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REVIEW

Neutrophil elastase and cancer

Takashi Sato[a], Satoshi Takahashi[b], Takao Mizumoto[c], Michiko Harao[c], Miwa Akizuki[d], Miyuki Takasugi[d], Takashi Fukutomi[d], Jun-ichi Yamashita[b,*]

[a]*Department of Otolaryngology, Aichi-Gakuin University, Suemori-dori 2-11, Chikusa-ku 464-8651, Aichi, Japan*
[b]*Department of Breast Oncology, Okazaki City Medical Association Public Health Center, Tatsumi-Nishi 1-9-1, Okazaki 444-0875, Aichi, Japan*
[c]*Department of Digestive Surgery, Honjo 1-1-1, Kumamoto 860-8556, Japan*
[d]*Department of Breast and Endocrine Surgery, Aichi Medical University, Aichi 480-1195, Japan*

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Summary
This mini-review summarizes our recent experimental and clinical studies on neutrophil elastase (NE) and cancer based on our original view point. Neoplasms metastasize as a result of a complex series of events. This process requires various degradative enzymes including proteases. NE has broad substrate specificity under physiological conditions, and excessive NE results in digestion of not only elastin, but also other extracellular matrix proteins. Several cell lines from human breast cancer and human lung cancer produce immunoreactive NE. The amount of immunoreactive NE in tumor tissue is an independent prognostic indicator of patients with breast cancer and lung cancer. Furthermore, a specific NE inhibitor completely suppressed growth of cancer cells transplanted into severe combined immunodeficiency mice. The use of NE inhibitor would seem to be a promising way to prevent the invasion and metastasis of cancer.

Contents

*Corresponding author. Tel.: +81 564 52 1572; fax: +81 564 54 0102.
E-mail address: j-yamashita@okazaki-med.or.jp (J.-i. Yamashita).

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Cancer cells closely resemble neutrophils

An understanding of the process that is involved in metastasis and its regulation is crucial to the development of new strategies for the treatment and prevention of human cancers. Fig. 1 shows the idea of this study that neutrophils and cancer cells are similar in character. The process by which cancer cells metastasize is composed of a complex series of events. Cancer cells enter the circulation and attach to endothelial cells (adherence) to pass through them (penetration) and migrate over a distance (migration) to enter the tissue of the metastatic organ to proliferate there. In the same way, neutrophils drift in blood and adhere loosely to adhesive molecules on the endothelial cells in an inflamed area. They roll along the endothelial cells and then adhere closely to the endothelial cells to penetrate vessel wall. Neutrophils can destroy the basement membrane and migrate over a distance to fight against foreign bodies. Neutrophils can play an important role to maintain the homeostasis of a living body.

Thus, neutrophils and cancer cells closely resemble to each other. The only difference between them is that cancer cells neither become apoptosis nor die in the tissue. Cancer cell growth requires new blood vessels, while neutrophils become apoptosis after entering tissue, and die within 72 h of leaving the bone marrow. This is the only difference between cancer cells and neutrophils. The process that both of them follow, i.e., entering blood vessels and invading the tissue of an organ after adhering to the wall of the blood vessels, is quite the same.

Some cancer cells have neutrophil elastase

During the invasion and metastasis formation process, cancer cells confront a variety of natural tissue barriers *in vivo*, such as basement membranes and surrounding tissue stromal matrices composed of elastins, collagens, and proteoglycans. It is thus necessary for cancer cells to enhance their invasiveness through an increased proteolytic activity. The production of tumor cell proteases has been implicated in the invasion of tumor cells into adjacent host tissues and metastasis [1–3].

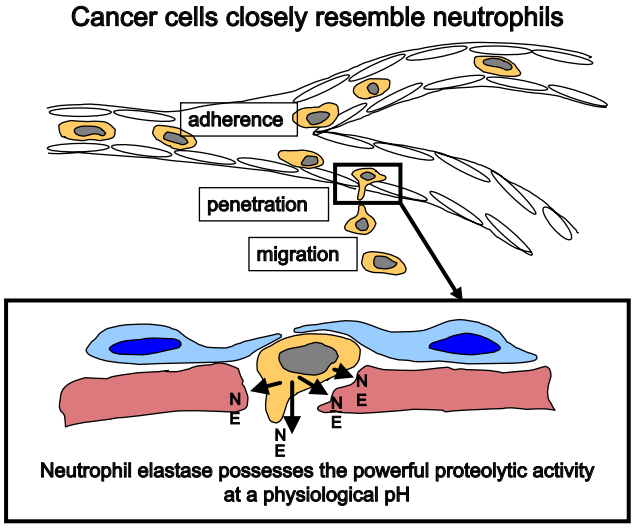

Fig. 1 The idea of the study that neutrophils and cancer cells bear a close resemblance.

There are three well-characterized mammalian elastases. The best characterized is the porcine pancreatic elastase I, first described by Balo and Banga [4], which is a serine protease secreted in a zymogen form by pancreatic acinar cells. The second class of mammalian elastase is neutrophil elastase (NE), the neutral protease found in granules of human neutrophils [5,6]. A third mammalian elastase is a metalloprotease, secreted by inflammatory macrophages [7]. Of these elastases, NE is the only neutral protease that is able to degrade insoluble elastin [5]. NE can also hydrolyze other extramatrix proteins, including fibronectin, proteoglycans, ad type IV collagen [8,9].

Since the composition of the invaded tissues consists mainly of these components, we could guess that cancer cells might produce NE. In order to verify this hypothesis, an *in vitro* experiment by an immunoassay has been conducted using two breast cancer cell lines and seven lung cancer cell lines. This assay is a highly sensitive and specific one that enables rapid measurement of both free-form and alpha1-protease inhibitor-complexed form of immunoreactive NE [10]. We found that NE was produced in all of them except one lung cancer cell line, PC-3 (Fig. 2) [11,12].

The presence of elastinolytic activities in human breast cancer tissue has been demonstrated by Hornbeck et al. [13], but in their study it was not determined whether the activity could be attributed specifically to breast cancer cells. Thereafter, several investigators have described elastinolytic enzyme production by human and rodent mammary tumor cells [14–16]. However, these enzymes have not been isolated or characterized. We first demonstrated that immunoreactive NE was produced by lines of breast cancer and lung cancer cells *per se*. In addition, we revealed that two normal breast epithelial cell lines, HBL-100 and Hs 578Bst, produced no detectable immunoreactive NE. In a separate investigation, we showed that NE immunoreactivity is seen solely in the breast cancer cells and not in the stromal cells (data not shown), suggesting that NE is synthesized by the epithelial component of breast cancer tissues.

NE in cancer tissue as an independent prognostic factor

Immunoreactive NE concentration in tumor extracts of primary breast cancer was determined with the same immunoassay, and the relation between the amount of NE and the prognosis for the patients has been examined. It was found that higher the amount of NE in the tissue, the worse the prognosis for the patients with breast cancer [17] (Fig. 3). Breast tumors are heterogeneous with varying tumor cellularity and varying amounts of stroma with infiltration of macrophages, lymphocytes, neutrophils, and fibroblasts. It is, therefore, possible that some of the protein detected in the study that assayed tumor cytosols was extracted from infiltrating inflammatory cells and that the inflammatory cell involvement correlates with poor prognosis. There is indeed evidence that inflammatory cell