Paratopic interaction, a mechanism in the generation of structure bound enzymatic activity

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Summary. A general mechanism is recognized that can cause specific enzymatic activity at interphases. It consists of 2 proteins bound in close juxtaposition at a micelle or membrane surface. One, the enzyme *sensu strictu*, bears the active site, the other, the paraenzyme, is essential for generation or specific modification of the enzymatic activity.

It is the purpose of this report to draw attention to a kind of interaction between protein molecules and an interface, that can regulate, or even generate, enzymatic activity. The basic unit of this concept consists of 2 different protein molecules adsorbed next to each other onto an interface. This configuration constitutes an enzymatically active moiety. The active site is present on one of the 2 molecules, called the active site carrier; the enzymatic activity, however, is governed by the presence of the second protein molecule, called the paraenzyme. For this kind of interaction we suggest the name *paratopic interaction*.

Enzymatic activities generated by paratopic interaction

<table>
<thead>
<tr>
<th>Surface</th>
<th>Active site carrier</th>
<th>Para-enzyme</th>
<th>Substrate</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipid micelle</td>
<td>Factor X&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Factor V&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Prothrombin</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Phospholipid micelle</td>
<td>Factor IX&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Factor VIII&lt;sub&gt;a&lt;/sub&gt;</td>
<td>Factor X</td>
<td>C&lt;sub&gt;4&lt;/sub&gt; and C&lt;sub&gt;2a&lt;/sub&gt;</td>
</tr>
<tr>
<td>Erythrocyte surface</td>
<td>C&lt;sub&gt;1&lt;/sub&gt;</td>
<td>C&lt;sub&gt;1&lt;sub&gt;q&lt;/sub&gt; and antibody</td>
<td>C&lt;sub&gt;4&lt;/sub&gt; and C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>Erythrocyte surface</td>
<td>C&lt;sub&gt;2a&lt;/sub&gt;</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;</td>
<td>ATP</td>
<td>C&lt;sub&gt;2&lt;/sub&gt; and C&lt;sub&gt;1&lt;sub&gt;c&lt;/sub&gt; and C&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>TUA-particles</td>
<td>F&lt;sub&gt;1&lt;/sub&gt;</td>
<td>F&lt;sub&gt;2&lt;/sub&gt;</td>
<td>(Rutamycin-sensitive)</td>
<td>ADP+P&lt;sub&gt;i&lt;/sub&gt;</td>
</tr>
<tr>
<td>Phospholipid - F&lt;sub&gt;4&lt;/sub&gt;</td>
<td>SDH</td>
<td>cyt. b</td>
<td>Ubiquinone Oxidised (TTB-sensitive)</td>
<td>Reduced</td>
</tr>
</tbody>
</table>
paratopic interaction (from the Greek para – next and topos – place). It is fundamentally different from allo-
steric interaction in that it occurs at an interface only and from allotropic interaction in that an interaction
between proteins is essential.

Materials and methods. Paratopic interaction in general is
recognized by a) solubilizing the intact system which
step can be omitted in the systems existing in blood plasma
as they are already in a solubilized form. Then b) separa-
tion of the constituents which can be increased 1000fold by addition of phospholipid and factor V4; b) when both proteins are
bound to the same micelle, prothrombinase activity generates;
c) the kinetics for the formation of prothrom-
binase activity are in accordance with the model proposed.

In the prothrombinase complex, the active site is located
in the factor Xa molecule, because a) pure factor Xa has a
small but detectable prothrombinase action that can be
increased 1000 fold by addition of phospholipid and factor V4; phospholipid and factor V4 have no prothrom-
binase action either alone or in combination; b) factor Xa is an esterase that can split synthetic esters (e.g. tosylargininemethylester) and that can be inhibited by diisopropylfluorophosphate. No enzymatic properties of factor V4 have been found.

Another example of paratopic interaction is the enzyme
that converts factor X into its activated form via the
intrinsic blood coagulation pathway. It consists of the
coagulation factors IXa and VIIla adsorbed onto a phos-
pholipid micelle. Factor IXa is the active site here and factor VIIla is the paraenzyme. Paratopic interactions
are not restricted to the blood coagulation reactions.
The component C1a is a proenzyme which, when bound to a cell surface via C1a and one IgM or 2 adjacent IgG antibody molecules, develops into an active esterase. The natural substrates of this esterase are the complement factors C4 and C2 that are converted into active
forms. The latter 2 components are capable of combining and can also be adsorbed onto a cell surface.

A surface bound enzyme then results that can convert
a small but detectable prothrombinase action that can be
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A surface bound enzyme then results that can convert

phosphorylation. In this work it is shown that among
others the protein fraction F3 and F4 can be prepared
from the inner membrane of beefheart mitochondria. F3 has
ATPase activity, but only when combined with F4 and
a particular fraction from the inner mitochondrial
membrane called TUA particles, this ATPase becomes
sensitive to rutamycin (or oligomycin) as in the intact
mitochondrion. A 6th example can be found in the mitochondrion. Isolated succinate dehydrogenase (SDH) only accepts ubiquinone as a substrate and is only sensitive to inhibition by 4,4,4-
trifluoro-1-(2-thienyl)-1,3-butanedione (TTB) when
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