Review

Force-dependent breaching of the basement membrane

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Abstract

Clinically, non-invasive carcinomas are confined to the epithelial side of the basement membrane and are classified as benign, whereas invasive cancers invade through the basement membrane and thereby acquire the potential to metastasize. Recent findings suggest that, in addition to protease-mediated degradation and chemotaxis-stimulated migration, basement membrane invasion by malignant cells is significantly influenced by the stiffness of the associated interstitial extracellular matrix and the contractility of the tumor cells that is dictated in part by their oncogenic genotype. In this review, we highlight recent findings that illustrate unifying molecular mechanisms whereby these physical cues contribute to tissue fibrosis and malignancy in three epithelial organs: breast, pancreas, and liver. We also discuss the clinical implications of these findings and the biological properties and clinical challenges linked to the unique biology of each of these organs.

Introduction

One hallmark of epithelial cancers is the infiltration of malignant cells through the basement membrane, which heralds the difference between non-lethal neoplastic lesions and invasive cancers with associated high mortality. The basement membrane is an important histologically identifiable barrier between non-invasive (i.e., carcinoma in situ) and invasive forms of cancer. Identifying factors that induce and enable transformed cells to cross this barrier is an active area of investigation. Emerging evidence indicates that basement membrane invasion by malignant cells is substantially influenced by cross-talk between three inter-related factors: stromal stiffening, epithelial cytoskeletal contractility, and growth factor/cytokine signaling (Fig. 1). Activation of stromal cells and immune cell infiltration lead to interstitial stromal stiffening in the tumor microenvironment, which stimulates the cytoskeletal contractility of transformed epithelial cells. Conversely, increased epithelial contractility induces greater stromal stiffening as well as formation of invadosomes and production of matrix metalloproteinases (MMPs) required for basement membrane invasion. Importantly, both stromal stiffening and epithelial contractility serve to amplify growth factor and cytokine signaling pathways that are implicated in promoting basement membrane invasion. In this review, we discuss recent data that illustrate these fundamental principles in three different epithelial organs: breast, pancreas, and liver. We highlight the clinical significance of understanding the molecular mechanisms that promote basement membrane

invasion in the development of adenocarcinoma in these organs and recent scientific advances that shed light on this important checkpoint in cancer progression. Two unifying themes emerge from synthesis of the literature. First, matrix rigidity is an important risk factor and mediator of tumor progression, and second, oncogenic mutations and signaling pathways act in concert with the stromal microenvironment to promote tumor cell invasion through the basement membrane.

Clinical significance of basement membrane invasion

Breast, pancreas, and liver cancer are three important malignancies of epithelial origin that occur with considerable incidence and affect distinct demographic populations. The three organs have distinct anatomy and microenvironments and the molecular compositions of their basement membranes are different (Fig. 2). Clinically, each of these carcinomas pose a unique set of challenges to diagnosis and treatment. However, for all three tumors, breaching of the basement membrane remains the key step that differentiates a lesion that is easily treatable from one that is highly lethal. For each type of cancer, the need to understand the factors that regulate basement membrane invasion is critical for different reasons.

Ductal carcinoma in situ (DCIS) is the earliest detectable form of breast cancer and the most common (80–90%) in situ carcinoma of the breast [1]. Histologically, it is characterized by proliferation of neoplastic cells within the lumen of mammary ducts. The surrounding layer of myoepithelial cells and the basement membrane essentially remain intact in these lesions [2]. This is in contrast to invasive breast cancer (IBC) in which malignant cells invade and break through the basement membrane. Since the advent of screening mammography, the incidence of DCIS diagnosis has increased dramatically and DCIS now accounts for 20% of all breast cancers [3]. DCIS is thought to be a non-obligate precursor to IBC because the vast majority of IBCs are accompanied by adjacent DCIS [4,5]. However, only 20–50% of patients with DCIS later develop IBC in the same quadrant of the same breast [6,7], indicating that a significant proportion of DCIS never progresses to IBC. Although DCIS is non-lethal, IBC is frequently a systemic disease in which patients succumb to metastatic spread of the cancer. Therefore, the current recommendations for DCIS treatment include surgery, radiation, and hormone therapy upon diagnosis, which are essentially the same as for IBC, except for systemic chemotherapy. Because of the high rate of DCIS detection in asymptomatic individuals and its poorly quantified risk of progression to IBC, there is concern that prevailing standards of care over-diagnose and

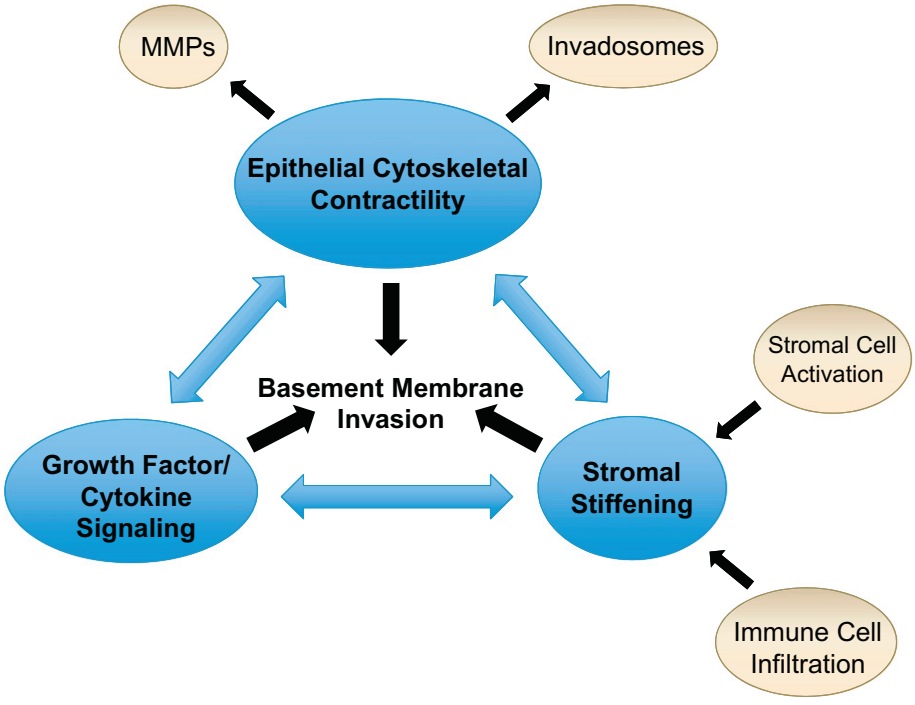

Fig. 1. Inter-related and cross-regulating factors that promote basement membrane invasion in cancer progression. MMPs, matrix metalloproteinases.