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                  10        20        30        40        50        60        70        80        90
                   .         .         .         .         .         .         .         .         .
Accutin                                                GAQCTAGPCCWPCFKLKEGTICRRARGDDLDDYCNGISADCPRNPYY
Echistatin                                               ECESGPCCRNCKFLKEGTICKRARGDDMDDYCNGKTCDCPRNPHKGPAT
Eristocophin                                           RQEEPCATGPCCRRCKFKRAGKVCRVARGDWNNDYCTGKSCDCPRNPWNG
Eristostatin                                           QWWPCATGPCCRRCKFKRAGKVCRVARGDWNDDYCTGKSCDCPRNPWNG

Albolabrin             EAGEDCDCGSPAN --- PCCDAATCKLLPGAQCGEGLCCDQCSFMKKGTIRRARGDDLDDYCNGISAGPRRNPLHA
Barbourin              EAGEECDCSSPEN --- PCCDAATCKLRPGAQCADGLCCDQCRFMKKGTVCRVAKGDWNDDRCTGQSADCPGLYG
Flavoridin(triflavin)    GEECDCGSPSN --- PCCDAATCKLRPGAQCADGLCCDQCEFKKKTGICRIARGDFPDDRCTGLSMDCPRWNDL
Halysin                EAGEECDCGSPGN --- PCCDAATCKLRQGAQGADGLCCDQCRFMKKGTVCRIARGDDMDDYCNGISAGCPRNPF
Kistrin (rhodostomin)    GKECDCSSPEN --- PCCDDATCKLRPGAQCGEGLCCEQCKFSRAGKICRIPRGDMPDDRCTGQSADCPRYH
Trigramin              EAGEDCDCGSPAN --- PCCDAATCKLIPGAQCGEGLCCDQCSFIEEGTVCRIARGDDLDDYCNGRSAGCPRNPFH

Bitistatin VSPPVCGNKILEQGEDCDCGSPAN CQD QCCNAATCKLTPGSQCNHGECCDQCKFKKARTVCRIARGDWNDDICTGKSSDCPWNH
 (arietin)          .         .         .         .         .         .         .         .         .
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Fig. 1. Amino acid sequences of disintegrins in single-letter code. Spaces are inserted into amino acid sequences of medium disintegrins for better alignment with bitistatin (arietin).

of homology with each other in the arrangement of cysteines, except for the extra cysteine in the C-terminal portion of short disintegrins and the extra disulfide bridge, Cys^{3}-Cys^{24} of bitistatin.[25] It has been confirmed that an RGD sequence appears in a hairpin loop composed of 13 amino acids, and is maintained in an appropriate conformation by S-S bridges. NMR studies on disintegrins have revealed that the RGD sequence stands at the apex of the mobile loop.[26] The RGD sequence substitutions of ^{24}Arg in echistatin[27] and ^{49}Arg and ^{51}Asp in kistrin[28] result in loss of disintegrin activity. The S-S bridging pattern in disintegrins has been determined in 5 disintegrins: (1) albolabrin, (2) kistrin and flavoridin, and (3) echistatin and eristostatin.[25,29] Upon reduction of the S-S bridge, "linear" disintegrins display little biological activity.

Over the last decade, extensive research on RGD disintegrins focused on their interaction with platelet integrin $\alpha_{IIb}\beta_3$, and this effort led to the development of novel antiplatelet and antithrombotic drugs patterned on the disintegrin structure.[30,31]

Applications of Disintegrins

Disintegrins were once considered to be highly potential antiplatelet drugs; however, thrombocytopenia was observed as a side effect with echistatin when it was infused into baboons.[32,33] In addition, possible antigenicity and a brief half-life in circulation limit the development of intact disintegrins as therapeutic agents. However, many extensive studies have revealed some potential uses of disintegrins in the design of antithrombotic agents, diagnosis of cardiovascular diseases, and as novel tools for the study of cell adhesion, cell migration, angiogenesis and some integrin-related diseases.

Design of Antithrombotic Drugs

Abnormal platelet hyperactivity contributes significantly to the formation of arterial thrombi in coronary atherosclerotic diseases and embolic stroke, leading to occlusion of arterial vessels, and the subsequent deficient oxygen supply to vital organs such as the heart and brain.[11,12] Thus, the reduction of platelet hyperactivity is an important therapeutic approach. The pivotal role of the RGD motif in integrin-mediated cell adhesion with extracellular matrices and plasma proteins has inspired many investigators to design RGD-mimetics as antithrombotic agents.[34] Although smaller linear peptides containing the RGD sequence have been shown to inhibit fibrinogen binding to activated platelets and platelet aggregation, they only exhibit low affinity toward platelet integrin $\alpha_{IIb}\beta_3$, with weak antiplatelet activity.[35] In contrast, the naturally occurring disintegrins are about 500~1000 times more potent than the linear RGD-mimetics in inhibiting platelet aggregation. Based on the specific steric structure of the RGD loop of these disintegrins, a series of RGD/KGD-mimetics, including cyclic derivatives have