP (*1*, *2*). The regulatory events responsible for U1 dosage compensation do not seem to affect the other snRNP's: the ratio of total U1 to U2 snRNA in the mouse cell was not increased by addition of human U1 genes. Thus, the second model, which in its simplest form predicts an imbalance among the different snRNA species, cannot account for our data. More complex regulatory circuits might combine features of both models. Although we have shown only that mammalian cells regulate the total level of U1 RNA, it is reasonable to suggest that this will be the case for other snRNA's as well.

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23. We thank D. Pintel for advice and for C127 cells, P. Howley for BPV plasmids, P. Tattersall and co-workers for sharing their tissue culture facilities and knowledge, and J. Steitz and co-workers for providing antibodies. Supported by grant GM31073 and GM31335 from the NIH, PCM 83-15602 from the NSF, and NIH postdoctoral fellowship GM09148 (M.A.).

31 January 1985; accepted 8 May 1985

Presence of Laminin Receptors in *Staphylococcus aureus*

Abstract. *A characteristic feature of infection by* Staphylococcus aureus *is bloodstream invasion and widespread metastatic abscess formation. The ability to extravasate, which entails crossing the vascular basement membrane, appears to be critical for the organism's pathogenicity. Extravasation by normal and neoplastic mammalian cells has been correlated with the presence of specific cell surface receptors for the basement membrane glycoprotein laminin. Similar laminin receptors were found in* Staphylococcus aureus *but not in* Staphylococcus epidermidis, *a noninvasive pathogen. There were about 100 binding sites per cell, with an apparent binding affinity of 2.9 nanomolar. The molecular weight of the receptor was 50,000 and* p*I was 4.2. Eukaryotic laminin receptors were visualized by means of the binding of* S. aureus *in the presence of laminin. Prokaryotic and eukaryotic invasive cells might utilize similar, if not identical, mechanisms for invasion.*

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Adhesion is an important prerequisite for bacterial infectivity. Specific molecules are involved in bacterial adhesion at both the bacterial and host cell surfaces (*1*). The role of laminin, the major glycoprotein of the basement membrane, in the adhesion of pathogens such as bacteria has not been clearly established. Laminin is a noncollagenous, high molecular weight (10^6) protein composed of polypeptide chains with molecular weights of approximately 200,000 and 400,000 (*2*). It interacts with glycosaminoglycans and promotes adhesion of various cell types (*3*). Laminin receptors occur on cells that normally interact with basement membranes (*4*) as well as on cells that extravasate, such as metastasizing cancer cells (*5*), macrophages (*6*), and leukocytes (*7*).

Once a devastating pathogen, with over 80 percent mortality, *Staphylococcus aureus* is now the most common cause of severe infection in the nonimmunocompromised patient. In the industrialized world, it is responsible for endocarditis, osteomyelitis, arthritis, soft tissue infection, and pneumonia. In underdeveloped countries, staphylococcal infection is even more serious, with untreated disease often leading to fatal bacteremia (*8*).

Staphylococcus epidermidis is considered to be a nonpathogenic organism (*9*); it can, however, be an important pathogen when delivered to the actual site of infection by prosthetic devices or intravascular catheters (*10*). *Staphylococcus aureus* is able to colonize quickly and invade through minor breaks in skin and mucous membranes and reach the bloodstream. Once bloodborne, *S. aureus* can cause acute endocarditis and widespread metastatic abscesses (*11*). We now report the presence of laminin receptors on *S. aureus* (Cowan I strain), but not on *S. epidermidis*.

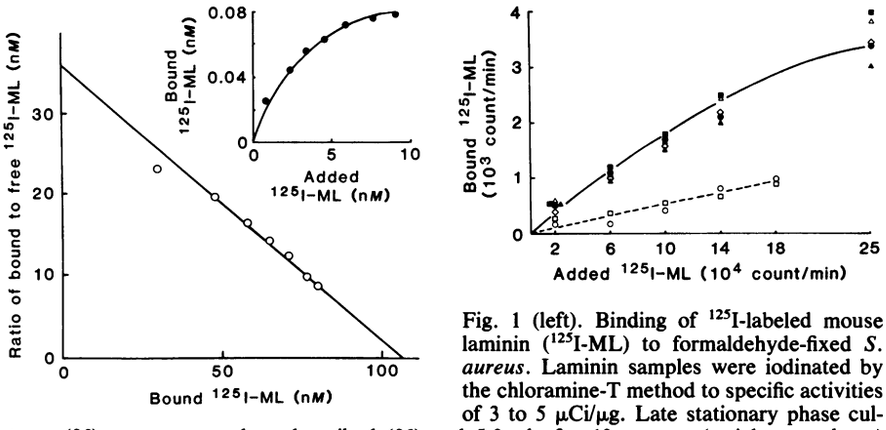


Fig. 1 (left). Binding of ^{125}I-labeled mouse laminin (^{125}I-ML) to formaldehyde-fixed *S. aureus*. Laminin samples were iodinated by the chloramine-T method to specific activities of 3 to 5 μCi/μg. Late stationary phase cultures (*20*) were prepared as described (*21*) and 5.0 μl of a 10 percent (weight to volume) suspension (3.4×10^6 bacterial cells) was used for each point. Assays were performed in NET-BSA buffer [150 m*M* NaCl, 5 m*M* EDTA, 50 m*M* tris-HCl (*p*H 7.4), containing 0.1 percent of bovine serum albumin]. After incubation for 2 hours at 37°C, bacteria were washed twice by centrifugation and their radioactivity determined in an LKB Minigamma counter. Fig. 2 (right). Inhibition of binding of ^{125}I-labeled mouse laminin (^{125}I-ML) to *S. aureus* by a 200-fold excess of protein A from *S. aureus* (◇), fibronectin (■), normal rabbit serum (▲), mouse IgG_{2A} (△), unlabeled laminin (○), and by previous trypsinization of the bacteria (□); uninhibited binding (●). Mouse IgG_{2A} is a monoclonal antibody against carcinoembryonic antigen produced in our laboratory. Trypsinization of cells was performed with a 0.25 percent (weight to volume) trypsin/EDTA (Sigma) solution in 0.9 percent NaCl for 10 minutes with agitation. The reaction was stopped by addition of RPMI 1640 culture medium containing 10 percent fetal bovine serum (Gibco). Cells were washed twice in NET-BSA buffer and used for binding tests.

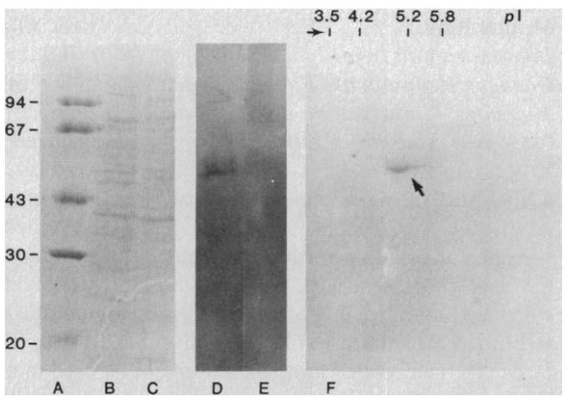
Binding of ^{125}I-labeled laminin by *S. aureus* was saturable, with an apparent binding affinity (K_d) of 2.9 n*M* and there were about 100 sites per cell (Fig. 1) (*12*). Binding was not affected by 200-fold excess staphylococcal protein A, mouse immunoglobulin G (IgG_{2A}) (*12a*), normal rabbit serum, or fibronectin; it was blocked by unlabeled laminin and prior trypsinization of cells. *S. epidermidis* did not bind laminin (Fig. 2). Western blots of electrophoretically separated extracts of *S. aureus* and *S. epidermidis* that were reacted with laminin and rabbit antibody to laminin showed a single 50,000-dalton protein band in *S. aureus* with a *p*I of 4.2 (Fig. 3).

Another receptor has been identified in some *Streptococcus pyogenes* strains freshly isolated from pharyngitis patients (*13*). This receptor, however, had a high molecular weight ($>10^6$) and an affinity constant at least one order of magnitude lower than that reported here.

Specific antigens were demonstrated at the surface of *Trypanosoma cruzi* cells by means of their interaction with the corresponding antibodies that had been attached to staphylococcal protein A on the surface of *S. aureus* cells (staphylococcus adherence test, SAT) (*14*). We have demonstrated the presence of laminin receptors at the surface of highly metastasizing murine melanoma B16 F10 cells by the adherence of *S. aureus* in the presence of laminin as a bridge (Fig. 4A). When laminin was excluded from the incubation mixture, there was no binding of microorganisms (Fig. 4B).

The role of fibronectin in *S. aureus* pathogenicity is controversial. It may act as a binding site since specific receptors have been described (*15*). Initial colonization of fibronectin-containing platelet-fibrin clots occurs in experimental and human endocarditis (*16*). On the other hand, circulating fibronectin may play a protective role since it is a complete opsonin, enhances macrophage phagocytosis (*17*), and reduces metastatic potential of murine melanoma (*18*). Laminin, however, mediates attachment of highly metastasizing tumor cells to type IV collagen substrates and increases the formation of lung colonies in vivo by cells previously exposed to it (*19*).

By analogy with tumor cells, the metastasizing capacity of *S. aureus* might be



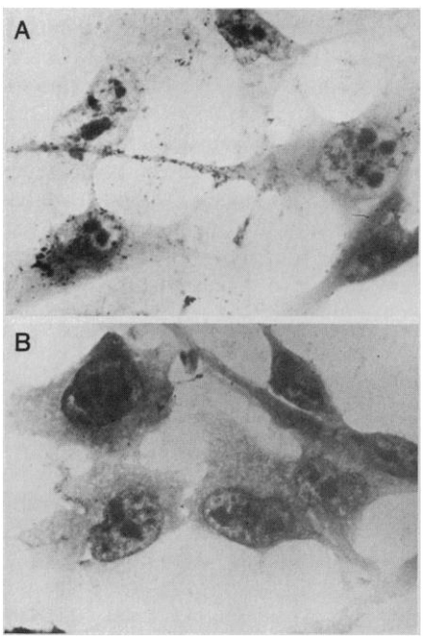


Fig. 3 (left). Detection of *S. aureus* laminin receptor by electrophoretic transfer from sodium dodecyl sulfate–polyacrilamide gel electrophoresis (SDS-PAGE) to nitrocellulose. Two-dimensional gel electrophoresis was performed by nonequilibrium *p*H gradient gel electrophoresis (NEPHGE) followed by SDS-PAGE in 10 percent acrylamide gels. The protein was then transferred to nitrocellulose filter sheets as described (*22*). Lanes A to C show SDS-PAGE analysis after Coomassie blue staining of (lane A) low molecular weight standards (Pharmacia Fine Chemicals); (lane B) *S. aureus* extract; (lane C) *S. epidermidis* extract. For Western blots, whole-cell extracts of *S. aureus* and *S. epidermidis* were electrophoretically transferred to nitrocellulose filters and then sequentially treated with phosphate-buffered saline (PBS) and 3 percent BSA, laminin, antibody to laminin (antilaminin), and horseradish peroxidase–conjugated antibody to rabbit IgG (*23*). (Lane D) Western blot of *S. aureus* extract; (lane E) Western blot of *S. epidermidis* extract; (lane F) Western blot of a two-dimensional gel of a whole-cell *S. aureus* extract after similar laminin-antilaminin treatment. Arrows show the direction of migration. Fig. 4 (right). Binding of *S. aureus* to laminin receptors on the surface of B16-F10 mouse melanoma cells. Cells were grown on cover slips in RPMI (Gibco) containing 10 percent fetal bovine serum (KC Biologicals) without antibiotics. Cover slips were washed with PBS and fixed for 60 minutes in Bouin's solution, incubated for 60 minutes in a solution of 25 m*M* tris-HCl, *p*H 7.4, 5 m*M* $CaCl_2$, 0.15*M* NaCl, and 1 percent BSA, and then incubated in the same buffer with (A) or without (B) 20 μg/ml of unlabeled laminin for 30 minutes at 37°C. After thorough washing, cover slips were incubated with a 0.2 percent (weight to volume) *S. aureus* suspension for 30 minutes at 37°C in the same buffer, as described (*14*). After washing, cover slips were stained with Leishman's eosin-methylene blue stain (Sigma) and examined (magnification, ×400).

related to its ability to bind specifically to basement membranes. This binding capacity could contribute significantly to the organism's extreme virulence.

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23. Bacterial cell pellets from 1-liter cultures were suspended in 8.0 ml of 50 m*M* tris-HCl (*p*H 8.0) containing 25 percent sucrose, 1 m*M* *N*-ethylmaleimide, 1 m*M* phenylmethylsulfonyl fluoride, and 1 m*M* EDTA. Lysozyme (3 mg) and Nonidet P-40 (final concentration 1 percent) were added and the suspension was incubated at 37°C for 60 minutes. Cell extracts were used for SDS-PAGE (*22*). After blotting, filters were incubated for 60 minutes with 3 percent BSA in PBS containing 0.03 percent Tween 20, then immersed in 25 m*M* tris-HCl (*p*H 7.4) containing unlabeled laminin (20 μg/ml), 5 m*M* $CaCl_2$, 5 m*M* $MgCl_2$, and 0.15*M* NaCl for 120 minutes at room temperature and washed in the same buffer without laminin. Affinity-purified rabbit antibody to mouse laminin, prepared in our laboratory by intramuscular injections of laminin in complete Freund's Adjuvant into New Zealand rabbits, was diluted 20-fold and added to the filters. The filters were incubated for 120 minutes at room temperature and developed with a horseradish peroxidase–conjugated goat antibody to rabbit IgG (Miles Laboratories) as described (*22*).

24. We thank L. L. Villa for helping with preparation of cell extracts and determinations of cell numbers; R. Hartfiel and G. Mota for their able technical assistance. B16 F10 mouse melanoma cells were gifts from I. Hart, Imperial Cancer Research Fund, London, and L. Liotta, NCI; *S. aureus*, Cowan I strain, was a gift from E. P. Camargo and *S. epidermidis* was a gift from L. R. Trabulsi, Escola Paulista de Medicina, Sao Paulo; laminin samples were gifts from R. Timpl, Max Planck, Martinsried, West Germany and L. Liotta, NCI.

12 February 1985; accepted 23 May 1985

Induced Expression of the Glucocorticoid Receptor in the Rat Intermediate Pituitary Lobe

Abstract. *Synthesis and release of pro-opiomelanocortin–derived peptides are under differential regulation in the anterior and intermediate lobes of the pituitary. Glucocorticoids inhibit synthesis of pro-opiomelanocortin–related peptides in the anterior lobe but not in the intermediate lobe. These two lobes are also characterized by differences in neural innervation and blood flow, both of which may represent routes of access for regulatory factors (the intermediate lobe is avascular). Immunoreactive glucocorticoid receptor, which can be demonstrated in many tissues, is absent from the intermediate lobe. Immunocytochemistry was used to demonstrate the presence of immunoreactive glucocorticoid receptor in the intermediate lobe after pituitary stalk transection, neurointermediate lobe grafts to kidney capsule, or monolayer culture of neurointermediate pituitary cells. This appearance of the glucocorticoid receptor is presumably a consequence of removal of intermediate pituitary cells from neural influences that may be responsible for inhibiting their expression under normal conditions in vivo.*

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Adrenocorticotropic hormone (ACTH) and lipotropic hormone (β-LPH), initially isolated from anterior pituitary lobe (AL) extracts, are derived from a common precursor molecule, pro-opiomelanocortin (POMC) (*1*). This precursor molecule is also present in the intermediate pituitary lobe (IL), in which ACTH and β-LPH are further processed to generate α-melanocyte stimulating hormone (α-MSH) and β-endorphin–related peptides (*2*). There is a differential regulation of synthesis and release of POMC and its derived peptides in AL and IL (*3*). Whereas the AL of virtually all species is regulated by way of central nervous system–derived (humoral) factors (peptides, biogenic amines) that are transported by the hypophyseal portal system, the only nerve supply to AL is a limited one, arriving via sympathetic innervation of blood vessels. Abundant serotonergic fibers were found in rat AL (*4*), although this was not confirmed in another study (*5*). Muscarinic (*6*), dopaminergic (*7*), and adrenergic receptors (*8*) are present in AL, and serotonergic uptake mechanisms (*9*, *10*) are reported to be present therein.

In contrast to the AL, the IL is poorly vascularized and receives essentially a dopaminergic and serotonergic innervation arising from the hypothalamus (*11*). Glucocorticoids, which are potent inhibitors of stimulated ACTH secretion from AL, act at a transcriptional level to inhibit both synthesis and release of POMC-related peptides in AL (*12*). Similar glucocorticoid treatment of AL and IL resulted in suppression of POMC messenger RNA (mRNA) in IL that was only one-tenth of that seen in AL (*13*); in another study, no suppression of POMC mRNA was observed (*14*). Glucocorticoid effects on AL, as in all other glucocorticoid-sensitive tissues, are mediated through interaction with a cellular receptor (*15*). The lack of effect of glucocorticoids on IL POMC levels is thought to be secondary to the lack of detectable glucocorticoid receptors in this lobe (*16*, *17*). Using immunocytochemistry, we localized the glucocorticoid receptor in the AL but not in adjacent cells of the IL (*16*). In other instances of glucocorticoid resistance, the glucocorticoid receptor decreased (*18*). In contrast to glucocorticoid, dopamine inhibited the release of POMC-derived peptides from IL but not AL (*19*). Administration of dopamine antagonists and agonists, respectively, increases and decreases POMC mRNA in neurointermediate lobe (NIL) but has no effect on the concentration of POMC mRNA in AL (*19*).

Because glucocorticoid receptors are found in nearly all tissues studied to date (*15*), and because of the wide range of metabolic actions of glucocorticoids subserved by such receptors, we investigated the reasons that glucocorticoid receptors are not detected in IL. One possibility is that glucocorticoid receptor expression is suppressed in IL. The release of IL peptides and the synthesis of IL POMC, as noted above, as well as IL cell growth (*20*) appear to be inhibited by