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Mini Review

Dock-family exchange factors in cell migration and disease

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ABSTRACT

Dock family proteins are evolutionary conserved exchange factors for the Rho GTPases Rac and Cdc42. There are 11 Dock proteins in mammals, named Dock1 (or Dock180) to Dock11 that play different cellular functions. In particular, Dock proteins regulate actin cytoskeleton, cell adhesion and migration. Not surprisingly, members of the Dock family have been involved in various pathologies, including cancer and defects in the central nervous and immune systems. This review proposes an update of the recent findings regarding the function of Dock proteins, focusing on their role in the control of cell migration and invasion and the consequences in human diseases.

Introduction

Cell adhesion and migration are regulated by a wide variety of chemical and physical extracellular cues: cytokines, growth factors, tension, shear stress, stiffness... These signals are transmitted to the intracellular medium by membrane receptors such as cytokine and growth factor receptors, integrin and cadherin adhesion receptors. Such receptors further drive the reorganization of the actin cytoskeleton downstream of the activation of Rho GTPases by their exchange factors.

There are 20 Rho GTPases in the human genome, among which RhoA, Rac1 and Cdc42 are the most studied (Boureux et al., 2007). Two classes of exchange factors were described for Rho GTPases: the classical Dbl-related exchange factors and more recently the atypical Dock family exchange factors. Dbl/MCF2 was described as an activator of Rho GTPases in 1984. Since then, about 80 Dbl-related proteins were identified. They are characterized by a 200 amino acid Dbl-homology (DH) domain, which catalyzes

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Table 1
Phenotypes and diseases associated with the suppression and mutation of Dock genes in mouse and human.

Gene	Mouse KO phenotype	Reference	Human mutation	Associated disease	Reference
Dock1	Lethal before weaning	Laurin et al. (2008)	ND		
Dock2	Immune system defects	Cook et al. (2013), Fukui et al. (2001), Sakai et al. (2013)	ND		
Dock3	Axonal degeneration	Chen et al. (2009), Tachi et al. (2012)	ND		
Dock4	ND		Promoter methylation	Myelodysplasic syndrome	Zhou et al. (2011)
			Pro1718Leu	Prostate and ovarian cancer	Kuo et al. (2009)
Dock5	High bone mass, cataract	Omi et al. (2008), Vives et al. (2011)	ND		
Dock6	Shortened peripheral neuronal fibers	Miyamoto et al. (2013)	Truncation	Adams–Oliver syndrome (limb development and ectopic calcification)	Shaheen et al. (2013), Shaheen et al. (2011)
Dock7	Pigmentation defects	Blasius et al. (2009)	ND		
Dock8	T and B cell defects	Crawford et al. (2013), Randall et al. (2009)	Various	Autosomal recessive hyper IgE syndrome	Alsum et al. (2013)
Dock9	ND		Gln754His	Keratoconus, corneal disorder	Czugala et al. (2012)
Dock10	ND		ND		
Dock11	ND		ND		

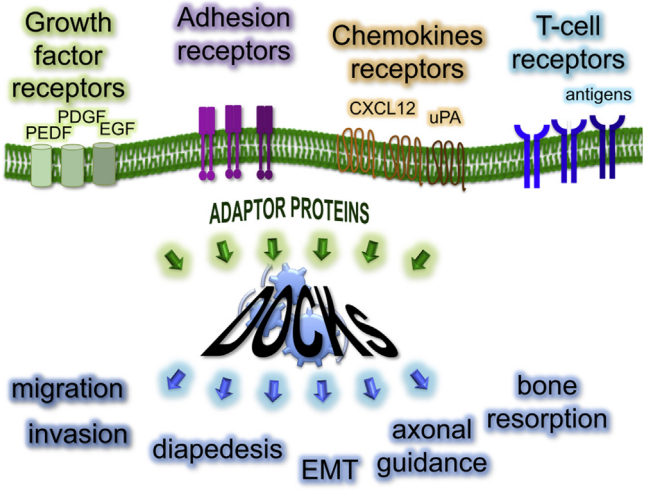

Fig. 1. Schematic representation of Dock proteins in various cellular signaling downstream of membrane receptors. After binding of their ligands, surface receptors recruit Dock proteins through adaptor molecules. In turn, Dock proteins trigger activation of Cdc42 or Rac to promote various cellular processes.

the nucleotide exchange reaction. They have been widely studies for their functions in regulating cell adhesion and migration via the activation of Rho GTPases. Several among the 80 Dbl-related GEFs have been involved in different types of cancers and various pathologies including central nervous system and immune system (Cook et al., 2013). The Dock-family of exchange factors emerged only 12 years ago as a novel class of Rho GTPase activators, in particular of Rac(1/2/3) and Cdc42 (Cote and Vuori, 2002). Since then, they have been involved in the regulation of a wide variety of cellular pathways downstream of membrane receptors (Fig. 1). Here we propose an overview of the signaling pathways involving the GEFs of the Dock family, their impact on cell adhesion and migration and their implication in cancer and various pathologies (Table 1).

Dock protein-mediated activation of Rho GTPases

The human genome contains 11 genes encoding Dock1-related proteins that function as exchange factors (GEFs) for the Rho GTPases Rac and Cdc42. Dock proteins are qualified atypical Rho GTPase GEFs (Rho GEFs) as compared to the typical Dbl family of Rho GEFs. Dock proteins are large polypeptides characterized by the presence of two domains: DHR1 (or Docker or CZH1) domain, which is 200–250 aminoacid long and binds phospholipids, and DHR2 (or CZH2) domain that is 450–550 aminoacid long and bears the guanine nucleotide exchange activity (Brugnera et al., 2002; Cote and Vuori, 2002; Meller et al., 2005). Dock proteins are well conserved through evolution. They are present in a wide variety of eukaryotes including Dictyostelium, *C. elegans*, fungi, *Drosophila* and higher vertebrates with related proteins in plants and early eukaryotes (Meller et al., 2005).

Dock proteins are classified in four subgroups (Cote and Vuori, 2007), based on sequence similarity and domain organization. The Dock-A subgroup contains Dock1 (also called Dock180), Dock2 and Dock5; the Dock-B subgroup includes Dock3 (also called PBP Presenilin Binding Partner, PBP or MOdifier of Cell Adhesion, MOCA) and Dock4. Proteins in the Dock-A and B subgroups contain an amino-terminal SH3 domain that can bind the adaptor proteins ELMO (Engulfment and Motility) 1, 2 and 3 and a proline rich carboxy-terminal domain that binds Crk proteins. The Dock-C subgroup contains Dock6, Dock7 and Dock8 (also called Zir (for Zizimin related) 1, 2 and 3 respectively). Finally, the Dock-D subgroup includes Dock9, Dock10 and Dock11 also called Zizimin (Ziz) 1, 3 and 2 respectively), which have an amino-terminal PH domain.

Dock-A and Dock-B proteins are exchange factors for the GTPase Rac and Dock-D proteins are GEFs for Cdc42 (Gadea et al., 2008; Hiramoto-Yamaki et al., 2010; Vives et al., 2011; Xiao et al., 2013). Dock-C proteins are considered dual specificity GEFs for Rac and Cdc42, but this is still a mater of debate (Harada et al., 2012; Kulkarni et al., 2011; Miyamoto et al., 2007; Watabe-Uchida et al., 2006). The DHR2 domain catalyzes nucleotide exchange through a mechanism distinct from the Dbl Homology (DH) domain of Dbl exchange factors. This involves a nucleotide sensor region within an insert in the a10 helix of the DHR2 domain. The a10 helix insert bears an essential Valine residue conserved among all Dock proteins that senses the GDP bound to the GTPase and excludes the Mg^{2+} ion from the nucleotide pocket. This destabilizes the binding of GDP to the GTPase. Further binding of GTP to the GTPase induces a displacement of the a10 helix insert and conformational changes of the GEF allowing to the release of the activated GTPase (Yang et al., 2009).

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