Mem. Inst. Oswaldo Cruz, Rio de Janeiro, Vol. 86, Suppl. III, 37-41, 1991

MICROORGANISMS-EXTRACELLULAR MATRIX INTERACTIONS: RELATION TO PATHOGENICITY — REVIEW

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Cell adhesion is the first necessary step for tissue invasion. It is a complex phenomenon shared by both, inflammatory and tumor cells, as well as by pathogenic microorganisms (Lopes et al., 1988). The unquestionable biological importance of cell adhesion prior to invasion, under normal or pathological conditions, led many groups to investigate its mechanisms.

Using different experimental models, it has been shown that selectivity is a major characteristic of cell adhesion. It assumes the existence of complementary molecules that promote cell-cell and cell-extracellular matrix (EM) interactions, although electrical charges and other non-specific binding forces may also be involved (Beachey, 1981). EM has been defined as a complex network of collagen and elastic fibers embedded in an amorfous and viscous substance constituted by proteoglycans and glycoproteins (Liotta et al., 1983). As a consequence, many of its components may be involved in cell adhesion.

This review will focus only on microorganisms-EM proteins specific interactions, aiming to present the state of the art on this particular aspect of microbial adhesion.

It has been only for the last twelve years that adherence of microbial pathogens to EM proteins has been adressed. At the present time all the major EM components (fibronectin, fibrinogen, vitronectin, collagen and laminin) have been associated with selective microbial attachment, and some specific receptors to these proteins have also been described.

Among parasitic protozoans that cause human disease, it has been shown that fibronectin binds specifically to trypanosomatids as *Trypanosoma cruzi* (Quaissi et al., 1984; Wirth & Kierzenbaum, 1984) and *Leishmania* (Wyler et al., 1985), and it has been suggested that these interactions should be important to parasites attachment and invasion of host cells. Another recent report has shown that the invasive parasite *Entamoeba histolytica* presents a fibronectin surface binding protein of 37 kDa (Talamas-Rohana & Meza, 1988). It was also demonstrated that this binding of fibronectin to ameba induces cytoskeleton reorganization as well as secretion of proteases leading to fibronectin degradation. These findings were correlated to the ability of *E. histolytica* to cause tissue damage, since the same results were not obtained when a non-invasive ameba strain was tested.

Binding to laminin, a major non-collagenous protein of basement membranes, have also been associated with protozoan pathogenicity. Silva-Filho et al. (1988) have demonstrated that an agressive strain of *Trichomonas vaginalis* presents a laminin receptor of 118 kDa. Moreover, a rapid rupture of an epithelial cell monolayer by the parasite was observed in the presence of laminin. These results pointed to the importance of laminin receptors for a closer contact between host cells and the parasite.

The role of laminin in enhancing parasitic damage was also suggested by Bouchara et al. (1990) who described laminin-binding proteins on *Candida albicans*. This opportunistic fungus has the ability to bind to exposed basement membranes, assumed as the first necessary step for systemic candidiasis (Klotz & Maca, 1988). This especies of yeast presents about 8000 laminin-binding sites per cell, composed by two molecules on cell extracts by immunoblotting: a 68 kDa band and a 60-62 kDa doublet. However, these proteins seem to be non-specific or multifunctional structures because fibrinogen and C3d are also recognized by them (Calderone et al., 1980).

Although the results obtained with these eukaryotic parasites are well documented, no further molecular characterization of these receptors have been achieved.

As bacteria are concerned, it is undoubtful that the number of reports showing bacteria-EM proteins interactions is greater than for parasitic eukaryotes. Table I shows a list of reports that demonstrate that several bacteria adhere to the EM

different proteins and point to the importance of this ability to virulence, as also stated by Vercellotti et al. (1985). None of these mentioned pathogens had either the molecules or the genes codifying for their putative receptors yet identified.

However, there are two receptors for EM proteins on bacteria that have their genes already cloned. One, is an uropathogenic *Escherichia coli* adhesin (Nowicki et al., 1987) which binds specifically to collagen type IV (Westerlund et al., 1989), and the other one is the *Staphylococcus aureus* fibronectin-binding protein (Flock et al., 1987; Signas et al., 1989). The *E. coli* fimbrial 15 kDa adhesin is considered a virulence factor, *vis a vis* its ability to promote an early bacteria interaction with intersticial tissue elements. This interaction may determine chronic nephritis. By its turn, the *S. aureus* fibronectin receptor has a molecular mass of 210 kDa and contains several fibronectin binding sites. Furthermore, this protein is sensitive to endogenous proteases and it was suggested that this characteristic should be important in the spreading of an infection, since bacterial detachment from the initial adhesion site seems necessary for progressive invasion (Froman et al., 1987).

Table II shows that *S. aureus* is the bacteria that has received most of the attention, probably because of its virulence. It presents, added to the above mentioned fibronectin receptor, a collagen binding protein of 135 kDa (Switalski et al., 1989), and its expression could be related to the ability to colonize collagen-rich tissues. Some of these sites are the targets of some strains of *S. aureus* that cause osteomyelitis and arthritis. Furthermore, our group have characterized a *S. aureus* 50 kDa laminin-binding protein (Lopes et al., 1985) which was not found on *S. epidermidis*, a non invasive bacteria. As the presence of laminin binding proteins on tumor cells have also been related to their invasive behavior (reviewed by Brentani et al., 1988), we decided to verify their eventual similarities. We started raising monoclonal antibodies against the affinity purified *S. aureus* receptor (Mota et al., 1988). The obtained IgM MAbs were shown to crossreact with tumor mammalian cells,

TABLE I

Specific interactions between various bacteria and extracellular matrix (EM)

Bacteria	EM components[a]	References
T. pallidum	Fn	Peterson et al. (1983)
	Fn, Ln and Col	Fitzgerald et al. (1984)
	Fn	Thomas et al. (1985)
	Fn	Thomas et al. (1986)
E. coli	Ln	Speziale et al. (1982)
	Fn	Froman et al. (1984)
S. enteritidis	Fn	Baloda (1988)
oral bacteria	Fn	Abraham et al. (1983)
	Fn	Simpson & Beachey (1983)
	Fn	Babu et al. (1983)
	Fg	Lantz et al. (1986)
	Ln	Switalski et al. (1987)
	Fn, Ln and Col	Winkler et al. (1987)
	Fn	Lowrance et al. (1988)
Streptococci	Ln	Switalski et al. (1984)
	Fn	Courtney et al. (1986)
	Fn	Butler et al. (1987)
	Vn	Valentin-Weigand et al. (1988)
Mycobacteria	Fn	Abou-Zeid et al. (1988)

a Fn: fibronectin; Ln: laminin; Col: collagen; Fg: fibrinogen; Vn: vitronectin.

and the best studied one (MAb SAR 1H12) was also able to bind to the surface of the protozoan *T. vaginalis* (Lopes et al., 1988). Moreover, it was demonstrated that mice injected with *ras* transfected fibroblasts preincubated with MAb 1H12 had a reduced number of lung colonies (Brentani et al., 1989). The same MAb was also successfully used for the prediction of human breast carcinoma prognosis (Marques et al., 1990). These results led us to postulate a possible evolutionary conservation of laminin-binding proteins from prokaryotes to eukaryotes (Brentani et al., 1987). In order to corroborate this hyphotesis, we are raising IgG MAbs against the 50 kDa *S. aureus* laminin receptor as well as studying in more depth the molecular interactions *per se* . We have recently verifyied that *S. aureus* adhesion to laminin is a divalent cation independent process that involves carbohydrate moieties of laminin molecule (manuscript in preparation).

Taken together, presented data claim for further molecular characterization of specific cell interactions with EM by microbial pathogens and by tumor cells, in order to develop new therapeutic approaches for these disabling diseases.

TABLE II

Staphyloccous aureus specific interactions with EM

EM components	References
Fn	Kuusela (1978)
Fn	Espersen & Clemmensen (1982)
Fn	Proctor et al. (1982)
Fn	Ryden et al. (1983)
Fn	Kuusela et al. (1984)
Fn and Col	Vaudaux et al. (1984)
Fn and Fg	Kuusela et al. (1985)
Ln	Lopes et al. (1985)
Col	Holderbauem et al. (1986)
Fn	Maxe et al. (1986)
Vn	Chhatwal et al. (1987)
Fn	Froman et al. (1987)
Fn	Flock et al. (1987)
Fg and Col	Ohtomo & Yoshida (1988)
Fn, Fg and Ln	Herrmann et al. (1988)
Fn	Signas et al. (1989)
Col	Switalski et al. (1989)
Fn	Vann et al. (1989)
Fn and Col	Miedzobrodzki et al. (1989)

ACKNOWLEDGMENT

To our student Edilberto Postol for typing the manuscript.

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