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MMP inhibitors:>From Bench to Clinic

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Matrix metalloproteinases (MMPs) are the family of proteinases with similar characteristics of 1) proteolysis of extracellular matrix(ECM) components, 2) requiring zinc ion for the activation and being inhibited by zinc chelating agents, 3) being secreted as a zymogen form and activated for proteolytic activities, 4) being in balance with natural inhibitors, such as tissue inhibitor of matrix metalloproteinase (TIMP). MMPs are known to be involved in many physiologic and pathologic processes such as development, wound healing, ovulation, menstruation, inflammation and cancer. MMPs are important in invasion, metastasis and angiogenesis in cancer, which implies the potential target of cancer treatment.

Among many MMPs (Table 1), MMP-2 and MMP-9 are known to be the most significant MMPs in cancer. The 72kDa MMP-2 (gelatinase A) is constitutively expressed in endothelial cells and epithelial cells, and the 92kDa MMP-9 (gelatinase B) in inflammatory cells including blood neutrophils and tissue macrophages. Cancer stromal cells are secreting MMPs in response to cancer cells' stimuli, but there are also many reports that cancer cell itself is secreting MMPs. In addition, cancer cells might function as a receptacle for stromal MMPs. Sato et al. found the novel MT-1 MMP which is bound to cell membrane and is important for MMP-2 activation. The types and the expression amount of each MMP are different based on the tumor types and the different disease stage.

The balance between the MMPs and TIMPs is the important factor for pathologic processes. With the many evidences that MMPs activities are related to cancer progression and poor prognosis, there have been many efforts to develop MMP specific inhibitors. There are several groups of MMPIs (Table 2), 1) natural inhibitors: TIMPs, non-specific protease inhibitors, 2) chelating agents: EDTA, 3) peptidomimetics: batimastat, marimastat 4) non-peptidomimetics: AG-3340, Bay 12-9566, BMS-275291, and 5) tetracycline analogues: Col-3.

Even though with numerous efforts for MMPI development, current randomized phase III studies showed the disappointing results with MMPIs both in efficacy and toxicity. For

developing MMPIs, there are many factors to consider, 1) the oral bioavailability, 2) the target specificity, 3) the toxicity spectrum with long term administration, 4) the drug availability, 5) the proper clinical trial design to evaluate the benefit of cytostatic agents, 6) the proper biomakers for patient selection and tumor response evaluation. We are looking forward to see the results of currently developing novel MMPs such as Col-3 (Metastat) and BMS-275291.

References

1. Stetler-Stevenson WG. Progelatinase A activation during tumor cell invasion. Invasion Metastasis 1994:14:41
2. Stetler-Stevenson WG, Hewitt R, Corcoran M. Matirx metalloproteinases and tumor I nvasion: from correlation and causality to the clinic. Seminars in Cancer Biology 1996:7:147
3. Sato H. et al., A matrix metalloproteinase expressed on the surface of invasive tumour cells. Nature 1994: 370: 61
4. Chung HC et al. Expression of matrix-metalloproteinases(MMP-2, MMP-9) in gastric cancer as new targets for biotherapy. J Korean Cancer Assoc 1995:27:897
5. Rha SY et al. Different expression patterns of MMP-2 and MMP-9 in breast cancer. Oncology Reports 1998:5:875
6. Rosemurgy et al. A randomized study comparing marimastat to gemcitabine as first line therapy in patients with non-resectable pancreatic cancer. Proc Am Soc Clin Oncol 18:26a, 1999(abstr 1005)
7. Shephard FA et al. Randomized double-blind placebo controlled study of marimastat in patients with small cell lung cancer following response to first-line chemotherapy. Proc Am Soc Clin Oncol 20:4a, 2001(abstr 11)

Table 1. MMPs family and substrates

MMP	Protein	Main substrate(s)
MMP-1	interstital collagenase	fibrillar collagen
MMP-2	gelatinase A (72 kDa)	type IV and V collagens, fibronectin
MMP-3	stromelysin 1	laminin, fibronectin, non-fibrillar collagen
MMP-7	matrilysin, pump-1	laminin, fibronectin, non-fibrillar collagen
MMP-8	PMN collagenase	fibrillar collagens
MMP-9	gelatinase B (92 kDa)	type IV and V collagens
MMP-10	stromelysin 2	laminin, fibronectin, non-fibrillar collagen
MMP-11	stromelysin 3	serpin

MMP-12	metalloelastase	elastin
MMP-13	collagenase-3	fibrillar collagens
MMP-14	MT1-MMP	pro-MMP-2
MMP-15	MT2-MMP	not determined
MMP-16	MT3-MMP	pro-MMP-2
MMP-17	MT4-MMP	not determined
MMP-18	not determined	
MMP-19	not determined	

Table 2. MMPIs in clinical development with substrate specificities

MMPI	Activity spectrum	Targets	Status
Peptidomimetics inhibitors			
Batimastat (British Biotech)	broad	1,2,3,7,9	Halted (1996.11)
Marimastat(British Biotech)	broad	1,2,7,9	II/III
Nonpeptidomimetics inhibitors			
AG3340 (Agouron)	selective	2,3	I/III
BAY 12-9566 (Bayer)	selective	2,3	Halted (1999. 9)
BMS-275291 (BMS)	selective	2,9	I
CGS 27023A (Novartis)	broad		
D2163 (Chiroscience)	selective		
Ro32-3555	selective	1	I/II
Modified tetracycline			
Col-3	selective	2,9	I