SIGNIFICANTLY ELEVATED PLASMA MMP-8 LEVELS ARE PRESENT FOR TWO WEEKS AFTER COLORECTAL CANCER RESECTION AND MAY BE RELATED TO THE WOUNDS WHICH HAVE MMP-8 LEVELS THAT ARE 11-52 TIMES HIGHER.

SAGES 2022
Abstract ID: 118137
P194

HMC Shantha Kumara[1], N Mitra [1], SD Samarakoon[1], Xiaohong Yan[1], Vesna Cekic[1], Richard L Whelan[1,2]
1.Department Of Surgery, Lenox Hill Hospital, Northwell Health Cancer Institute, New York, NY USA,
2.Long Island Jewish Medical Center, New York, NY, USA

Introduction

Matrix metalloproteinase-8(MMP-8) also known as neutrophil collagenase or collagenase 2 , is a member of matrix metalloproteinase family of zinc- and calcium-dependent endo-peptidases(1). MMP-8 is expressed by a variety of cells including macrophages(2), fibroblasts, chondrocytes and endothelial cells(3). Many cytokines such as IL-1, IL-8, TNF-α, and GM-CSF, stimulate the release of MMP-8 from neutrophils during pathological processes such as inflammation(4). As a protease, MMP8, is capable of catalyzing the break down the extracellular matrix (ECM) and plays key roles in tissue remodeling and wound healing(5,6). MMP-8 also facilitates cancer growth by promoting invasion and via regulation of growth signaling, angiogenesis and immune responses (7). MMP8 knockdown in human umbilical vein endothelial cells (HUVEC's) with MMP-8 shRNA impaired HUVEC's pro angiogenic effects (8). MMP-8 expression has been noted in a variety of cell types, as mentioned, as well as in many cancers (9, 11). Elevated blood levels have been noted in colorectal cancer (CRC) patients and significantly elevated plasma MMP-8 levels were noted for a month after CRC resection (12). We hypothesize that the healing wound may be a source of MMP-8 to the bloodstream. This study's aim was to measure perioperative MMP-8 levels in blood and wound fluid (WF) samples obtained after CRC resection.

Methods

Consenting CRC resection patients in an IRB approved tissue (plasma, wound fluid) /data bank in whom an intra-abdominal Jackson Pratt (JP) drain had been placed made up the study population. The group's demographic, clinical and pathologic data were reviewed. Preoperative (preop) and post-operative (postop) blood and wound fluid (WF) samples were simultaneously collected Preop and on post operative day(POD) 1, POD3 and 1 or more later time points. Blood and WF samples were centrifuged and the resulting plasma and clear WF supernatant were stored at -80˚ C until use. Late samples (POD 7-13) were bundled into 7 day blocks and considered as single time points. MMP-8 levels were determined in duplicate via ELISA and data presented as median and 95%CI. The Wilcoxon and Mann and Whitney test were used for analysis (significance p<0.05).

Parameter	Result
Demographic & Operative Data	N =27 patients
Age, years (mean ± SD)	66.3± 12.7
Sex: Male	11(41.0%)
Female	16 (59.0%)
Incision size: cm (mean ±SD) Surgical methods: LAP/Hand or Open methods	9.3±3.8 (lap /hand) 26.0±8.3 (open op)
Surgery time, min (mean ± SD)	466.1± 108.1
Length of stay, days (mean ± SD)	9.3± 5.7

Table 1: MMP-8 protein levels in preop and post op Plasma vs. postop Wound fluids

Time	Plasma (ng/ml)	(n)	Wound fluids (ng/ml)	(n)	*p*
PreOp	5.59; 95% CI:2.99-8.23	27	N/A	N/A	N/A
POD1	16.82;95%CI:8.03-27.26	27	876.7; 95%CI: 511.3-45. 1952.7	26	< 0.0001
POD3	26.65;95%CI:11.42-45.52	26	286.8;95%CI: 180.5-652.7	24	< 0.0001
POD 7-13	11.11;95%CI: 5.82-20.91	16	328.1;95%CI: 121.2-1819.8	16	< 0.0001

Figure 1: Surgical procedure

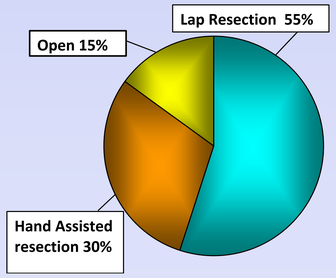
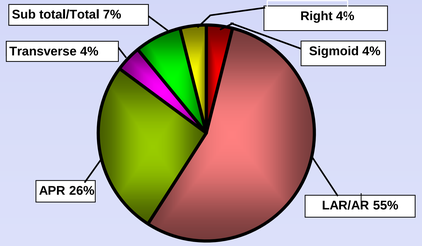


Figure 2: Types of Resection



Results

The study population consisted of 27 elective CRC patients (pts) (colon, 4; rectal, 23) for whom adequate plasma and WF samples were available. The demographics can be found in the adjacent Table. The surgical methods used were laparoscopic (15pts, Incision length (IL) 8.3±3.5 cm); hand assisted laparoscopic (8pts, IL: 14.5±9.0 cm), and open (4pts,IL: 23.7±7.8))(figure 1). The majority of patients in the study underwent Low anterior resection or Anterior resection (55%) followed by APR resection (26%) and sub total/total colectomy (7%) (Figure 2). The mean length of stay was 9.2± 5.8 days. Plasma MMP-8 levels were significantly elevated on POD 1(P<0.001), POD 3(P<0.001), and POD 7-13 (P=0.01) versus preop levels. Of note, WF MMP-8 levels were 10-52 higher than the corresponding plasma levels at all postop time points (p<0.001)(Table 1).

Conclusion

Post op plasma MMP 8 levels were, again, shown to significantly elevated vs preop baseline levels for the 2 weeks studied. Further, wound MMP 8 levels were 11 to 52 times higher than the corresponding plasma levels. These results demonstrate that MMP 8 plays a role in wound healing and support the hypothesis that the origin of the added MMP 8 in the plasma postop is most likely the healing wounds. Elevated plasma MMP-8 may promote the growth of residual tumor deposits after surgery. Further study is warranted.

References

1. Cui N, Hu M, Khalil RA. Biochemical and Biological Attributes of Matrix Metalloproteinases. Prog Mol Biol Transl Sci. 2017;147:1-73
2. Yonggang Ma et al. Cross Talk Between Inflammation and Extracellular Matrix Following Myocardial Infarction, Editor(s): W. Matthijs Blankesteijn, Raffaele Altara, Inflammation in Heart Failure, Academic Press, 2015, Pages 67-79
3. Herman, M. P., G. K et al.2001. Expression of neutrophil collagenase (matrix metalloproteinase-8) in human atheroma: a novel collagenolytic pathway suggested by transcriptional profiling. Circulation 104:1899.
4. Tschesche, H. and M. Pieper (1998) in Handbook of Proteolytic Enzymes, Barrett, A.J. et al. eds.,Academic Press, San Diego, pp1162-1167.
5. Nwomeh BC et al. MMP-8 is the predominant collagenase in healing wounds and nonhealing ulcers. J Surg Res. 1999 Feb;81(2):189-95
6. Armstrong DG, Jude EB. The role of matrix metalloproteinases in wound healing. J Am Podiatr Med Assoc. 2002 Jan;92(1):12-8
7. Quintero-Fabián S et al.Role of Matrix Metalloproteinases in Angiogenesis and Cancer. Front Oncol. 2019 Dec 6;9:1370
8. Fang C et al. An important role of matrix metalloproteinase-8 in angiogenesis in vitro and in vivo. Cardiovasc Res. 2013 Jul 1;99(1):146-55
9. Juurikka K et al., The Role of MMP8 in Cancer: A Systematic Review. Int J Mol Sci. 2019 Sep 11;20(18):4506.
10. Allemani C et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): Analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391:1023–1075
11. Roy R et al. Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer. Off. J. Am. Soc. Clin. Oncol. 2009;27:5287–5297
12. Shantha Kumara HMC, Mitra N, Hedjar Y, Yan X, Cekic V, Martz J, Agnew J, Whelan RL Plasma levels of MMP 8, a tumor angiogensis promoting protein, are persistently elevated during the first month after minimally invasive colorectal cancer resection (MICR) which may promote residual tumor metastasis DDW 2022- May 21-24, in San Diego, California-USA