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Commentary

Molecular interphase between extracellular matrix & cancer cells

Tumorigenesis and tumour progression are highly complex biological processes where normal control over cell growth is modified by various genetic mutations[1]. Cancer progression depends on tumour cell *per se* and the microenvironment in which tumour cells are embedded. Interaction between tumour cell and microenvironment results in the activation of various molecular pathways including angiogenesis as a mode to supply essential nutrients[2]. Concept of a permissive environment in promoting tumour growth has interesting history. In the early 1850s, the German pathologist and scientist Rudolf Ludwig Carl Virchow had hypothesized the possible roles of inflammatory cells and abnormal extracellular matrix (ECM) biosynthesis on tumour progression[3]. A few years later, an English surgeon named Sir Stephen Paget postulated the "Seed and Soil" theory in 1889[4]. His hypothesis was contradicted by many scientists. Much later, his view has been supported and re-confirmed by numerous researchers. The potential of tumour cells to metastasize depends on the interactions with the tumour microenvironment factors that promote tumour growth, survival, angiogenesis, invasion and metastasis[5]. Several years down after, Dvorak[6] re-described that the desmoplastic stroma or the granulation tissue surrounding tumour cells did not heal, unlike other inflammatory granulation tissue. He further emphasized importance of certain key factors present or expressed by the reactive or desmoplastic stroma which include cancer-associated fibroblasts (CAFs), inflammatory cells, cells constituting blood vessels and ECM[7]. These mutual interactions and cross-talks between tumour cells and stroma promote tumour progression in many ways. A cancer cell has the propensity to secret various types of growth factors, such as transforming growth factor beta (TGF-β), epidermal growth factor (EGF), basic fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF). Under the influence of these many growth factors, a cancer cell may change the property of microenvironment. Fibroblasts get converted to large spindle-shaped CAFs acquiring expression for alpha smooth muscle actin associated with increased proliferative index and rapid collagen biosynthesis, producing an altered or modified ECM[8]. On the flip side, the CAF of the specialized ECM secrets increased amount of tenascin C, thereby reducing adhesive property of the cancer cells promoting their motility and metastasis. CAFs are also documented to secrete (*i*) proteases that degrade ECM releasing cytokines facilitating tumour angiogenesis and metastasis, (*ii*) insulin-like growth factor, and (*iii*) hepatocyte growth factor, thereby increasing and promoting tumour cell survival and motility[9]. Inflammatory cell present in ECM induces enhanced cytokines and chemokines production by tumour cells[10], which appears to be a counter-intuitive function as leucocytes have the property to attack and destroy tumour cells. Recruitment of immune cells facilitates further tumour growth and metastasis via secretion of matrix-degrading enzymes such as matrix metalloproteinases (MMPs), urokinase-type plasminogen activator (uPA) and heparanases[11].

MMPs are calcium-dependent endopeptidases which require a coordinated activity with zinc ion to mediate catalysis. The active function of MMPs is to mediate degradation of different ECM components[12]. The biochemically active components of MMPs and their enzyme activities have been classified into five major groups[13]: (*i*) true collagenases that have the property to cleave major fibrillar collagens; (*ii*) gelatinases that proteolyse denatured collagen; (*iii*) stromelysin which is the most diverse component that has the capacity to activate other MMPs; (*iv*) the next group is the matrilysins that may be either in secreted form or intracellular. The active cytoplasmic form helps in maintenance of innate immune system by activating defensin; and (*v*) the last major group encompasses collagen, cell surface molecules and

bioactive molecules. MMPs participate almost in every biological processes involving remodelling of ECM, embryo implantation to tissue necrosis. There are certain MMP isoforms expressed in non-primates with minimal knowledge of their function and structures[14].

Physiological transcription of MMPs is governed by tightly regulated pathways and detectable in very low amount. Further regulation of MMP activity is post-translational by modifying the production of zymogens required for activation and co-expression of tissue inhibitors of metalloproteinases[15]. Any situation resulting in dysregulation of the regulatory mechanisms may lead to worsening of a given disease condition. Despite the concept of a clear association between MMPs and cancer progression, there is still a big lapse in the field of translational research in objectiveness of the roles played by MMPs, basically due to failures of the MMP inhibitors in multiple phase III trial[16]. The reasons for the failure to inhibit the MMPs may presumably be explainable hypothetically for various reasons, but the two critical issues are lack of specificity and dose-limiting side effects that are poorly understood. Some potential inhibitors recently recognized include MT1-MMPI, MMP-7 inhibitors, FGF-2 antagonist PTX3 and all-trans retinoic acid[17]. Increased MMP levels within a tumour may be the tumour cells or peri-tumoural activated fibroblasts or inflammatory cells, and the serum concentration of specific MMP has been described to be enhanced in certain select cancers[17] and body fluids[18].

There are limited reports on pancreatic cancer where raised MMP-2 plasma levels have been observed[19,20]. The study[21] in this issue, however, failed to find any significant relationship between plasma MMP-2 level with tumour stage and disease outcome. The authors have observed a significant correlation between MMP-2 plasma level with plasma carbohydrate antigen (CA) 19-9. Patients who had tumour recurrence with distant metastasis after surgery showed higher plasma levels of both MMP-2 and CA19-9 compared to patients having only local recurrence. Moreover, patients with no recurrent disease at three months post-surgery exhibited low MMP-2 values. The authors also observed a positive correlation between MMP-2 levels in plasma and tumour tissue. The study highlighted the important implication of serum MMP-2 in pancreatic cancer in predicting tumour outcome. This observation however, requires further verification in more number of randomly selected cancer patients before and after surgery.

In conclusion, MMPs including MMP-2 remain a cryptic but viable biomarker in cancer diagnosis and in assessing the treatment outcome. The futuristic translational research for therapeutically implacable MMP inhibitors to be clinically successful, the target MMP needs to be identified and characterized at molecular level. MMP inhibitor(s) need(s) to be highly selective so that it can produce the desired effect. Moreover, it also needs to be a highly specific biomarker having the property of selective accumulation in the targeted diseased organ with no or minimal adverse clinical effect.

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