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Review

Caspase-8 function, and phosphorylation, in cell migration

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ABSTRACT

Caspase-8 is involved in a number of cellular functions, with the most well established being the control of cell death. Yet caspase-8 is unique among the caspases in that it acts as an environmental sensor, transducing a range of signals to cells, modulating responses that extend far beyond simple survival. Ranging from the control of apoptosis and necroptosis and gene regulation to cell adhesion and migration, caspase-8 uses proteolytic and non-proteolytic functions to alter cell behavior. Novel interacting partners provide mechanisms for caspase-8 to position itself at signaling nodes that affect a variety of signaling pathways. Here, we examine the catalytic and noncatalytic modes of action by which caspase-8 influences cell adhesion and migration. The mechanisms vary from post-cleavage remodeling of the cytoskeleton to signaling elements that control focal adhesion turnover. This is facilitated by caspase-8 interaction with a host of cell proteins ranging from the proteases caspase-3 and calpain-2 to adaptor proteins such as p85 and Crk, to the Src family of tyrosine kinases.

Contents

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1. Overview of caspases, integrins and cell migration

Cell migration is a process, predating metazoans, which is absolutely critical for establishing and maintaining multicellular organisms. In vertebrates, cellular migration plays essential roles during development, wound healing and immune responses [1]. However, cell migration is not a normal day-to-day activity from most cells. Cell migration poses inherent risk to an organism, as it has the potential for pathological disordering, or degeneration, of tissues. The cells in the retinal vascular bed offer a primary example. The disruption of retinal function leading to blindness that occurs during macular degeneration results from endothelial cell invasion of the retina [2]. In other cases, cell migration can promote the progression of life-threatening malignancies, most notably in cancer dissemination. Considering the context of these biological processes, it is perhaps not completely unexpected that cell migration pathways should interact with signaling pathways that control cell survival. Programmed cell death is, itself, an over-riding mechanism by which cell migration can be limited. After all, dead cells don't migrate.

1.1. Integrins

Integrins are an ancient family of proteins [3] that act as the principle biomechanical mediators of cell adhesion to components of the extracellular matrix (ECM) such as collagen, laminin and fibronectin, as well as to adhesion molecules (most frequently members of the immunoglobulin family) on neighboring cells [4]. Integrins act to both sense and transduce mechanical and chemical signals, allowing a cell to interpret and react to its local environment while facilitating cell migration.

Integrins are present in metazoans as early as the sponges [5]. Both the function and the number of different integrins in the genome becomes increasingly complex with metazoan evolution (Fig. 1). Integrins form α/β heterodimeric complexes as the nascent α and β integrin subunits traverse the endoplasmic reticulum. Heterodimerization stabilizes the integrin heterodimer, and permits maturation of surface sugars and trafficking to the cell surface. The specific α/β subunits that comprise the heterodimer (there are 24 different combinations in man) also dictates the lateral and cytosolic interactions of the integrin, and determine the specific ECM ligand(s) recognized by that integrin. With a singular exception (integrin β4), all integrins have small cytosolic domains of 30–60 amino acid residues. The cytosolic domains do not transduce signals themselves, but are dependent upon interaction with a host of different cellular effectors for both chemical and biomechanical signaling. Integrins tend to cluster following ligation, which facilitates their capacity to signal via Src family kinases (SFK), focal adhesion kinase (FAK), phosphinositide 3′ kinase (PI3K), p21-activated kinases, p190 Rho kinase, small GTPases, and adaptor proteins such as paxillin, Grb2, p130Cas, and many, many others [1]. The associations of these proteins occur in a spatio-temporal manner following integrin ligation, acting to transduce signals that provide static or dynamic anchorage points for the cell. Integrins have long been established to play a role in cell survival [6], and integrin ligation promotes signals which can actively block the activation of caspases following DR antagonism. [7–9].

A single α/β integrin heterodimer is relatively large, with a mass of 250-350kD and engages a single ECM or cell surface ligand. In addition to allowing the integrin to project away from the cell surface, the size and structure conveys the ability to assume a range of functional states with increasing affinity for ligand. These states exist in a dynamic equilibrium influenced by the availability of divalent cations, the local ECM concentration and composition, and critically by the interaction of the cytosolic domains of the integrins with cytoskeletal proteins or other signaling elements [1,10]. The accumulation of integrins within focal adhesions, and their subsequent 'turnover' (they are cycled out, internalized, then recycled to the cell surface to re-engage ligands) can globally influence cell signaling. Among non-migrating cells, focal adhesions can grow to large size and function as 'phosphotyrosine sanctuaries.' One of our earliest understandings in integrin biology was that receptor tyrosine kinase signaling is compromised in cells lacking integrin receptor ligation [11].

1.2. Caspases

Caspases also first appear in metazoans [12] (Fig. 1), although simple organisms, such as yeast, express related molecules. While it unclear if caspases originally executed roles other than programmed cell death, the death-inducing role is already present in phyogenetically 'primitive' creatures; executioner caspase homologs mediates programmed cell death during development in C. elegans and during metamorphosis in Cnidaria. Although different caspases share general features, including the hallmark ability to undergo proteolytic maturation, it is apparent that the signaling networks that govern caspase activity are finely tuned to the specific organism that the caspases have evolved in. For example, *C. elegans* Ced-3 mutants are viable, and are more robust than *wild type* worms in some cases [13] but less robust in others [14]. By contrast, caspase-3 knockout is generally lethal in mice [15]. This variation in phenotype illustrates the concordance between the complexity of the organism and the complexity of the caspase regulation within an organism. More caspases (Fig. 1) and generally more finely-tuned caspase cascades tend to be present in more complex organisms [12]. Caspase-8 is a prodomain-containing vertebrate caspase that is not present in *C. Elegans,* nor is caspase-8 mRNA expressed in mouse embryonic cell mass prior to implantation (unpublished data) yet caspase-8 is critical for mouse survival by supporting the subsequent development of key tissue compartments, most notably the placenta [16]. Complex networks have arisen during evolution to incorporate feedback between increasing complex cellular systems. Caspase-8 plays a key role in regulating the innate immune response in all creatures that express it. Human cells exhibit cross-talk between caspases and other cell signaling and cell survival systems, but not all of these are precisely conserved across model organisms.

2. Many roles for caspase-8 in cell fate

As a vertebrate caspase, caspase-8 was first identified for its ability to promote cell death in response to extrinsic cues. The complexity of the system and the breadth of caspase-8 interactions are such that, more than 20 years later, we are still discovering the

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