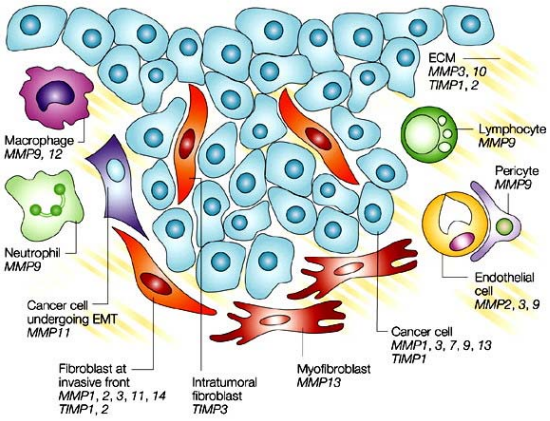
Espressione di MMPs e di TIMPs nei carcinomi mammari

Seminario



Oltre alle **cellule tumorali**, i tumori mammari contengono **cellule stromali**, che includono **fibroblasti**, **miofibroblasti**, **cellule endoteliali**, **periciti**, **macrofagi**, **mast cells**, **neutrofili** e **linfociti**. Differenti metalloproteinasi (MMPs) e inibitori tissutali delle metalloproteinasi (TIMPs) sono sintetizzati dalla cellule stromali, dalle cellule tumorali e dalle cellule tumorali nel corso della transizione EMT.

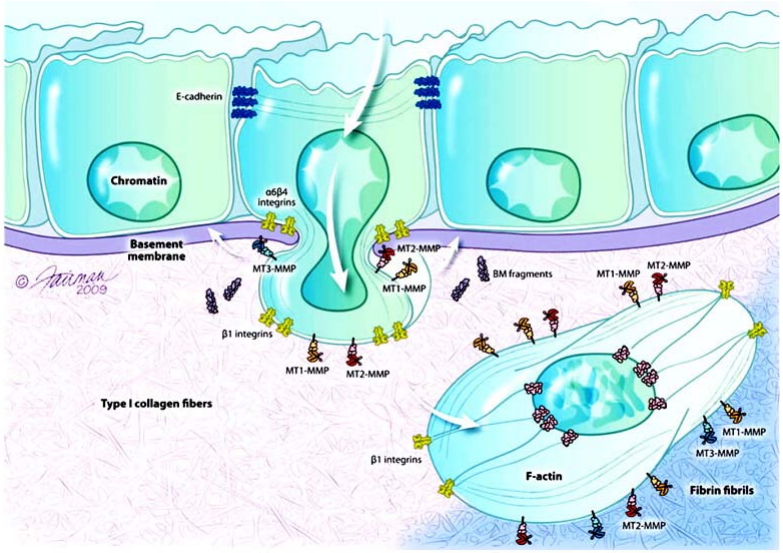
Egeblad M, Werb Z. **New functions for the matrix metalloproteinases in cancer progression**. Nat Rev Cancer. 2002 Mar;2(3):161-74.

Navigating ECM Barriers at the Invasive Front: The Cancer Cell–Stroma Interface

- Un evento di fondamentale importanza nella progressione tumorale è la **capacità della cellula neoplastica di mobilizzare il macchinario necessario per fare delle brecce nelle circostanti barriere di MEC** mentre **orchestra una risposta stromale nell'ospite che alla fine sostiene i processi invasivo e metasta**tico.
- Con più di 500 enzimi proteolitici identificati nel genoma umano, sono stati postulati reti di interconnessione fra processi proteasi-dipendenti e proteasi-indipendenti che guidano i programmi di invasione tumorale, mediante schemi di scoraggiante complessità.
- Un sempre maggiore numero di evidenze sperimentali tuttavia sta emergendo a favore di un **modello unificato** in cui un piccolo gruppo di enzimi ancorati alla membrana ("membrane-type metalloproteinases, **MT-MMPs**) gioca un ruolo predominante nella regolazione del traffico non solo delle cellule tumorali ma anche di quelle stromali attraverso le barriere della MEC assemblate dal tessuto dell'ospite in vivo.
- **Capire i meccanismi alla base della regolazione e della funzione di questi metalloenzimi** mentre le popolazioni dell'ospite attraversano la matrice extracellulare dinamica assemblata durante gli stadi neoplastici dovrebbe fornire teorie nuove e verificabili sull'invasione e metastatizzaione tumorale.

Rowe RG, Weiss SJ. Navigating **ECM barriers at the invasive front: the cancer** cell-stroma interface. Annu Rev Cell Dev Biol. 2009;25:567-95.

The 2-dimensional (2-D)-to-3-dimensional (3-D) transition



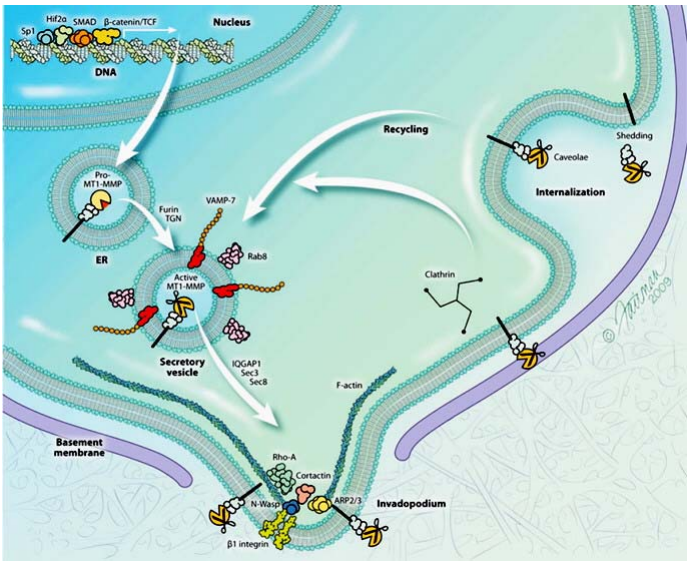
Rowe RG, Weiss SJ. **Navigating ECM barriers at the invasive front: the cancer cell-stroma int**erface. Annu Rev Cell Dev Biol. 25:567-595, 2009.

Didascalia figura Rowe & Weiss

The 2-dimensional (2-D)-to-3-dimensional (3-D) transition. **A differentiated epithelial cell normally exists atop the 2-D extracellular matrix (ECM) of the basement membrane (BM).** During carcinoma progression, a malignant epithelial cell punctures the BM via the action of membrane-type 1,2,3 matrix metalloproteinases (MT1,2,3-MMPs) and transmigrates into the 3-D environment of the interstitial ECM. **BM degradation products with biological activity signal to the invading cell and host stroma to modulate cell function**. Within the 3-D ECM, collagen fibrils are remodeled by MT1-MMP and MT2-MMP and fibrin fibrils via MT1,2,3-MMPs. This 2-D to 3-D transition process is accompanied by disruption of cell:cell adhesion complexes (including adherens junctions containing E-cadherin), loss of cell polarity, protease activation, cytoskeletal and nuclear remodeling, and integrin switching. **Collectively, these phenotypic changes result in the malignant epithelium assuming a nonpolar, mesenchymal-like phenotype for growth, migration, and survival within the 3-D interstitial ECM**.

Rowe RG, Weiss SJ. **Navigating ECM barriers at the invasive front: the cancer cell-stroma int**erface. Annu Rev Cell Dev Biol. 25:567-595, 2009.

Regulation of membrane-type 1 matrix metalloproteinase (MT1-MMP) expression, processing, traffic, and activity at the cell surface



Rowe RG, Weiss SJ. **Navigating ECM barriers at the invasive front: the cancer cell-stroma interface**. Annu Rev Cell Dev Biol. 25:567-595, 2009.

Didascalia figura precedente, Rowe & Weiss

Regulation of membrane-type 1 matrix metalloproteinase (MT1-MMP) expression, processing, traffic, and activity at the cell surface.

Triggered by a variety of signaling cascades, Pol II transcription at the MMP14 gene and subsequent translation in the endoplasmic reticulum (ER) generate proMT1-MMP. ProMT1-MMP is proteolytically activated by proprotein convertases, such as furin, within the trans-Golgi network (TGN). MT1-MMP traffic to the cell surface is tightly regulated such that the active enzyme is delivered to focal zones of pericellular proteolysis that support 3-D growth and invasion. Vesicles containing active MT1-MMP are coated with VSV-G/Rab8 and trafficked via the exocyst complex to cortactin-rich invadopodia in which membrane fusion is mediated by VAMP-7. **MT1-MMP activity at invadopodia coordinates cytoskeletal dynamics, adhesion, and proteolysis into a concerted invasion process**. MT1-MMP cell surface activity is abrogated via mechanisms including endocytosis and shedding.

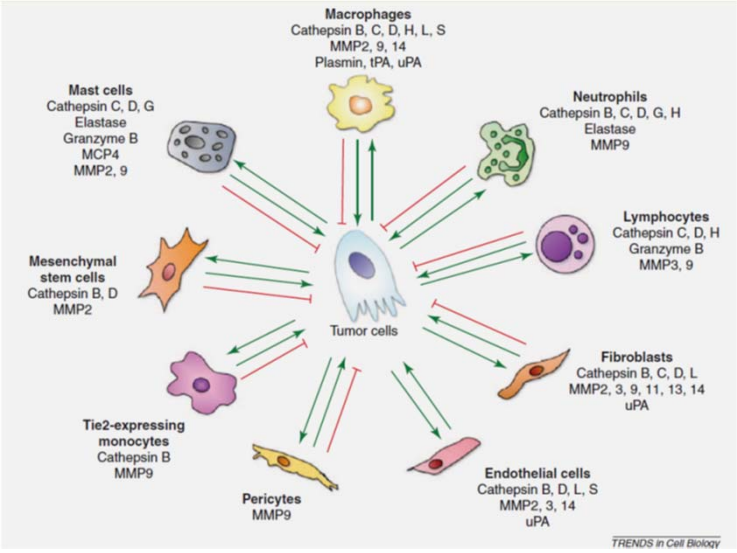
Rowe RG, Weiss SJ. **Navigating ECM barriers at the invasive front: the cancer cell-stroma interface**. Annu Rev Cell Dev Biol. 25:567-595, 2009.

Proteolytic networks in cancer

Steven D. Mason and Johanna A. Joyce *Trends in Cell Biology* April 2011, Vol. 21, No. 4

Proteases are important for multiple processes during malignant progression, including tumor angiogenesis, invasion and metastasis. Recent evidence reveals that tumor-promoting proteases function as part of an extensive multidirectional network of proteolytic interactions, in contrast to the unidirectional caspase cascade. These networks involve different constituents of the tumor microenvironment and key proteases, such as cathepsin B, urokinase-type plasminogen activator and several matrix metalloproteinases, occupy central nodes for amplifying proteolytic signals passing through the network. The proteolytic network interacts with other important signaling pathways in tumor biology, involving chemokines, cytokines, and kinases. Viewing these proteolytic interactions as a system of activating and inhibiting reactions provides insight into tumor biology and reveals relevant pharmaceutical targets. This review examines recent advances in understanding proteases in cancer and summarizes how the network of activity is co-opted to promote tumor progression.

Contributo delle varie cellule stromali dei tumori alla proteolisi



Mason SD, Joyce JA. **Proteolytic networks in cancer**. Trends Cell Biol. 2011 Apr;21(4):228-37.

MATRIX METALLOPROTEINASES AS MODULATORS OF INFLAMMATION AND INNATE IMMUNITY

William C. Parks[*‡], *Carole L. Wilson*[§] *and Yolanda S. López-Boado*[||]

As their name implies, matrix metalloproteinases are thought to be responsible for the turnover and degradation of the extracellular matrix. However, matrix degradation is neither the sole nor the main function of these proteinases. Indeed, as we discuss here, recent findings indicate that matrix metalloproteinases act on pro-inflammatory cytokines, chemokines and other proteins to regulate varied aspects of inflammation and immunity.

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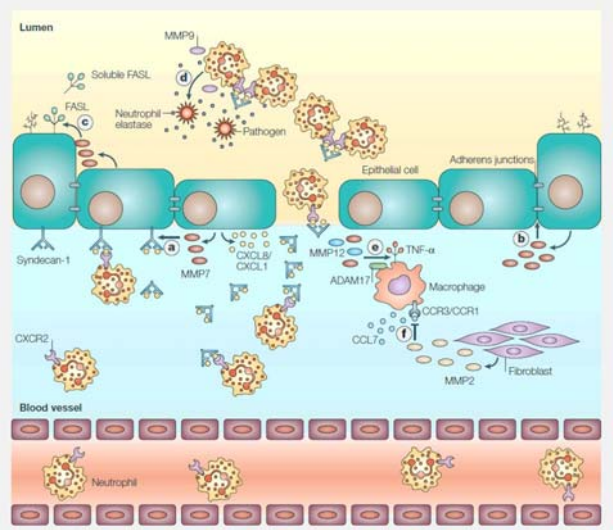
MMPs nell'infiammazione in risposta al danno tissutale



Parks WC, Wilson CL, López-Boado YS. **Matrix metalloproteinases as modulators of inflammation and innate immunity**. Nat Rev Immunol. 2004 Aug;4(8):617-29.

Metalloproteinases and their natural inhibitors in inflammation and immunity

Rama Khokha, Aditya Murthy and Ashley Weiss**

Abstract | Over the past 50 years, steady growth in the field of metalloproteinase biology has shown that the degradation of extracellular matrix components represents only a fraction of the functions performed by these enzymes and has highlighted their fundamental roles in immunity. Metalloproteinases regulate aspects of immune cell development, effector function, migration and ligand–receptor interactions. They carry out ectodomain shedding of cytokines and their cognate receptors. Together with their endogenous inhibitors TIMPs (tissue inhibitor of metalloproteinases), these enzymes regulate signalling downstream of the tumour necrosis factor receptor and the interleukin-6 receptor, as well as that downstream of the epidermal growth factor receptor and Notch, which are all pertinent for inflammatory responses. This Review discusses the metalloproteinase family as a crucial component in immune cell development and function.

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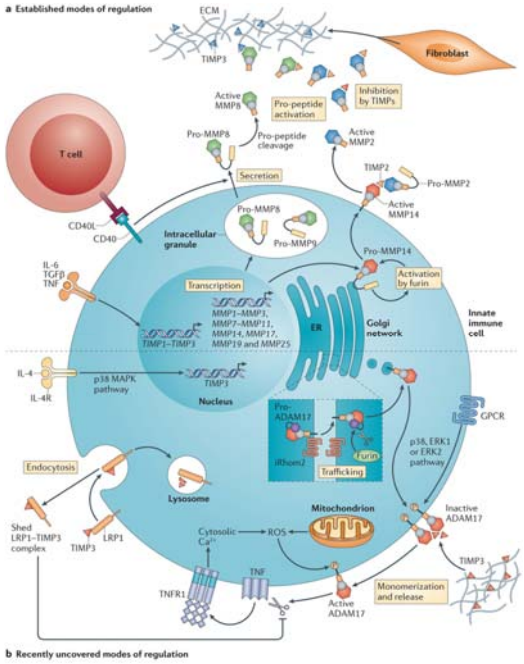

Khokha R, Murthy A, Weiss A. **Metalloproteinases and their natural inhibitors in inflammation and immunity**. Nat Rev Immunol. 2013 Sep;13(9):649-65.