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ORIGINAL ARTICLE

Integrin Activation—the Importance of a Positive Feedback

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Abstract Integrins mediate cell adhesion and are essential receptors for the development and functioning of multicellular organisms. Integrin activation is known to require both ligand and talin binding and to correlate with cluster formation but the activation mechanism and precise roles of these processes are not yet resolved. Here mathematical modeling, with known experimental parameters, is used to show that the binding of a stabilizing factor, such as talin, is alone insufficient to enable ligand-dependent integrin activation for all observed conditions; an additional positive feedback is required.

Keywords Talin · Integrin · Receptor activation · Master equation · Positive feedback

1. Introduction

Integrins, large membrane-spanning heterodimeric proteins, were so named for their ability to link the extracellular and intracellular skeletons (Tamkun et al., 1986). As an important class of cell adhesion receptors they participate in a wide range of biological interactions, including development, tissue repair, angiogenesis, inflammation and hemostasis (Horwitz and Webb, 2003). Cell adhesion and detachment as well as controlled actin polymerization inside the cell are of particular importance in cell migration. The speed of cell movement depends on the density of integrins and ligands as well as their affinity of binding (Palecek et al., 1997). Integrins are key components of focal adhesions, dynamic multiprotein complexes that are involved in the regulation of cell adhesion and migration. Focal adhesions (Zamir and Geiger, 2001) provide a physical link between integrins and the actin cytoskeleton as well as sites for signal transduction into the cell

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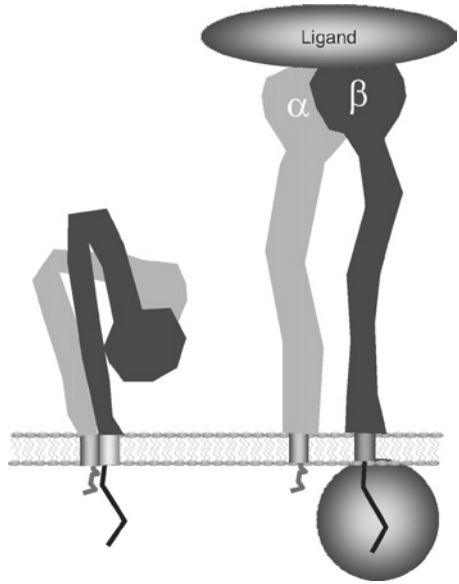

Fig. 1 A simple model of integrin activation. Integrins exist in either a closed (LHS) or open conformation (RHS); the open, high affinity form, can be stabilized by binding of extracellular ligand or intracellular proteins. The open conformation triggers downstream signaling and is termed active.

interior. Information about identified interactions and players in these complexes is ever-increasing but our overall understanding of how the ensemble works remains relatively poor.

According to the current model of integrin activation, ligand binding shifts the equilibrium between different integrin conformations to the active one (Hynes, 2002). The two extreme conformations of this allosteric protein are a bent or "closed" conformation which represents the low affinity state for ligand and an "open" conformation that will bind with high affinity to ligand (Fig. 1). Conformational changes in the extracellular domain affect the cytoplasmic tails, which are separated in the open conformation but not in the closed. Separation of the cytoplasmic domains promotes their interaction with cytoskeletal and signal transduction molecules, and thus the activation of integrins and downstream signaling. The conformational equilibrium can be influenced both by ligand binding to the extracellular domain (outside-in signaling) and by binding of cytoplasmic proteins to the separated cytoplasmic domains (inside-out signaling). Talin, a large intracellular protein that binds integrin cytoplasmic tails and the actin cytoskeleton is, for example, essential for integrin activation (Campbell and Ginsberg, 2004). As well as changes in affinity induced by structural changes, integrins can also modulate their avidity by clustering, thus changing the valency of their interactions with ligand (Carman and Springer, 2003).

Previous theoretical studies have addressed the mechanism of integrin clustering (Ward and Hammer, 1994; Irvine et al., 2002) but they have not yet explored whether ligand binding is sufficient or if other factors such as clustering are

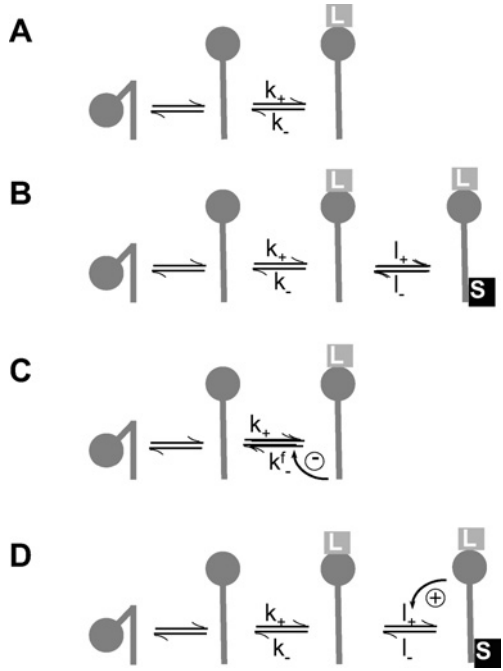

Fig. 2 Four possible mechanisms for integrin activation. (A) Ligand-binding is sufficient for integrin activation, other factors are only important for down-stream signaling events. (B) A stabilizing factor (such as talin) is necessary in addition to ligand binding. (C) A ligand induced positive feedback (based for instance on integrin self-interaction) induces integrin activation. (D) A positive feedback involving further signaling molecules is necessary for integrin activation. The symbols represent simple variants of those in Fig. 1. *L* refers to ligand, *S* to a stabilizing factor. The rate constants correspond to those used in the models.

necessary for integrin activation. In principle, ligand-dependent integrin activation can be enabled by any of the four different mechanisms depicted in Fig. 2. (A) Extracellular ligand alone is sufficient to activate integrins and other factors are only important for downstream signaling (Fig. 2A); (B) Ligand-dependent integrin activation requires the binding of an intracellular stabilizing factor that interacts with and stabilizes the on state (Fig. 2B). (C) A positive feedback, provided either by integrin–ligand pairs themselves or by self-interactions, is important (Li et al., 2003) (Fig. 2C); (D) A positive feedback that increases the activity of an intracellular stabilizing factor is required (Fig. 2D). The latter would need to be based on a larger intracellular signaling network.

Mathematical modeling is used in the following to evaluate the physiological potential of these mechanisms. The analysis suggests that, at least for some physiological conditions, binding of ligand (even if it is preclustered) and/or a stabilizing factor (Fig. 2A,B) are insufficient for ligand-dependent integrin activation; a positive feedback (Fig. 2C,D) is required which results in the further stabilization of the active conformation. Integrin clustering is a likely consequence of such a positive feedback.

2. A model for integrin activation

Overly simplified, integrins can be taken to exist in one of two states, a closed low affinity or an open high affinity conformation. In the absence of ligand the equilibrium is biased towards the inactive, low affinity conformation (Tadokoro et al., 2003). Binding of ligand (L) stabilizes the active, high affinity conformation. Under physiological conditions integrin activation therefore requires ligand binding and accordingly the physiological relevance of the mechanisms depicted in Fig. 2 can be evaluated by analyzing the extent to which they promote ligand binding. While the relationship between ligand binding and cellular action in response to integrin activation is unlikely to be linear we will show that the mechanisms differ substantially in the level to which they promote integrin–ligand binding such that they can be readily classified as "non-supportive" or "activating." The analysis can be greatly simplified if we determine the fraction of ligands bound by integrins rather than the fraction of integrins bound to ligands. In this case, integrins in the closed, low affinity conformation do not have to be considered explicitly. We will assume that there is a constant number of unbound integrins in the high affinity conformation since any integrin that binds to ligand can be replaced rapidly from the integrins in the low affinity conformation by conformational changes. While ligand binding will eventually deplete the pool of unbound integrins, this does not need to be included in an analysis of mechanisms for integrin signal initiation: if integrin–ligand binding occurs to a level that integrin depletion becomes relevant the activation mechanism can be considered successful independently of the exact final number of integrin–ligand complexes.

Under physiological conditions, the ligand is expected to be sufficiently dense that spatial details and diffusion constraints can be neglected in the initial steps of focal adhesion assembly. Transport of integrins from parts of the cell that are not in contact with the substrate is not relevant for the initial activation of cell adhesion signaling cascades and is not considered in this model.

The model follows the binding of single integrins to ligands; the probability of integrin–ligand complex formation can be calculated by solving the appropriate Master equation. The Master equation is a gain–loss equation for the probabilities of the separate states with n integrin–ligand complexes (van Kampen, 1992), from which the macroscopic kinetic equation can be derived when the density fluctuations are negligible. In order to decide which of the four mechanisms depicted in Fig. 2 is sufficient for ligand-dependent integrin activation, the fraction of ligand bound by integrin is determined for each case.

2.1. Ligand engagement is not sufficient for integrin activation

According to the first mechanism (Fig. 2A), ligand-dependent integrin activation does not require any further supporting processes and interactions. The Master equation for the formation of i integrin–ligand complexes is thus given as

$$\dot{p}_i = k_-(i+1)p_{i+1} + k_+(L-i+1)p_{i-1} - (k_- i + k_+(L-i))p_i \qquad (1)$$

with $p_i = 0$ if $i \notin [0, L]$, where p_i is the probability that i (open) integrins are bound to a ligand with L sites, k_+, k_- refer to the on- and off-rate of the integrins. The on-rates include the density of integrins which are taken to be constant (see previous section). The first two terms in (1) represent the gains of state i due to the transition from other states, that is due to unbinding of an integrin from a complex with $i + 1$ integrins (first term) or the binding to a complex with $i - 1$ integrins (second term). The bracketed term is the loss due to transitions from i into other states either by unbinding or binding of an integrin.

For the steady state ($\dot{p}_i = 0$) we obtain from (1)

$$p_i = \frac{\binom{L}{I}\left(\frac{k_i}{k_-}\right)}{\left(1 + \frac{k_+}{k_-}\right)^L}. \tag{2}$$

The expectation value for the number of integrins bound to a given ligand with L binding sites is given by $\langle I_b \rangle = \sum_{i=0}^{L} i p_i$. Integrin activation therefore requires $p_i \gg p_0 (i > 0)$ and thus $\frac{k_+}{k_-} \gg 1$ (Fig. 3), which corresponds to a high on- and low off-rate. This is because the probability of i bound integrins is proportional to the ith power of $\frac{k_+}{k_-}$ and only for $\frac{k_+}{k_-} > 1$ this probability increases with increasing i, that is with increasing numbers of integrins bound.

$k_- \sim 1\ \mathrm{s}^{-1}$ has been established experimentally (Vitte et al., 2004); the two-dimensional on rate is more difficult to determine and has to be calculated from the two-dimensional dissociation constant which itself is difficult to measure and often obtained via its three-dimensional counterpart $K_D^{3d} \sim 6 \times 10^{-8}$ M for the high affinity conformation (Faull et al., 1993; Suehiro et al., 1997) and $K_D^{3d} > 1\,\mu$M for the low affinity conformation (Faull et al., 1993). It is generally assumed that the two dissociation constants are linearly related such that $K_D^{2d} = \eta K_D^{3d}$, the value of the conversion factor η is, however, still a matter of debate (Moy

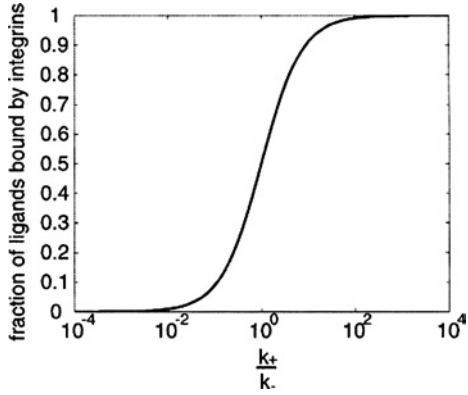

Fig. 3 Ligand engagement is not sufficient for integrin activation. The integrin saturation of the ligand, $\frac{\langle I_b \rangle}{L}$, is plotted against the integrin–ligand association constant $K_a = \frac{k_+}{k_-}$; $L = 10$. As discussed in the text, experimental data suggest that $\frac{k_+}{k_-} \ll 1$ such that the fraction of activated integrins would be very small.

et al., 1999), since theoretical estimates are not in complete agreement with latest experimental results. According to theoretical estimates for a protein complex that spans about 20 nm, $\eta = 1.2 \times 10^{19}\,\mathrm{m}^{-2}\,\mathrm{M}^{-1}$ (Bell, 1978). Studies employing protein-coated beads report $\eta = 8 \times 10^{24}\,\mathrm{m}^{-2}\,\mathrm{M}^{-1}$ (Moy et al., 1999) and $\eta = 10^{22}\,\mathrm{m}^{-2}\,\mathrm{M}^{-1}$ (Kuo and Lauffenburger, 1993). The lower η value is corroborated by measurements of the two-dimensional dissociation constant for the LFA-3/CD2 adhesion pair that were carried out using cells instead of beads (Dustin et al., 1996). While there are experimental difficulties involved in getting an exact measurement of this parameter, the discrepancy between the theoretical and experimental estimates may well reflect a lower affinity of integrins when membrane bound, possibly due to steric constraints which will have a profound impact on this allosteric protein. We will therefore follow Moy et al. (1999) who used $\eta = 10^{22}\,\mathrm{m}^{-2}\,\mathrm{M}^{-1}$ rather than their own estimate for converting integrin dissociation constants. For $\eta = 10^{22}\,\mathrm{m}^{-2}\,\mathrm{M}^{-1}$ we find $k_{\mathrm{on}} \sim 2 \times 10^{-3}\,\mu\mathrm{m}^2\,\mathrm{s}^{-1}$. In order to determine the frequency of integrin–ligand bond formation the density of open integrins needs to be taken into consideration. The average total (closed and open) integrin density on the cell surface has been estimated as $\rho \sim 1\text{–}3 \times 10^2\,\mu\mathrm{m}^{-2}$ (Wiseman et al., 2004). At least in some cells (e.g., platelets) more than 95% of all integrins are in the closed inactive conformation in the absence of ligand (Tadokoro et al., 2003); the density of integrin in the open conformation is therefore small ($\rho_o < 10\,\mu\mathrm{m}^{-2}$). Given that $k_+ = k_{\mathrm{on}}\rho_o$ this implies, using the experimental estimate for η, that $k_+ \sim 10^{-1}$ to $10^{-2}\,\mathrm{s}^{-1}$ such that $\frac{k_+}{k_-} \ll 1$, which is insufficient to drive integrin activation. A larger k_+ can be achieved if a larger fraction of integrins is in the open conformation already in the absence of ligand. However, this leads to ligand-independent integrin activation. We can conclude that for experimentally determined parameters the model predicts that ligand-dependent integrin activation will not occur without further supporting interactions.

2.2. A stabilizing factor is not sufficient for ligand-dependent integrin activation

Proteins that bind and stabilize the active integrin conformation have been suggested to be important for integrin activation (Fig. 2B). The Master equation derived in the previous section can be extended to include such factors that stabilize integrin–ligand binding. While talin is an excellent candidate for such a protein (and we will therefore call this factor talin in the following), the analysis is kept general enough such that it could be extended to any cytoplasmic protein that prolongs the open active conformation by binding to the active integrin.

Much as in the case of integrins, talins can be considered to exist in two forms of different activity. Cytoplasmic talin is inactivated by self-interactions and only the "open" conformation can bind to the membrane (PIP2), integrins and other proteins. Therefore, we can again simplify the model by only considering the open active form, whose concentration can again be taken to be constant, since any open talin bound to integrins can be expected to be rapidly replenished from the pool of closed talins. Given the low abundance of both open talin and integrin, complexes of the two are taken to be absent in the absence of ligand. The gains and losses of the state with i integrins and t talins bound can again be translated into the linear

Master equation

$$\begin{aligned}\dot{p}_{i,t} = {} & k_{-}(i+1-,t)p_{i+1,t} + k_{-}^{*}(t+1)p_{i+1,t+1} \\ & + k_{+}(L-i+1)p_{i+1,t} \\ & + l_{-}(t+1)p_{i,t+1} + l_{+}(i-t+1)p_{i,t-1} \\ & - (k_{-}(i-t) + k_{-}^{*}t + k_{+}(L-i) + l_{+}(i-t) + l_{-}t)p_{i,t}\end{aligned} \tag{3}$$

with $p_{i,t} = 0$ if $t > i; t, i < 0; t, i > L$. Here $p_{i,t}$ is the probability that i (open) integrins and t (open) talins are bound to the ligand with L sites, $p_{i,t} = 0$ if $t > i$ reflects the fact that talins can only attach to the ligand indirectly by binding to integrins. $k_{+}, k_{-}, l_{+}, l_{-}$ refer to the on- and off-rates of the integrins and talins respectively. The on-rates include the density of integrin and talin which are taken to be constant (see above). k_{-}^{*} refers to the integrin off-rate when talin is bound ($k_{-}^{*} \leq k_{-}$).

For the steady state ($\dot{p}_{i,t} = 0$) we obtain from (3)

$$p_{i,t} = \frac{\binom{L}{t}\binom{L-t}{i-t} a^{L-i} b^{i-1}}{\sum_{i=0,t=0}^{i=L,t=L} \binom{L}{t}\binom{L-t}{i-t} a^{L-i} b^{i-t}} \tag{4}$$

with $a = \frac{k_{-}(k_{-}^{*}+l_{-})+l_{+}k^{*}}{l_{+}k_{+}}$, $b = \frac{k_{-}^{*}+l_{-}}{l_{+}}$ for $i \geq t$ and $p_{i,t} = 0$ for $i < t$. The expectation value for the number of integrins and talins bound to a given ligand with L binding sites is given by $\langle I_{\mathrm{b}} \rangle = \sum_{i=0}^{L} i \sum_{t=0}^{L} p_{i,t}$ and $\langle T_{\mathrm{b}} \rangle = \sum_{t=0}^{L} t \sum_{i=0}^{L} p_{i,t}$, respectively. For strong ligand binding in the absence of talin binding $p_{L,0} \gg p_{0,0}$ we require $b > a$ and we recover the condition $k_{+} \gg k_{-}$ found in the previous section. If talin binds the condition becomes $\sum_{t=0}^{t=L} p_{L,t} \gg p_{0,0}$ and thus $a < b + 1$. This condition can be met if either $a < b$ or $a < 1$. Assuming that the integrin–ligand off-rate in the presence of talin is very small ($k_{-}^{*} \ll 1$), $a < b$ still requires $k_{-} < k_{+}$, (high integrin–ligand affinity) which we have found above to disagree with experimental estimates. The condition $a < 1$ can be met if either $k_{-} \ll k_{+}$ or if $k_{-} > k_{+}$ and $l_{-} \ll l_{+}$, that is integrin activation would be possible despite a low integrin–ligand affinity if the integrin–talin affinity were sufficient high (Fig. 4). However, such high integrin–talin affinity would also lead to integrin activation in the absence of ligand binding. We can therefore conclude that a stabilizing factor alone is not sufficient for ligand-dependent integrin activation.

2.3. A positive-feedback is required for ligand-dependent integrin activation

The remaining two mechanisms in Fig. 2 both involve a positive feedback. Here, Fig. 2C considers a feedback mechanism that only involves the integrin–ligand pair itself while according to Fig. 2D a larger network would be necessary. Both mechanisms are analysed in the following.

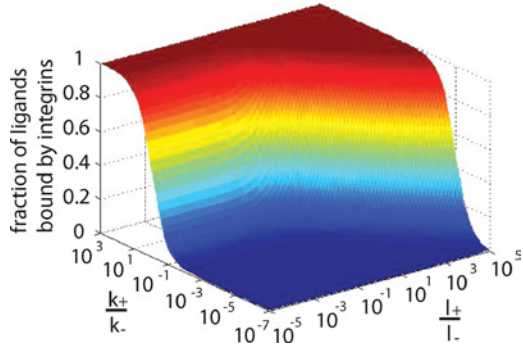

Fig. 4 A stabilizing factor is not sufficient for ligand-dependent integrin activation. The fraction of ligand bound by integrin, $\frac{\langle I_b \rangle}{L}$, is plotted against the integrin–ligand association constant $K_a = \frac{k_+}{k_-}$ and the integrin–talin association constant $K_a = \frac{l_+}{l_-}$ for $k_-^* = 0$; $L = 10$. For experimental estimates of these association constants the activated fraction is small.

2.4. A positive feedback that is based on the integrin–ligand pair

A positive feedback only involving the integrin–ligand pair (Fig. 2C) could either be enabled by integrin–integrin interactions in the open form (Li et al., 2003) or by a ligand-induced conformational change that leads to a higher affinity of binding. In both cases this positive feedback ought to be triggered once a certain (small) number of integrins is engaged in close proximity. Such interaction can thus be captured in the model by replacing k_- with k_-^f in (1) and setting $k_-^f = k_-^o/(1 + \frac{k_c i^n}{(i+K)^n})$, where k_-^o refers to the integrin–ligand off-rate in the absence of a positive feedback, k_c determines the strength with which the feedback reduces the integrin–ligand offrate, and K and n limit the effect of integrin–integrin interactions to local interactions. The model does not contain any spatial information and it is thus assumed that integrins either bind to preclustered ligand, or preferentially in the vicinity of other bound integrins. Note that the assumption that ligand–integrin interactions are short-lived in the absence of integrin–integrin interaction will lead to such preferential binding in the vicinity of bound integrins. For the steady state ($\dot{p}_i = 0$) we then obtain from (1)

$$p_i = \frac{\binom{L}{i}\left(\frac{k_+}{k_-}\right)^i \prod_{j=0}^{i}\left(1 + \frac{k_c j^n}{(j+K)^n}\right)}{\sum_{l=0}^{L}\binom{L}{l}\left(\frac{k_+}{k_-}\right)^l \prod_{j=0}^{l}(1 + \frac{k_c j^n}{(j+K)^n})}. \tag{5}$$

Given that K and n need to be chosen such that only local integrin–integrin interactions reduce the ligand–integrin off-rate, for sufficiently large k_c (5) can be approximated by

$$p_i = \frac{\binom{L}{i}\left(\frac{k_+ k_c}{k_-}\right)^i}{\sum_{l=0}^{L}\binom{L}{l}\left(\frac{k_+ k_c}{k_-}\right)^l} \tag{6}$$

(6) and (2) are similar and only differ in the factor k_c. The same argument thus applies such that $k_c \gg \frac{k_-}{k_+} \sim 10^2$–$10^3$ is required to enable ligand-dependent integrin activation (Fig. 3). In the analysis of (2) $\frac{k_+}{k_-}$ was determined for the high affinity integrin–ligand interaction and a further ligand-induced affinity increase by 100–1000 fold is impossible. Integrin–integrin interactions strong enough to reduce the high affinity dissociation constant by a further factor of 10^2–10^3 are also unlikely. Thus, a feedback loop only involving integrins is unlikely to drive ligand-dependent integrin activation.

2.5. A positive feedback loop based on a regulatory network can enable ligand-dependent integrin activation

The last mechanism (Fig. 2D) to be analyzed is one that considers a regulatory network that mediates the positive feedback. This mechanism involves a stabilizing factor whose activity is increased in response to ligand binding. Such positive feedback has indeed been reported in the form that ligand-bound integrins as well as talins trigger an increase in PIP2, which in turn increases the recruitment of talin to the membrane, and thereby the talin-integrin complex formation (l_+) (Garcia-Alvarez et al., 2003; Martel et al., 2001). The talin density on the membrane will thus be very small when integrins are inactive and increase when ligands increase the integrin activity. This positive feedback can be incorporated into the model as

$$l_+ = l_c \frac{(t+1)^n}{(t+1)^n + K^n}, \tag{7}$$

such that the talin on-rate l_+ depends on the number of talins in the integrin–ligand complex with K being the Hill constant, n the Hill coefficient and l_c some proportionality factor. While many other formulations of such feedback are possible, this saturation form captures the likely talin dependence of the membrane PIP2 concentration, which will be low below a certain talin threshold and eventually become saturated.

The steady state for $p_{i,t}$ is now more difficult to derive but numerical studies show that such positive feedback indeed enables ligand-induced integrin activation as long as $K/L \ll 1$ (Fig. 5). Note that, as before in the case of integrin–integrin interactions, ligand-dependent integrin activation requires the proportionality factor l_c to be of order 10^2–10^3 In case of talin recruitment this is reasonable since local PIP2 production may lead to a 100–1000 fold increase in the local membrane talin density. A ligand-independent increase in l_+, due to a signaling dependent increase in a factor that stabilizes the open integrin conformation, will also lead to integrin activation. This is likely to provide the mechanistic basis for inside-out signaling.

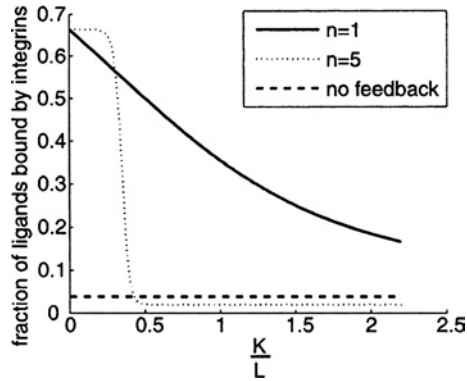

Fig. 5 A positive feedback enables ligand-dependent integrin activation. The fraction of ligand bound by integrin, $\frac{\langle I_b \rangle}{L}$, is plotted in the absence (–) or presence of a talin feedback regulation against the Hill constant K (Eq. 7) normalized by the number of binding sites L for different Hill coefficients $[n = 1(-); n = 5(\cdots)]$. Parameters were set to $L = 10, k_+ = 0.1, l_c = 10^2, k_- = 5, k_-^* = 10^{-3}, l_- = 1$ It can be seen that as long as positive feedback is initiated upon binding of few integrins (small $\frac{K}{L}$), a large active integrin fraction is obtained.

We thus conclude that ligand-dependent integrin activation requires $k_- \gg k_+, l_- \gg l_+$ in the resting and $k_- \ll k_+, l_- \ll l_+$ in the active state. The first condition is met by the binding of the stabilizing factor which reduces k_-, and the second condition is enabled by a positive feedback that leads to an increases in l_+ in the presence of ligand.

3. Conclusion

The analysis of possible mechanisms for integrin activation suggests that a positive feedback is required for ligand-dependent integrin activation. Thus the ligand-integrin affinity appears to be too low to stabilize the active integrin conformation in the absence of a further stabilizing factor such as talin. To ensure that ligand-independent integrin activation by such a stabilizing factor alone is impossible a positive feedback that upregulates the stabilizing factor upon ligand binding is required.

This conclusion strongly depends on the order of magnitude of the conversion factor η between the two- and three-dimensional dissociation constants and further careful measurements of this parameter will be important. While ligand-dependent integrin activation would be possible in the absence of further stabilizing interactions if the theoretical rather than the experimental estimates for η were correct (that is if η were 1000 times smaller), available experimental information is very much in favour of the experimental estimate that has been used in this study. In addition to the argument already given (see above) further experimental observations corroborate the notion that the physiological integrin–ligand affinity is tuned such that integrin activation depends on supporting factors. Thus, mutations in the β-tail that disrupt the talin–integrin interaction markedly reduce the fraction of

active integrins (Tadokoro et al., 2003). This reduction can be overcome by binding of an antibody that stabilizes the high affinity conformation (Tadokoro et al., 2003) which is in agreement with the model prediction that a higher ligand–integrin affinity can enable talin-independent integrin activation. With integrin activation balanced on a knife-edge small changes in the affinity, density and conformational bias of integrins can have a large impact on the cell's adhesiveness and motility—as is observed in experiments (Palecek et al., 1997).

An advantage of a positive feedback regulation is the regulatory potential. Signaling processes can affect the positive feedback, providing a basis for inside-out signaling. It is likely that the observed integrin clustering is a result of such a positive feedback mechanism; a local increase in the density of a stabilizing factor will facilitate the formation of further integrin–ligand bonds in the vicinity of existing ones. Clustering would then result from a process that enables long-lived integrin–ligand interactions but is not of itself essential. The concept that ligand binding and clustering are independent processes is in agreement with the observation in *Drosophila* that integrins can still bind to the extracellular matrix in the absence of talin but fail to cluster (Brown et al., 2002).

The feedback loop that is considered in the current model only comprises a stabilizing factor (such as talin) and a way of increasing the concentration of the stabilizing factor, such as by PIP2 formation. Many more players are known to be involved and understanding their relative contributions will be important. Here, especially the role of PIPKIγ will be of interest. While PIPKIγ produces PIP2 and thus increases talin recruitment to the membrane, PIPKIγ itself is recruited to the membrane by talin (Di Paolo et al., 2002) and competes with the integrin β tail for talin binding (de Pereda et al., 2005). Integrin activation leads to FAK activation and a FAK-enhanced Src-mediated phosphorylation of PIPKIγ further increases its affinity for talin (Ling et al., 2002; Arias-Salgado et al., 2003). PIPKIγ therefore appears to play an important role both in integrin activation and the turnover of focal contacts. A combination of modeling and experiment, of the sort described here, is expected to shed more light on this complex regulatory network.

Acknowledgements

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