NOTE

Cell Adhesion Molecules for Targeted Drug Delivery

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ABSTRACT: Rapid advancement of the understanding of the structure and function of cell adhesion molecules (i.e., integrins, cadherins) has impacted the design and development of drugs (i.e., peptide, proteins) with the potential to treat cancer and heart and autoimmune diseases. For example, RGD peptides/peptidomimetics have been marketed as anti-thrombic agents and are being investigated for inhibiting tumor angiogenesis. Other cell adhesion peptides derived from ICAM-1 and LFA-1 sequences were found to block T-cell adhesion to vascular endothelial cells and epithelial cells; these peptides are being investigated for treating autoimmune diseases. Recent findings suggest that cell adhesion receptors such as integrins can internalize their peptide ligands into the intracellular space. Thus, many cell adhesion peptides (i.e., RGD peptide) were used to target drugs, particles, and diagnostic agents to a specific cell that has increased expression of cell adhesion receptors. This review is focused on the utilization of cell adhesion peptides and receptors in specific targeted drug delivery, diagnostics, and tissue engineering. In the future, more information on the mechanism of internalization and intracellular trafficking of cell adhesion molecules will be exploited for delivering drug molecules to a specific type of cell or for diagnosis of cancer and heart and autoimmune diseases. J Pharm Sci 95:1856–1872, 2006

Keywords: cell adhesion; RGD; ICAM-1; LFA-1; targeted delivery; peptide; biomaterial; diagnostic; integrin

Abbreviations used: Ad2, Adenovirus type 2; APC, antigen-presenting cells; RGE, Arg-Gly-Glu; RGD, Arg-Gly-Asp; DGE, Asp-Gly-Glu; CAMs, cell adhesion molecules; cIBR, cyclic ICAM-1 blocker right; DHFR, dihydrofolate reductase; Dox, doxorubicin; D1, domain-1; ECM, extracellular matrix, ^{18}FB-RGD, ^{18}F-benzoyl-RGD; ^{18}FG-RGD, ^{18}F-galactose-RGD; FN, fibronectin; FG, fibrinogen; FMDV, foot-and-mouth disease virus; gpIIb/IIIa, glycoproteins IIb/IIIa; GPR, Gly-Pro-Arg; HCAEC, human coronary artery endothelial cells; HIV-1, human immunodeficiency virus-1; HPEV1, human parechovirus 1; HUVEC, human umbilical vascular endothelial cells; ICAM-1, intercellular adhesion molecule-1; i.v., intravenous; LDV, Leu-Asp-Val; LFA-1, leukocyte function-associated antigen-1; K, Lys; LCL, long circulating liposomes; MHC-Ag, major histocompatibility complex-antigen; MTX, methotrexate; mAb, monoclonal antibody; MadCAM-1, mucosal addressin cell adhesion molecule-1; HPMA, N-(2-hydroxypropyl)-methacrylamide; PTX, paclitaxel; PI_3K, phosphoinositide-3-OH kinase; PECAM-1, platelet endothelial cell adhesion molecule-1; PEG, poly(ethylene glycol); PEG-PLA, poly(ethylene glycol)-poly(D,L-lactic acid); PET, positron emission tomography; PRG, Pro-Arg-Gly; PKC, protein kinase C; sICAM-1, soluble ICAM-1; TCR, T-cell receptor; DOTA, 1,4,7,10-tetraazadodecane-N,N′,N″,N‴-tetraacetic acid; VCAM-1, vascular cellular adhesion molecule-1; VEGF, vascular endothelial growth factor; VN, vitronectin; VWF, von Willebrand Factor.

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INTRODUCTION

In the past two decades, many cell adhesion molecules (CAMs) have been discovered, and their functions in cell morphology, locomotion, mitosis, cytokinesis, phagocytosis, and the maintenance of cell polarity have been studied.[1–3] CAMs have important roles in different disease states such as cancer,[3–8] thrombosis,[9–11], and autoimmune diseases (e.g., rheumatoid arthritis and type-1 diabetes).[12–14] Thus, researchers have been actively investigating the structure, function, and recycling mechanisms of some CAMs, as well as how to modulate them for controlling disease progression.[14] In addition, CAMs have been implicated in pathogenic (i.e., virus and bacteria) infections.[15–17]

CAMs are glycoproteins found on the cell surface that act as receptors for cell-to-cell and cell-to-extracellular matrix (ECM) adhesion.[18–20] CAMs can be divided into four classes: integrins, cadherins, selectins, and the immunoglobulin superfamily. Some CAMs are internalized into the cytoplasm during the recycling process via the formation of clathrin-coated pits.[16,21] Thus, the internalization process of CAMs can be exploited for targeting drugs into a compartment of a specific cell type (i.e., cancer and leukemic cells).

In recent years, peptides, peptidomimetics, and proteins that bind to cell adhesion receptors have been investigated for targeting drugs, particles, and liposomes to specific cell-bearing cell adhesion receptors (i.e., integrin and immunoglobulin superfamily).[22–24] Although structure–activity relationships of some cell adhesion peptides/proteins have been elucidated, there are limited comprehensive reviews on their utility in targeted drug delivery, diagnostics, and biomaterial design. Thus, this review is focused on the current uses of cell adhesion peptides and proteins for drug targeting, tumor diagnostics, and biomaterial design. Specifically, these cell adhesion peptides are derived from the ECM proteins, the immunoglobulin family, and integrins. The ECM peptides (i.e., RGD) have been used to target integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$, and peptides derived from the intercellular adhesion molecule-1 (ICAM-1) have been used to target the $\alpha_L\beta_2$ integrin. Finally, peptides derived from $\alpha_L\beta_2$ can target ICAM-1-expressing cells.

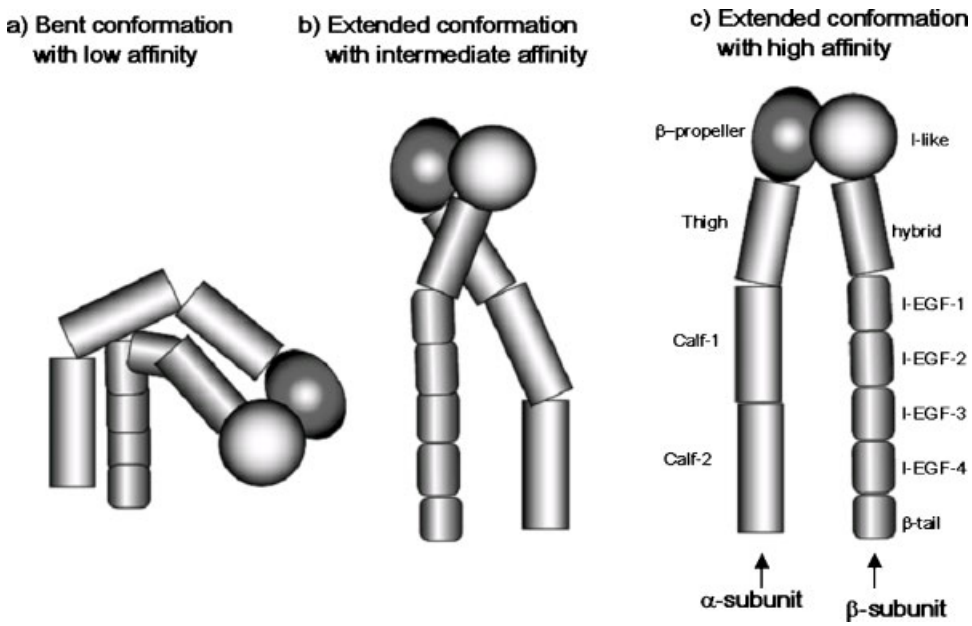

Figure 1. The general structure of integrins adapted from Shimaoka and Springer[14] showing different segments of the α- and β-subunits based on the structure of $\alpha_v\beta_3$. There are three possible conformations of integrins: (a) a bent conformation with a low affinity for the ligand, (b) an extended conformation with intermediate ligand affinity and closed headpiece, and (c) a high ligand affinity conformation with an extended conformation that has open headpiece when bound to RGD peptide.