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Review

Cell–matrix adhesion complexes: Master control machinery of cell migration

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Abstract

Cell–matrix adhesion complexes (CMACs) are foci of cellular attachment to the extracellular matrix (ECM). This attachment, mediated by integrins and adaptor proteins, provides both physical and regulatory links between the ECM and the cellular microfilament system. Through continual regulation and rearrangement of both ECM adhesion and actin structures, CMACs constitute core machineries of cell migration. To fulfill this role, CMACs are exceptionally flexible and dynamic complexes, and their components undergo rapid and regulated turn-over to maintain delicately balanced streams of mechanical and chemical information. Besides the critical role of CMACs in cell migration, signaling through these complexes provides influence over virtually every major cellular function, including for example cell survival, cell differentiation and cell proliferation. This review depicts the roles of CMACs in cell migration and discusses how CMACs integrate with other sub-cellular systems involved in cell motility. Importantly, we also present a rationalized view of CMACs as information handling machines, and suggest strategies that may facilitate better understanding of the complex cell migration phenomenon as a whole, through quantitative and integrative (systems biology) approaches.

Keywords: Cell motility; Cell adhesion; Integrin; Signaling; Polarity; Focal contacts; Focal adhesions; Systems biology; Actomyosin

Contents

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1. Introduction

Cell migration is a central process in development, as well as in many physiological and disease states. For example, mortality in cancer is mainly caused by metastatic dissemination from the original tumor. Tumor cells gain invasive capacity at the conversion from a benign to a malignant state and therefore invasive capacity is a key hallmark of malignant tumors. To gain an invasive capacity, tumor cells need to acquire capacities both for cell migration through and proteolysis of the extracellular matrix (ECM). At the core of the migratory machinery are cell–matrix adhesion complexes (CMACs) (see Fig. 1). CMACs are composed principally of integrins, the cytoplasmic tails of which interact with a wide array of recruited factors that: regulate integrin clustering and ECM-binding; interface with signaling networks; and provide a physical linkage between integrins and the microfilament system. Ultimately, CMACs emerge as diverse protein networks that dynamically link the ECM to filamentous actin and thus directly facilitate cell migration through the continual regulation and rearrangement of both ECM adhesion and actin structures. Accordingly, CMACs are highly flexible and dynamic complexes, the components of which undergo rapid and regulated turn-over to maintain delicately balanced streams of mechanical and chemical information. CMACs are able to transmit these signals in different directions, including from the ECM via integrins into the cell (outside–in integrin signaling), as well as from inside the cell to regulate integrin extracellular domain-mediated attachment to the ECM (inside–out integrin signaling) [1,2]. Information flowing into CMACs may directly influence cell migration by, for example, modifying mechanical integrin–ECM interactions. Conversely, CMAC chemical signaling outputs can regulate a range of additional cellular machineries fundamentally required during cell migration. Thus, CMACs are dominant regulatory entities in the cell migration system, and in this review we will attempt to clarify how CMACs control and coordinate cell migration and invasion as a whole.

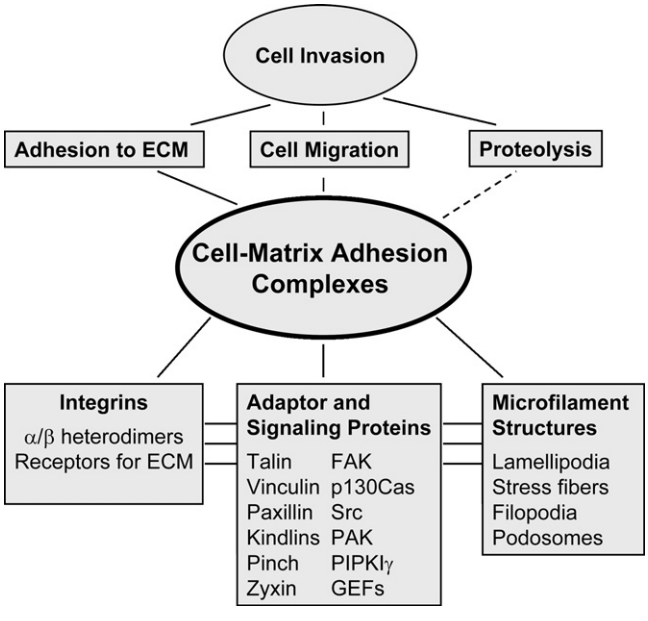

Fig. 1. Cell–matrix adhesion complexes as core machineries in cell migration and invasion. Cell–matrix adhesion complexes (CMACs) are at center stage during cell migration, when they attach cells to the ECM, physically link the ECM with actin microfilaments via integrins and adaptor proteins, and coordinate the processes of cell attachment and cytoskeletal rearrangement required for cell migration. CMAC are composed of transmembrane integrin receptors and an array of adaptor and signaling proteins (examples given in figure) which link to actin microfilaments. In addition to controlling cell adhesion and migration, CMACs are also functionally connected to proteolysis. Because cell adhesion, cell migration and proteolysis are the key components of cellular invasion, CMACs therefore represent core machineries of invasion.

1.1. Cell–matrix adhesion complexes

Cell–matrix adhesion complexes mechanically link the cell to the ECM [3,4]. CMACs form upon integrin ligation to the ECM and subsequent integrin clustering. This rapidly induces the recruitment of an array of CMAC signaling and adaptor proteins, forming large intracellular protein complexes bound both to clustered integrin cytoplasmic tails and to actin microfilaments. CMACs fulfill a variety of functions in the cell. Besides physically attaching cells to the ECM, CMACs also play important roles in the creation, mediation and sensing of tension [5]. In addition, CMACs are influential signaling hubs that detect, coordinate, transmit, adapt to and generate various signals regulating virtually all core cellular functions. Importantly, the concurrent association of CMACs with microfilaments and the ECM provides coordinated influence over both integrin-mediated cell–ECM attachment and microfilament remodeling, thus affording CMACs extensive control over cell migration.

CMACs differ significantly in features such as size, shape, location, componentry, dynamics and linkage to F-actin. Based on this, CMACs have been divided into a number of different categories [6,7]. Most of these CMAC categories represent different adhesion maturation states, including: focal points or nascent adhesions—small, often newly formed CMACs in the cellular periphery that link to an F-actin meshwork; focal complexes (FCs)—mid-size stationary contact sites linked to the cortical actin and/or the actin meshwork within lamellopodia; focal adhesions (FAs)—large adhesion sites that elongate along the axis of force application by actin stress fibers to which they connect; fibrillar adhesions—elongated adhesions that connect microfilament stress fibers with extracellular fibronectin fibers; and podosomes—invasive ring structures composed of adhesion machinery and filamentous actin. However, no unambiguous, commonly used collective term currently exists for the inclusive discussion of all these complexes. Somewhat confusingly, the terms focal adhesion and focal contact are sometimes used