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Reciprocal action of CD44 and neutral endopeptidase 24.11 in prostate cancer

Modulation of the intracellular cytoskeleton may have critical importance in the behavior of cancer cells. The organization of the cytoskeleton influences transmembrane proteins which interact via their extracellular domains with adjacent homotypic or heterotypic cells, and the extracellular matrix. Upon invasion of the vasculature, the cytoskeleton influences binding and exit from the circulation in metastatic sites. Conversely cell surface proteins regulate and activate intracellular signal transduction and intracellular protein–protein interactions. Reorganization of the cytoskeleton is critical to cell adhesion, cell motility, and cell migration; inhibition of the same will have a major effect on the behavior of cancer cells. The ezrin/radixin/moesin (ERM) proteins play an important role in the interactions of the cytoskeleton with transmembrane proteins, as they regulate the organization of the actin cytoskeleton through their role as crosslinkers between actin filaments and membrane proteins. The cell surface neutral endopeptidase 24.11 (NEP) is a metallopeptidase that inactivates physiologically active neuropeptides such as neurotensin, bombesin and endothelin-1. As a type II integral membrane protein, the NEP protein inhibits cell migration via intracellular protein-protein interactions. NEP is normally expressed by several tissues, including prostate, kidney, intestine, endometrium, and lung. In a report by **Iwase *et al*,**[1] NEP is shown to inhibit prostate cancer cell proliferation and cell migration by enzymatic inactivation of neuropeptide substrates and through binding to intracellular ERM proteins. These ERM binding interactions are independent of the extracellular peptidase activity of NEP. Prostate epithelial cells expressing NEP demonstrate decreased adhesion to hyaluronic acid and decreased cell migration. In particular, binding of ERM proteins to NEP results in decreased binding of these same ERM proteins to the hyaluronan receptor CD44, a main binding partner of ERM proteins. As shown by **Omara-Opyene *et al*[2]** in this issue, certain variant forms of CD44 are important mediators of the invasive behavior of prostate cancer cells. Hence, a compelling story emerges regarding the inverse relationships between prostate cancer expression of CD44, NEP expression, and their respective ERP binding partners. While expression of CD44 by cancer cells promotes tumor cell adhesion and/or invasion, NEP expression can suppress the interaction of ERM proteins to CD44 and inhibit tumor cell adhesion and migration.

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Including myopathy and Paget's disease of bone in the ubiquitination pathway disorders

Sir James Paget was a 19th century English surgeon with a portfolio of eponymic legacies: Paget's disease—both of the nipple areola and of bone (osteitis deformans); Paget's cells—malignant cells in breast ducts and areolar epidermis or of the vulvar region; and Pagetoid spread of cancer cells through the epidermis. Paget's disease of bone (PDB) is a chronic progressive disease of putative viral origin, with the paramyxovirus of the measles virus family implicated as the causative agent. Hereditary inclusion body myopathy associated with PDB and frontotemporal dementia, or IBMPFD, is not viral in origin. Rather, it is a rare, complex and ultimately lethal autosomal dominant disorder. The bone disease is early in onset, as is the dementia. Of 13 family pedigrees with IBMPFD, 82% had myopathy, 49% PBD, and 30% early-onset dementia. In both myopathic muscle and PDB osteoclasts, inclusions are present and appear similar. Although the disorder maps to chromosome 9p21–p12, the genetic basis was not known. In a report by **Watts *et al*,**[1] a candidate-gene approach for these 13 families was used to identify six missense mutations in the gene encoding valosin-containing protein (VCP), a member of the AAA-ATPase superfamily. Haplotype analysis indicated that descent from two founders in two separate North American kindreds accounted for IBMPFD in $\sim$50% of affected families. VCP is associated with a variety of essential cellular protein processing pathways, including the ubiquitin–proteasome degradation pathway, homotypic membrane fusion, and cell cycle control. Normally, it is located in the muscle fiber cytoplasm at low levels and in the immediate vicinity of intracellular

lipofuscin accumulations. It is also prominently expressed in the small endomysial capillaries. In muscles with IBMPFD, VCP was localized in large or small rounded aggregates in scattered muscle fibers. The identified mutations disrupt folding of the VCP protein, impairing binding to specific partner proteins. Interestingly, involvement of VCP in cell cycle and apoptosis pathways is not affected by the IBMPFD missense mutations. Rather, the mutations affect protein quality control and the ubiquitin protein degradation pathways. Specifically, VCP interacts directly with polyubiquitinated proteins, and colocalizes with ubiquitin-containing nuclear inclusions in the cerebral cortex in such neuronal degenerative disorders as Huntington's, Alzheimer's, Cruetzfeldt–Jacob's and Parkinson's disease's. It is therefore interesting that mutations in the ubiquitin-binding domain of the protein sequestosome 1 also cause autosomal dominant PDB. The authors propose that mutations in VCP similarly cause PBD by compromising ubiquitin-binding and the proteasome-mediated degradation of intracellular proteins. The identification of VCP as cause for IBMPFD has important implications for other inclusion-body diseases, including myopathies, dementias, Paget's disease of bone, and even alpha-1-antitrypsin storage disorder of the liver, as it focuses attention on impairments in the endogenous ubiquitin-based protein degradation pathway. This paper also provides an additional point of entry for understanding inclusion-body myopathies and dementias, as distinct from the pharmaceutically induced prion protein myopathy reported in this issue by **Furukawa *et al.*[2]**

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PDGFRA mutation: an important mutation in GISTs without KIT mutation

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The discovery of KIT mutations in more than 80% of GISTs and the availability of imatinib mesylate (Gleevec—STI 571) have revolutionized the management of this tumor. However, just like other neoplasms, GISTs are a heterogenous group of tumors and not all GISTs carry KIT mutations. KIT activation, even in the presence of wild-type KIT, has led to the investigation of the KIT-related receptor tyrosine kinase (RTK) in GISTs. The KIT-related RTK includes proto-oncogene FMS, which encodes, among other things, platelet-derived growth factor receptor (PDGFR) genes. Oncogenic mutations in the PDGFR alpha (PDGFRA) gene cause downstream signaling pathway activation identical to that seen with KIT mutations. PDGFRA can behave as another predisposing gene for familial GIST, as now described by **Chompret *et al*[1]** for a familial form of GIST. A kindred of five individuals exhibited an exclusive PDGFRA germline mutation at codon 846 (D846Y). Amino-acid sequence of PDGFRA and KIT genes revealed homologies between the mutated PDGFRA Asp846, and mutated KIT Asp 820 located within KIT tyrosine kinase II domain as previously described in familial GIST. Phenotypes such as hyperpigmentation and mast cell tumors, seen in individuals carrying germline KIT mutation, were not observed in the familial GISTs with the PDGFRA mutation. In contrast, all the PDGFRA mutation carriers displayed a congenital malformation of the hands not observed in the KIT mutation carriers. The current issue of Laboratory Investigation has an article by **Lasota *et al*[2]** demonstrating that the majority of GISTs with PDGFRA mutations arise in the stomach, have a purely or predominantly epithelioid morphology, a low mitotic activity, and follow a benign course. Based on these studies, KIT and PDGFRA mutations appear to be mutually exclusive oncogenic mechanisms leading to similar biological consequences. At the structural level, both PDGFRA and KIT belong to the same subfamily of RTKs, reinforcing the central role of RTK activation in promoting formation of GISTs. Because not all RTK-activating mutations are biologically equivalent, genotyping of GISTs may help predict response to targeted therapies.

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