MMPs & TIMPs – What Do You Need To Know?

October, 2023

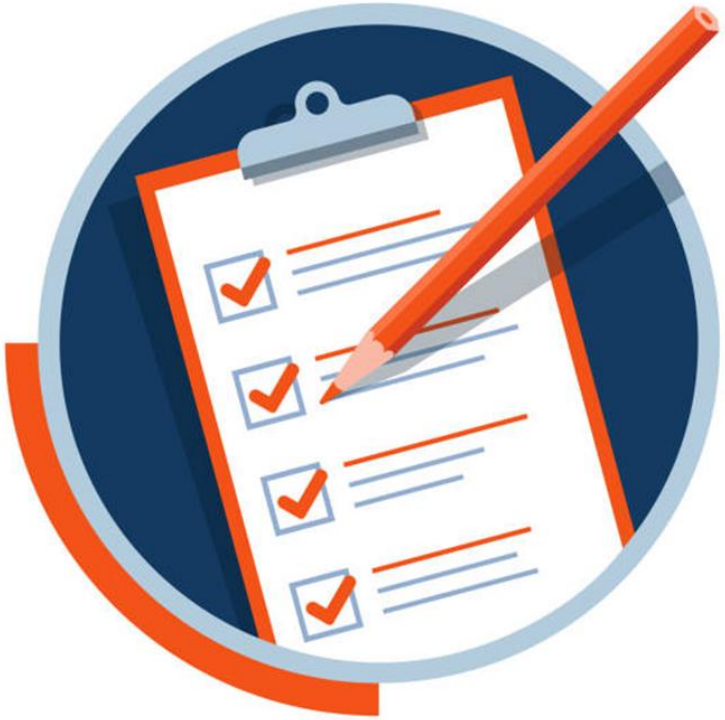
Agenda

What are MMPs and TIMPs

Connections to systems in the body

Connections to health conditions

Substances that help balance them

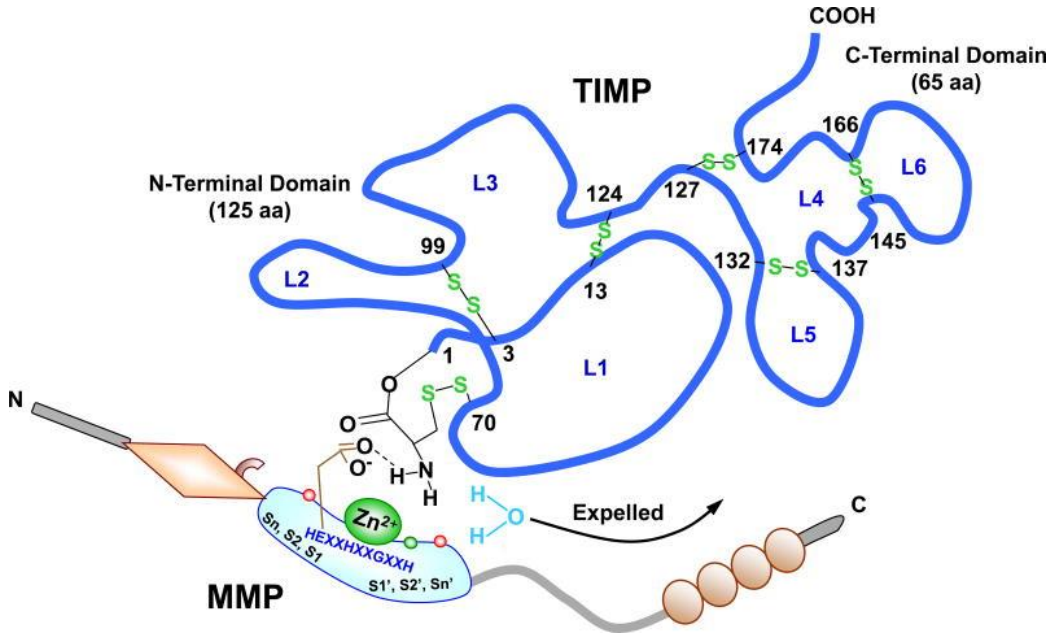


The purpose of this discussion is to be aware of MMPs and TIMPs

And a mechanism that may be playing a role in developing a health condition

We are always looking for answers

And knowing that these may influence what happens in the body and how they interact with other systems is helpful

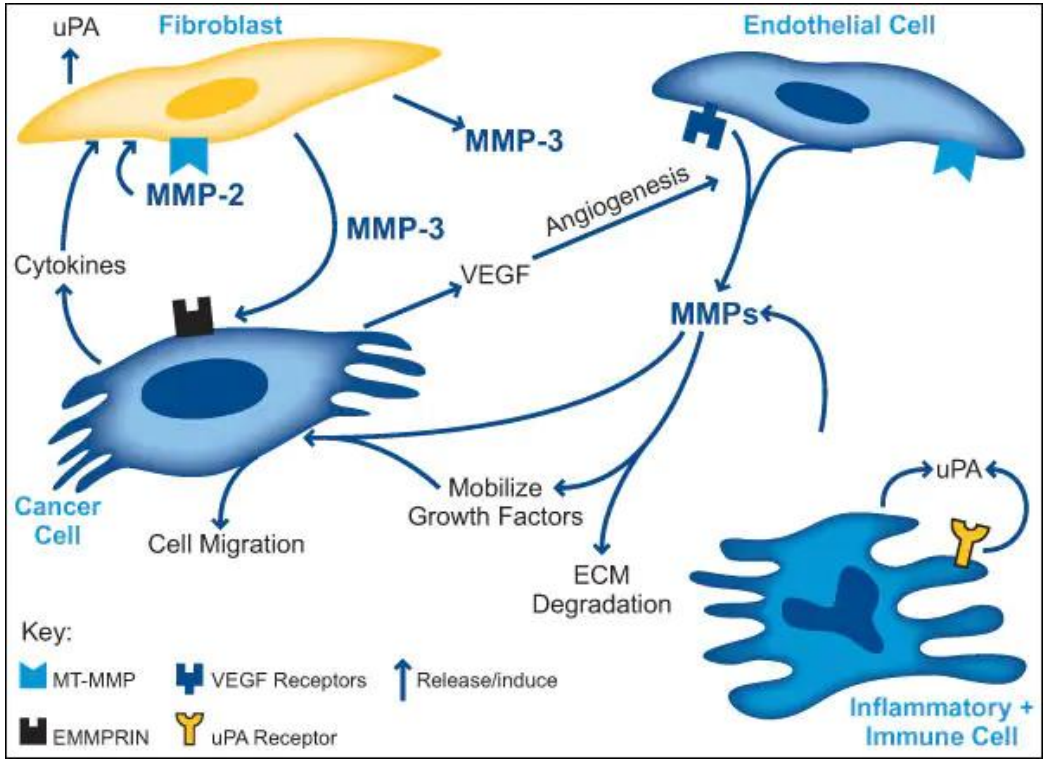


Matrix metalloproteinases (MMPs), (matrix metallopeptidases or matrixins) are calcium-dependent zinc-containing endopeptidases

Belong to the metzincin superfamily proteases

MMPs have a number of roles in a number of functions

They play a key role in ventricular remodeling by degradation of the extracellular matrix

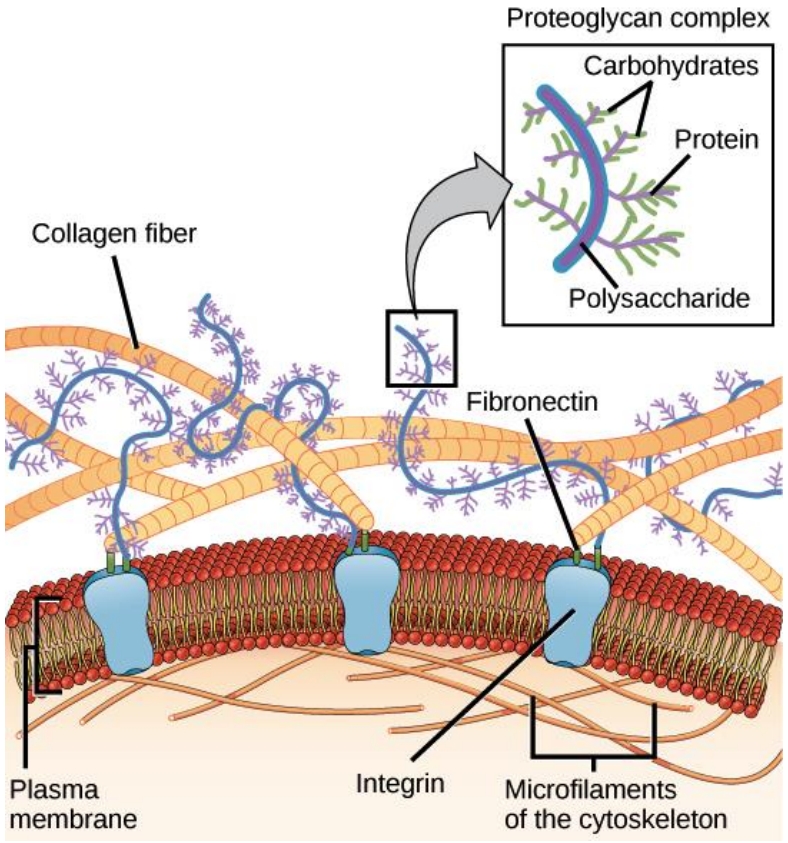


The extracellular matrix consists of macromolecules that support everything from local tissue growth to the maintenance of an organ

Many cell types including lung, epithelial, interstitial, vascular, and inflammatory cells

The pattern and levels of MMPs expressed vary among cell types and situations

Because of this, they can play a role in maintaining healthy tissue or in developing conditions



MMPs – The Good

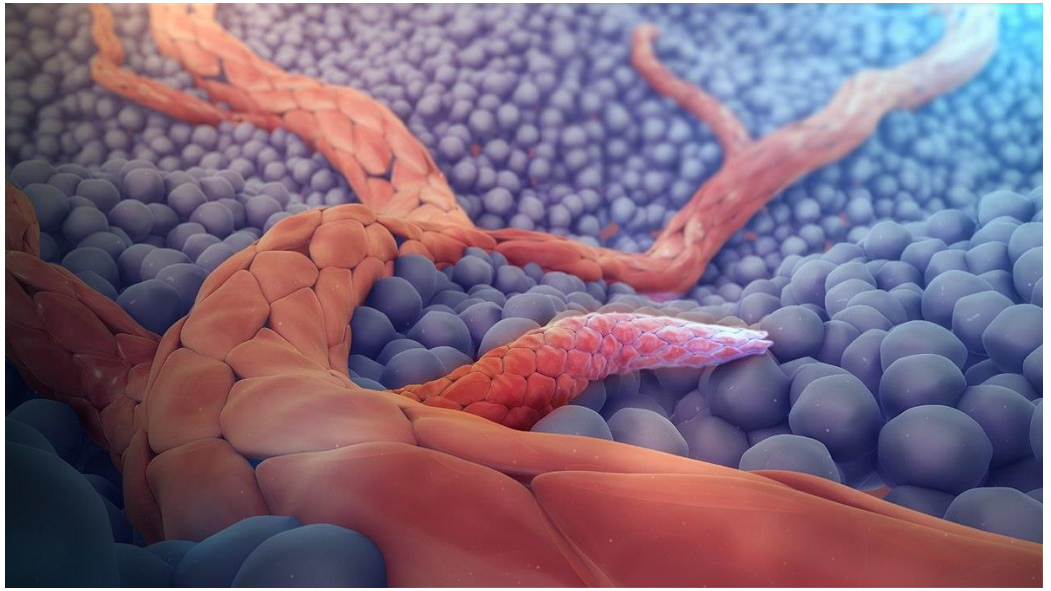
Can inactivate cytokines and chemokines which can lower inflammatory pathways

Also can help with apoptosis

Involved with cell proliferation, migration, and differentiation

Angiogenesis – new blood vessels from preexisting ones

Are part of the host's defense system



MMPs – The Bad

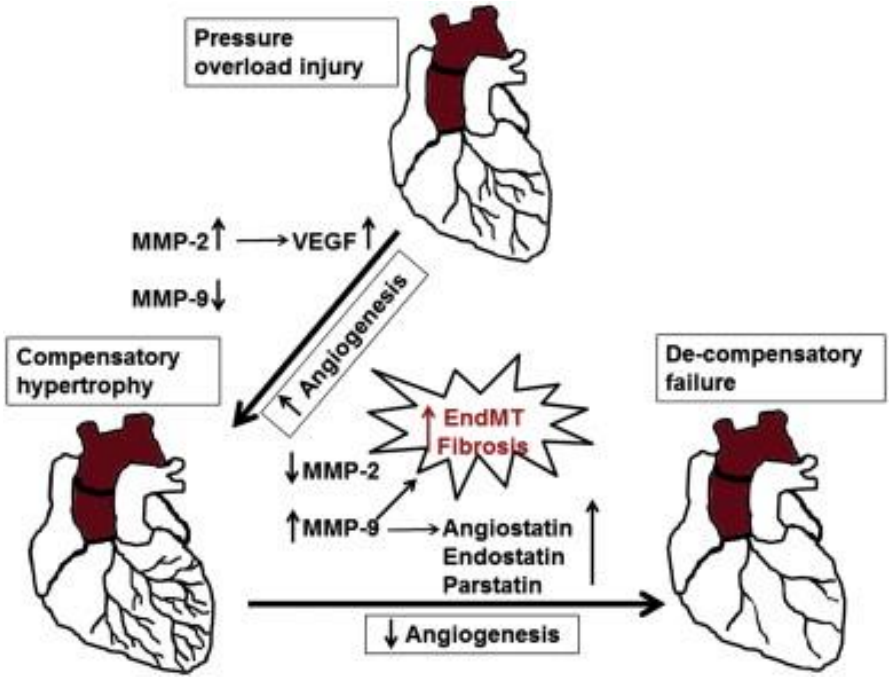
Play an important role in tissue remodeling

There have been 28 different MMPs and they are involved in different actions

ie: MMP2 and MMP9 are thought to be involved in metastasis – also involved with heart disease

ie: MMP1 is thought to play a role in rheumatoid arthritis and osteoarthritis

Some info indicates MMPs may be involved in aortic aneurysms

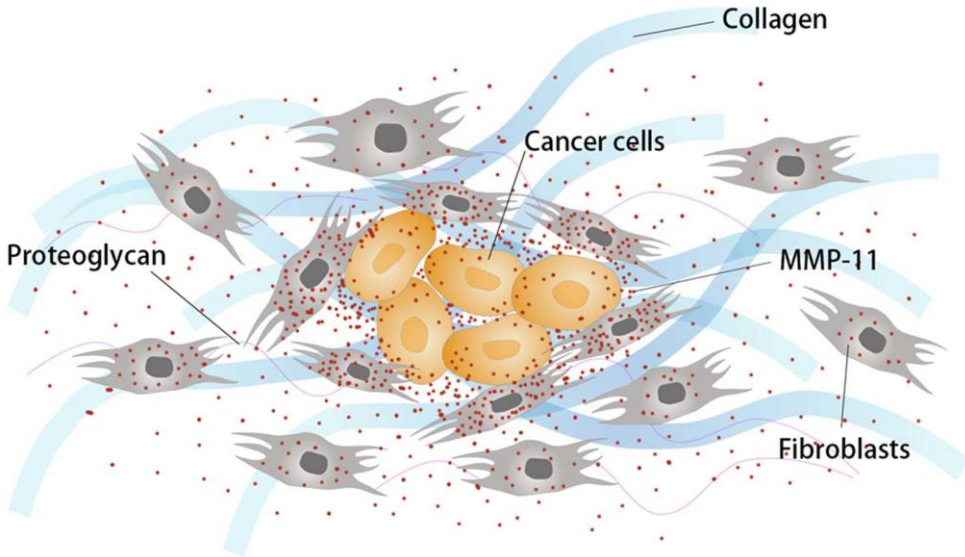


MMPs are not predictive for cancer

But kidney clear cell carcinoma (KIRC) show high expression of MMP7, MMP9, MMP14, MMP17, and MMP19 each individually correlated with shows significantly poorer survival in patients with KIRC

MMP11 is another potential biomarker for gastric, breast, and pancreatic cancer

MMP11 – dual role on tumors – can suppress apoptosis but can also suppress metastasis



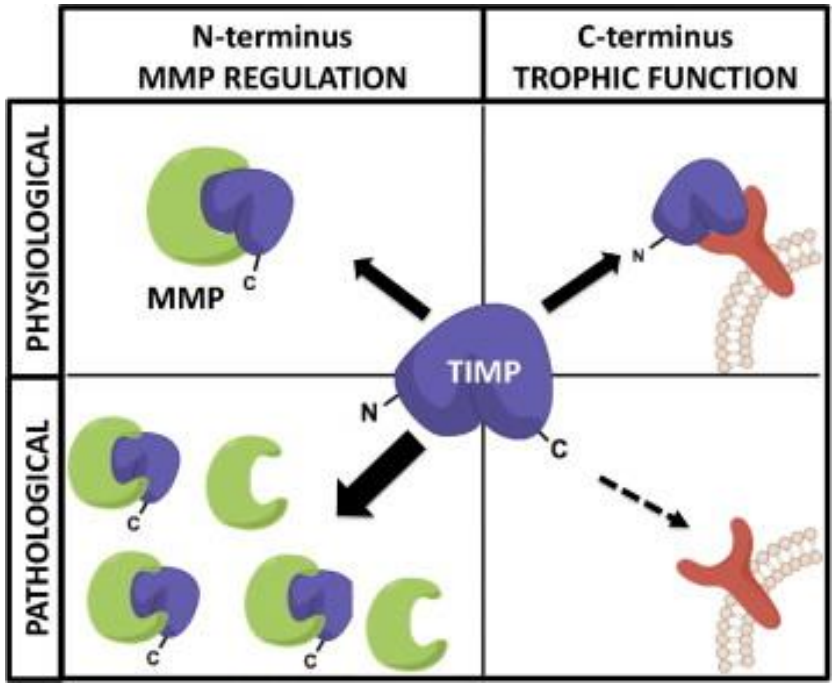
TIMPS

Tissue inhibitors of metalloproteinases: The regulators of MMPs

Have a key role in influencing the extracellular matrix, cell adhesion molecules, and many cytokines, chemokines, and growth factors on cell phenotype

They have been around for thousands of years

But not a lot is known about them

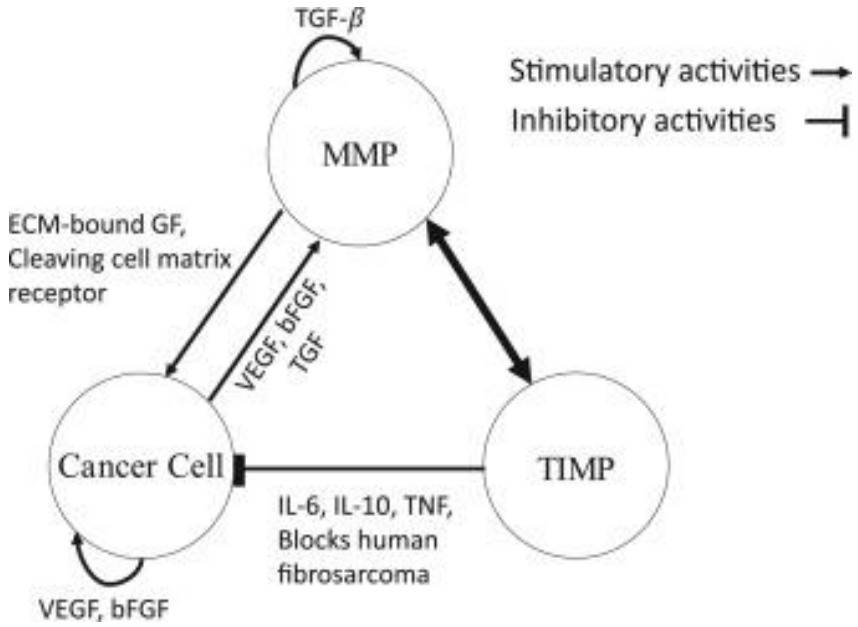


Protease inhibitors for MMPs

TIMP1, TIMP2, TIMP3, TIMP4

Down regulation of TIMP3 has been observed at different levels of malignancy in uterine cancer and could be a prognostic marker

MMP2 and MMP9 can form complexes with TIMPs when they are not fully developed and can inhibit their role in regulating MMPs



MMPs are inhibited by TIMPs when the TIMPs are activated

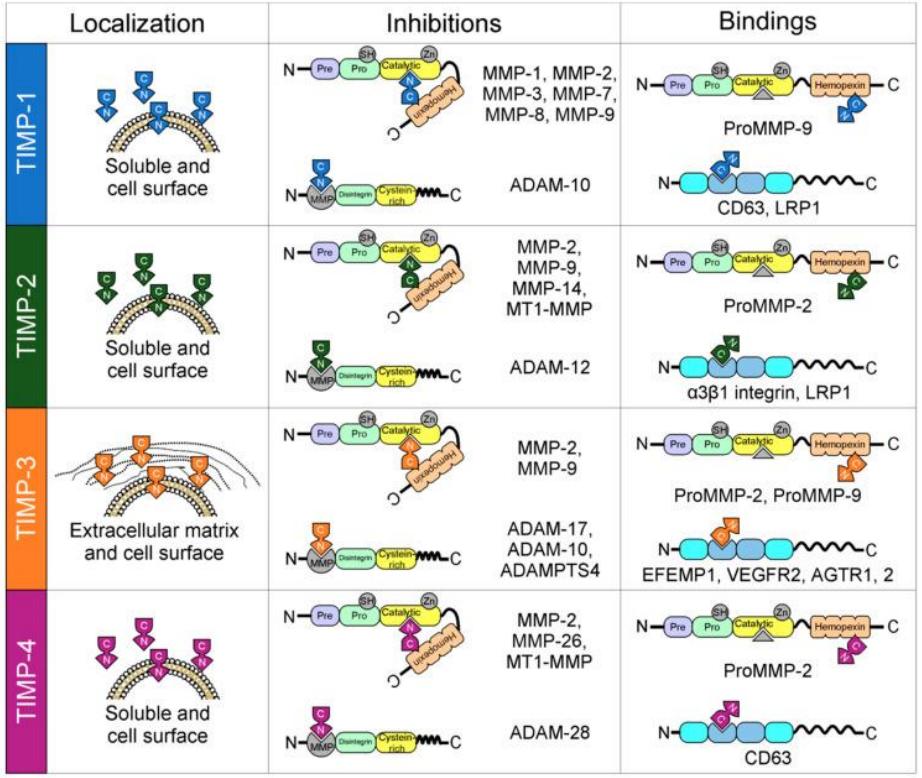
But in their unactivated form, they can form complexes with MMPs

And when this happens, TIMPs will not be regulating MMPs

The question is what influences this relationship to be one way or the other

Gut bacteria? Cytokines? Hormones?

All play a role in some fashion



The goal is to have MMPs help promote tissue we need and not promote aberrant tissue we don’t need or break done tissue we do need

We need TIMPs to help regulate the MMPs

Genes

Different MMPs, TIMPs are connected to different genes

ie: For MMP9, the gene coding for this enzyme has been found to be associated with various multifactorial diseases, including cancer

Polymorphisms of the MMP9 gene have been found to be correlated with the formation and the invasiveness of different types of cancer

Polymorphisms of the MMP-9 gene correlated with higher tumorigenesis and metastasis risk

Type of cancer	Polymorphism	Genetic model	Genotypes correlated with cancer risk	Polymorphism associated with tumorigenesis risk	Polymorphism associated with metastasis	References
Breast cancer	MMP-9-1562 C/T	Recessive	TT	✓	✓	34 35
Bladder cancer	MMP-9-1562 C/T	Recessive	TT	Unknown	✓	36
Colorectal cancer	MMP-9-1562 C/T	Recessive	TT	✓	✓	37 38
Gastric cancer	MMP-9-1562 C/T	Dominant	TT + CT	✓	✓	39
Lung cancer	MMP-9-1562 C/T	Dominant	CC + CT	✓	✓	40
Lymphoblastic leukemia	MMP-9-1562 C/T	Recessive	TT	✓	✓	41
Melanoma	MMP-9 2003 G/A	Recessive	GG	✓	✓	42
Oral cancer	MMP-9-1562 C/T	Dominant	CC + CT	✓	Unknown	43 44
Ovarian cancer	rs6094237 (T/A)	Dominant	AT + AA	✓	Unknown	45
Prostate cancer	MMP-9-836 A/G	Recessive	AA	✓	Unknown	46
Renal cancer	R279Q A/G	Dominant	GG + AG	Unknown	✓	47
Thyroid cancer	MMP-9-1562 C/T	Dominant	CT + TT	✓	✓	48 49

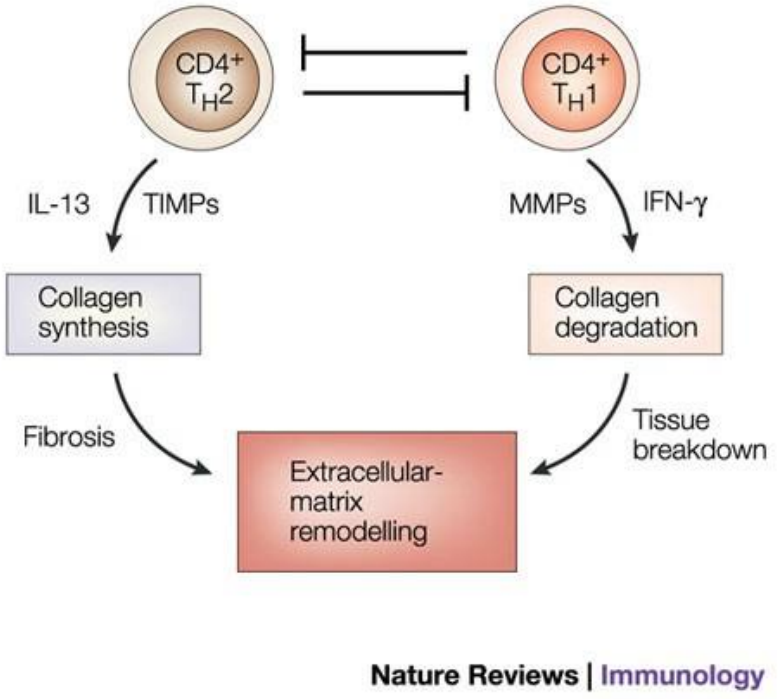
Immune System

There is a relationship between MMPs and TIMPs and the TH1/TH2 inflammatory pathways

Cytokines influence MMP/TIMP balance

ie: IL-4 and -13 increased production of collagen & modified the balance between MMP1 and TIMP1 – Th2 pathway for allergies

Ideally, MMP/TIMP is balanced because TH1/Th2 are also balanced and no tissue modulation that can cause issues occurs



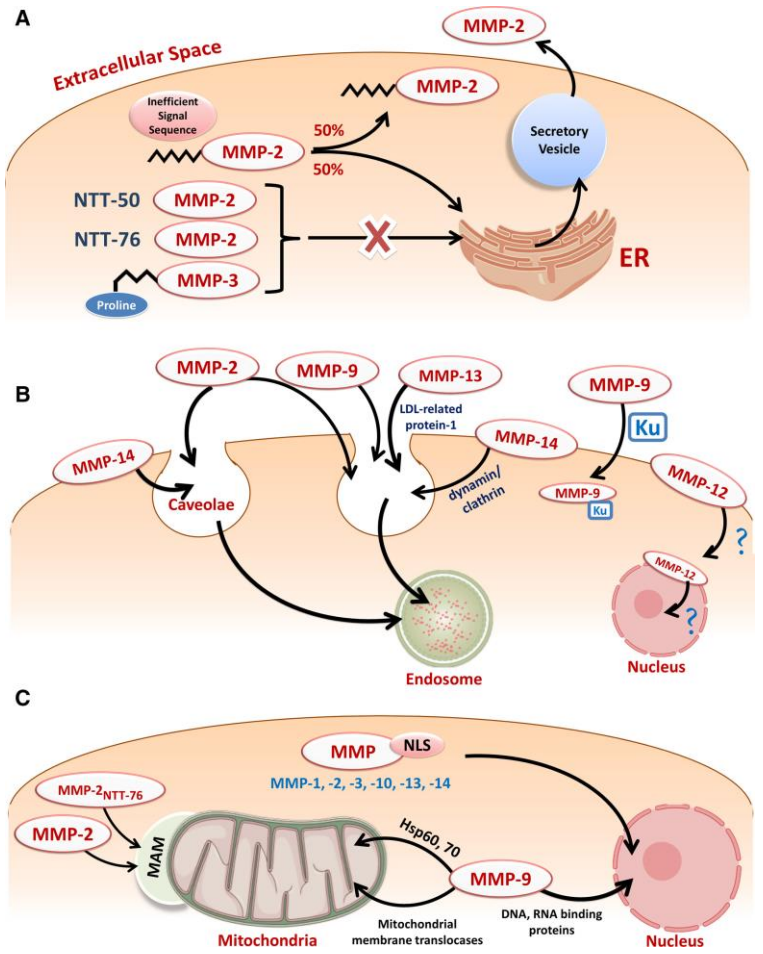
Hormones

Estrogen can have a protective effect by stimulating MMPs

ie: Estrogen can stimulate MMP2 to degrade beta-amyloid plaque

This can explain the protective effect estrogen can have

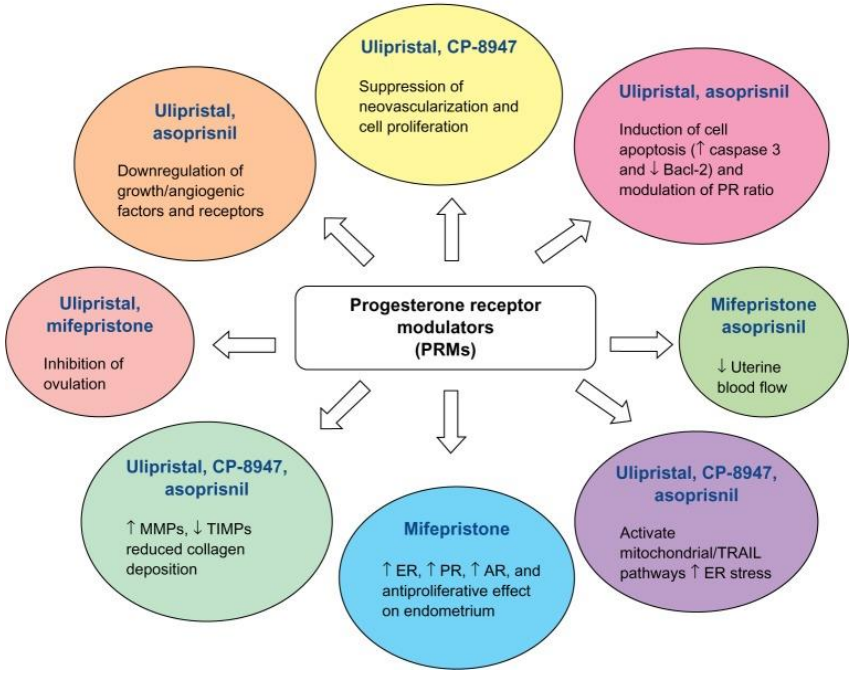
Excess estrogen has been implicated in increasing MMPs for both fibroids and endometriosis



Progesterone is believed to suppress MMPs (hence the development of fibroids is more prevalent when progesterone starts to decrease)

However, there is evidence that progesterone can play a role in developing fibroids – and its relationship with estrogen may be the key

Testosterone also can play a role in regulating MMPs and TIMPs although the relationship is unclear



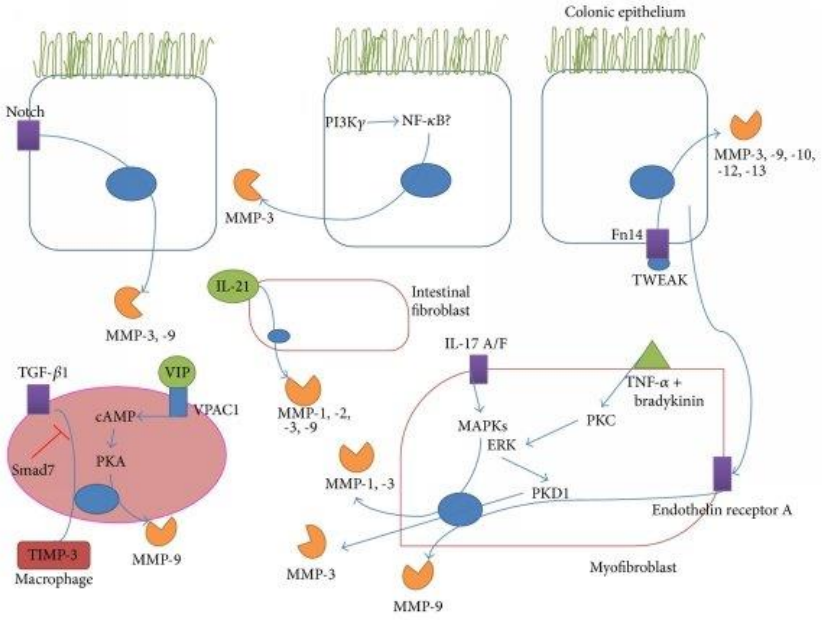
The Gut Connection

MMPs are involved in tissue injury and healing in the human gut

But epithelial cells and stromal cells produce large amounts of MMPs

ie: MMP2 and MMP9 are increased in the intestinal tissue and seem to be actively involved in the inflammatory and remodeling processes in inflammatory bowel disease

There were no major MMP differences between CD and UC

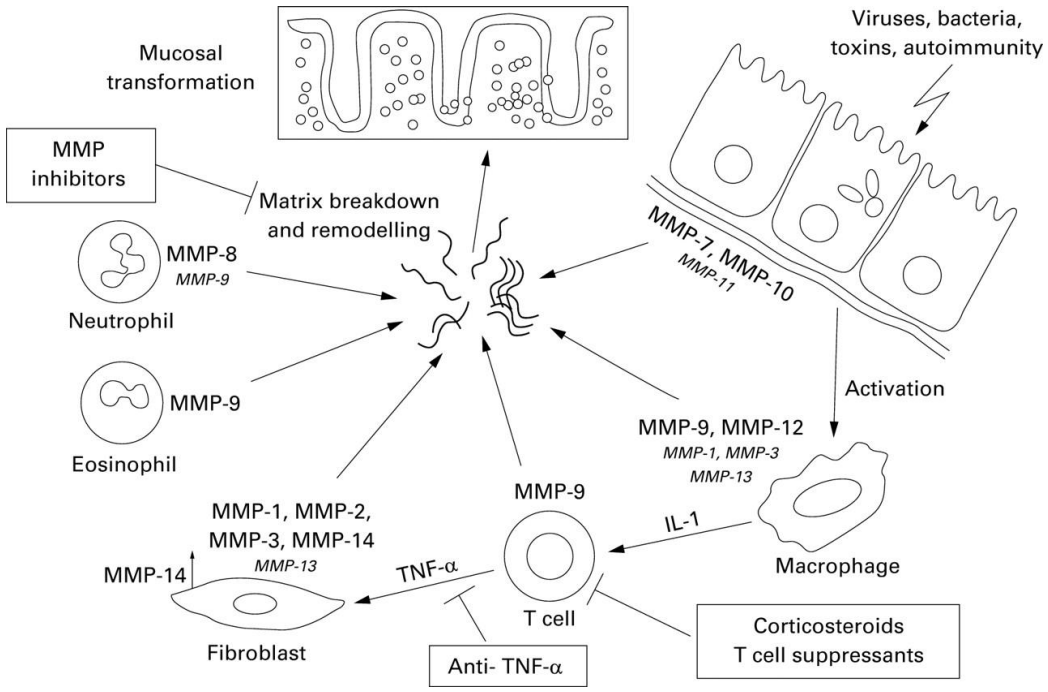


In a mouse study, MMP 9 increased the inflammatory response in mice infected with C. rodentium

– this was a protective mechanism to resolve the infection

Amount of c. rodentium decreased as a result

Also protected gut bacteria diversity from the infection

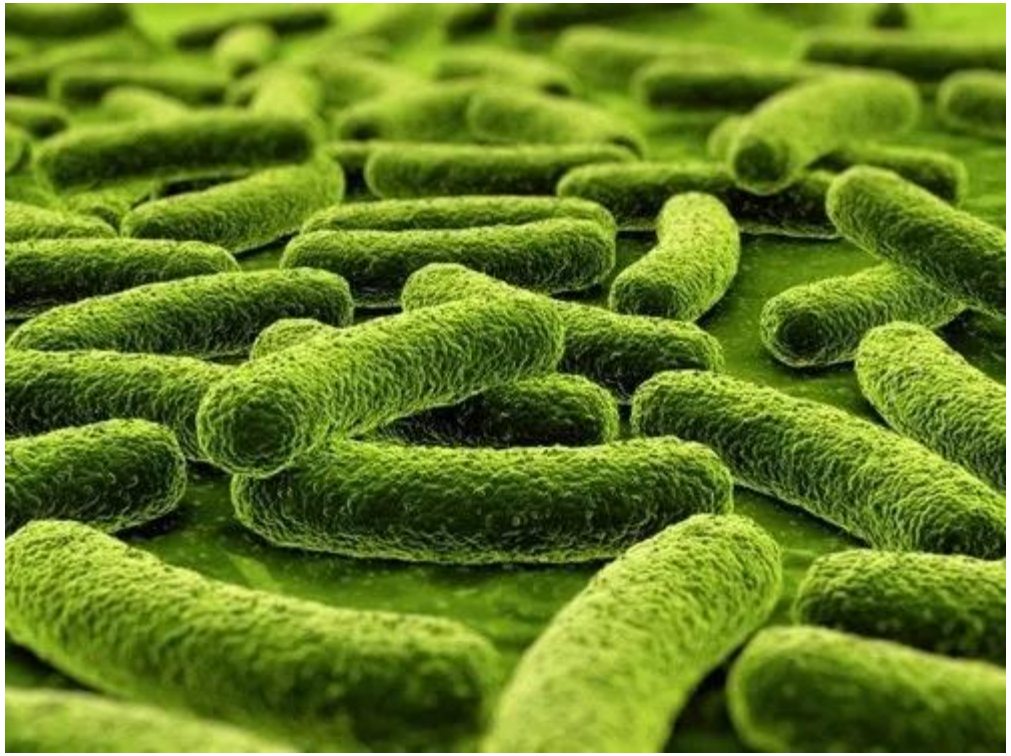


The bacteria connection is also involved

One human study found the probiotics l. rhamnosus GG and B. animalis subsp. lactis BB-12 increased MMP 9 and decreased TIMP1 in saliva

Researchers believed this indicated a protective role with regard to plaque and gingivitis

There’s much more to the regulatory relationship that still has to be researched



Heart Disease

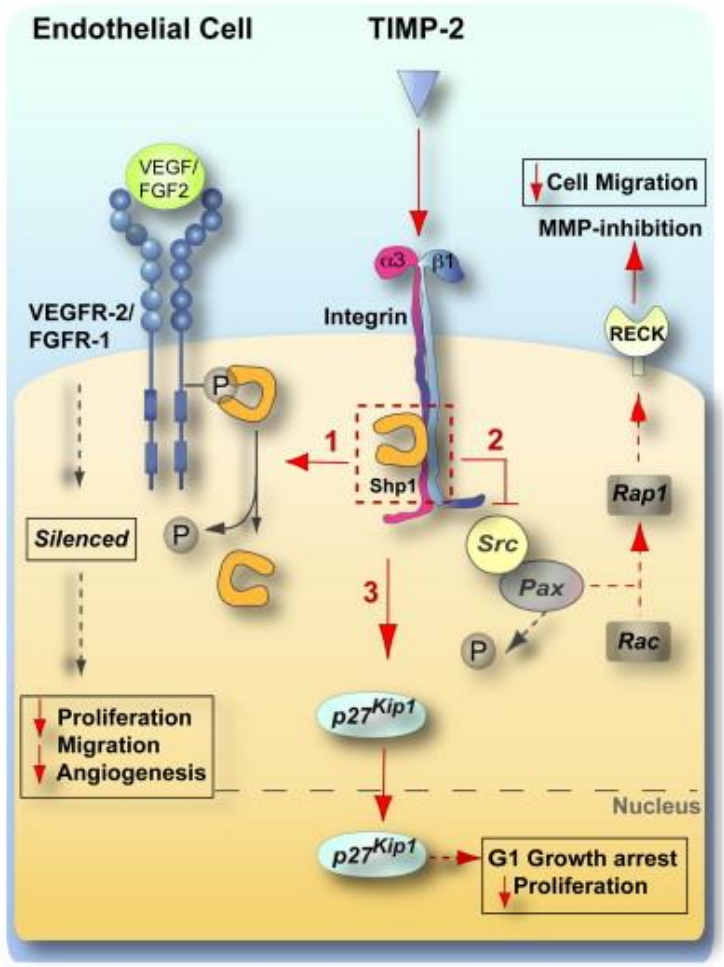
An issue with the MMP/TIMP balance can increase arterial plaque and the development of cardiac fibrosis after a heart attack

All of this can lead to heart failure

A mouse study found that MMP7 deficiency increases the risk of sudden death

MMP12 increased survival

Deficiency of MMP12, and MMP7 decreased the heart burden risks but increased if there was a deficiency of TIMP1



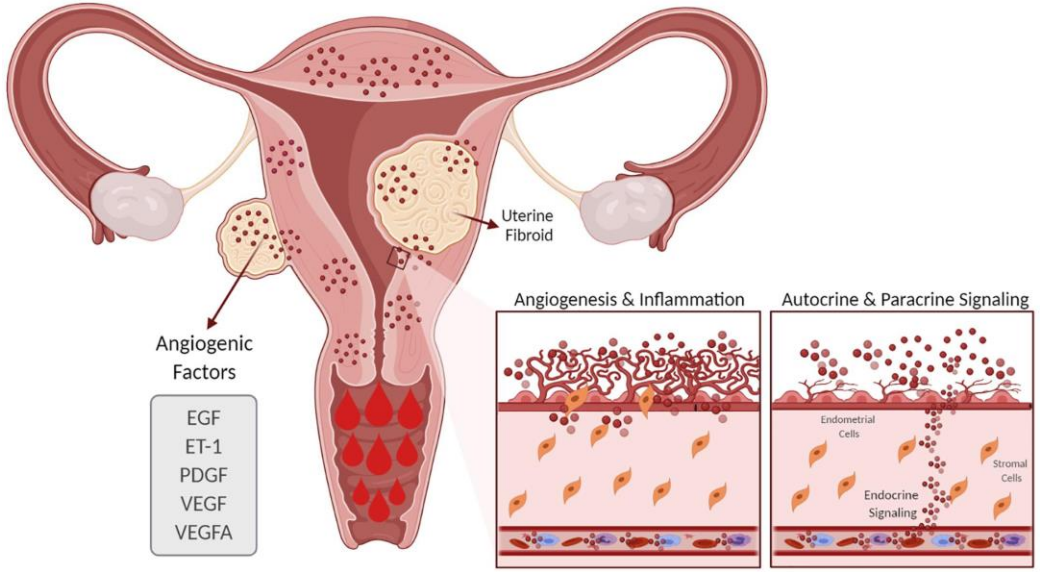
Fibroids

MMPs extend beyond simply degrading and remodeling extracellular matrix; MMPs also function as signaling enzymes

Multiple studies have found that elevated MMP2 in the development of fibroids

2 of the studies looked at estradiol and found it was elevated

Progesterone can play a role in controlling bleeding and reducing the fibroid



Joint Issues

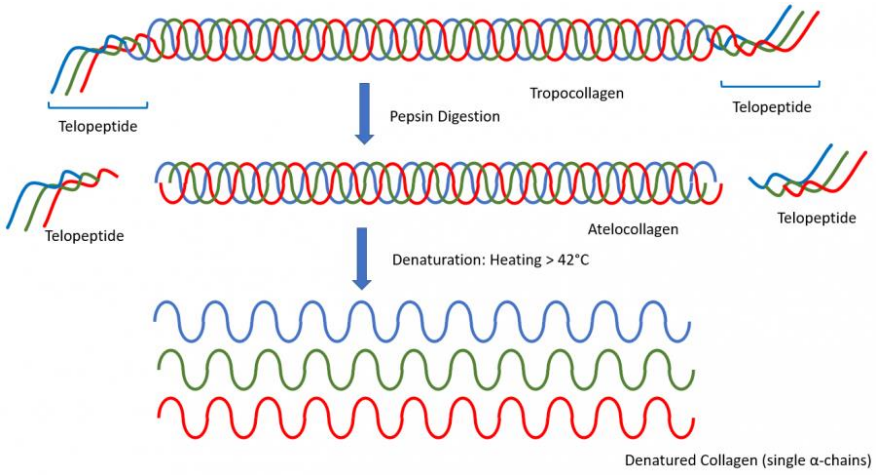
Both RA and osteoarthritis involve the degradation of cartilage

Collagen is essential for cartilage

Collagen Type 2 is associated with the strength of the cartilage

MMP1, MMP2, MMP8, MMP 13, MMP14 can degrade collagen type II

Collagen degradation is irreversible because articular cartilage cannot be repaired once collagen is lost



MS

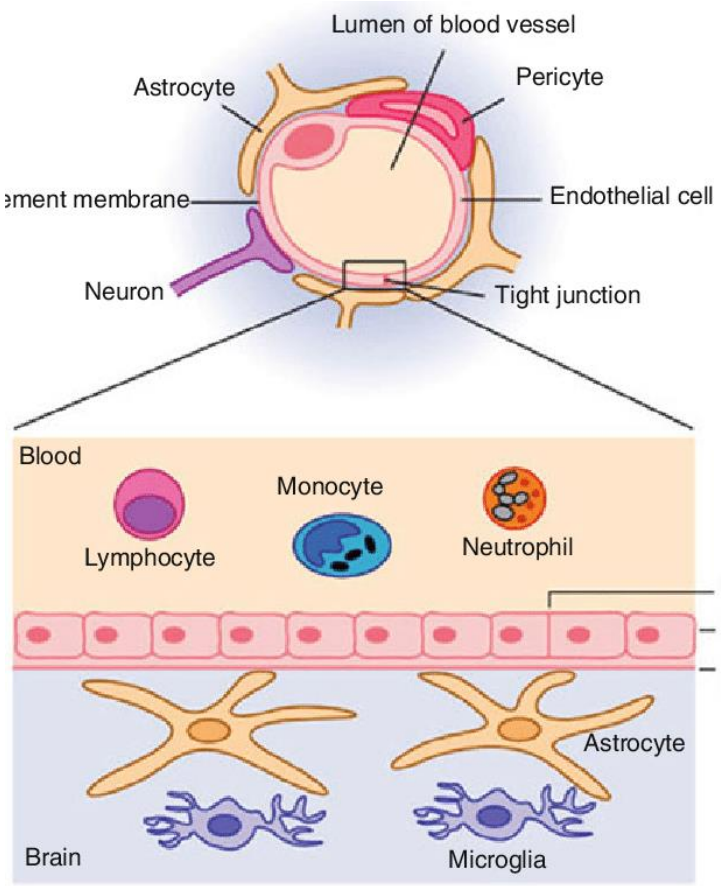
MMPs play an important role in the progression of MS

They disrupt BBB (blood-brain barrier), leading to a chronic inflammatory cascade, and also by breaking down myelin sheath within CNS

MMP-9 is upregulated in cerebrospinal fluid (CSF), blood, and brain tissue of MS patients

Blood level of MMP-9 and the MMP-9/TIMP-1 ratio were proven to be useful biomarkers for MS

These are lowered with the drug interferon-β used to treat MS



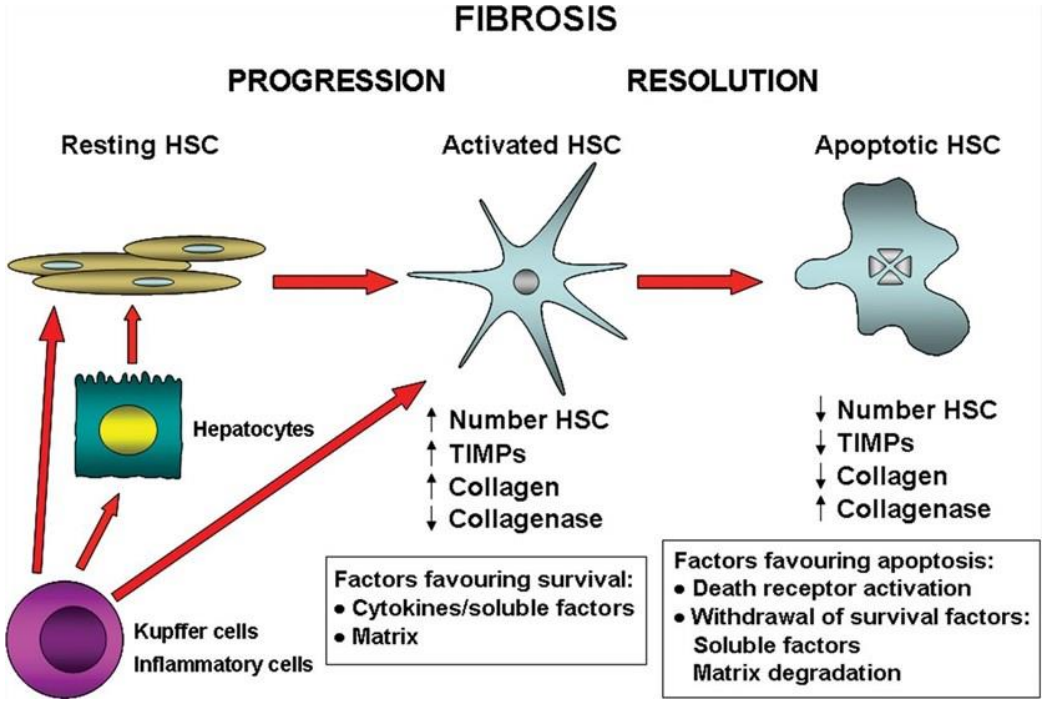
Liver Fibrosis

Due to chronic liver injury as seen in hepatitis, non-alcoholic and alcoholic liver issues - both MMPs and TIMPs are produced in the liver

MMP13 expressed by scar macrophages in fibrosis

MMP2 shows a protective effect by preventing the TIMP1 from performing an anti-protective role

MMP19 signals TGF beta which promotes fibrosis – in MMP19 deficient mice was reduced (without MMP19 present)

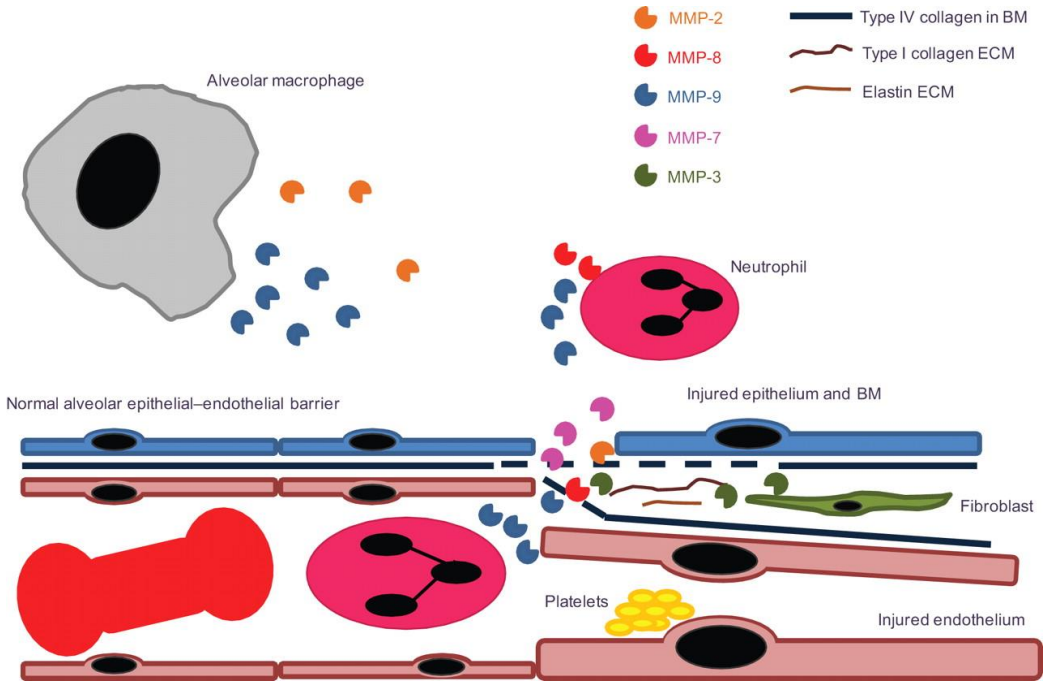


Destruction of ECM (extracellular matrix) is linked to Asthma, COPD, TB and interstitial lung disease

ECM consists of mainly collagen Type 1 which can be degraded by several MMPs

MMP1, MMP9, MMP12 is implicated in emphysema

Again this would be excess MMPs



Cancer

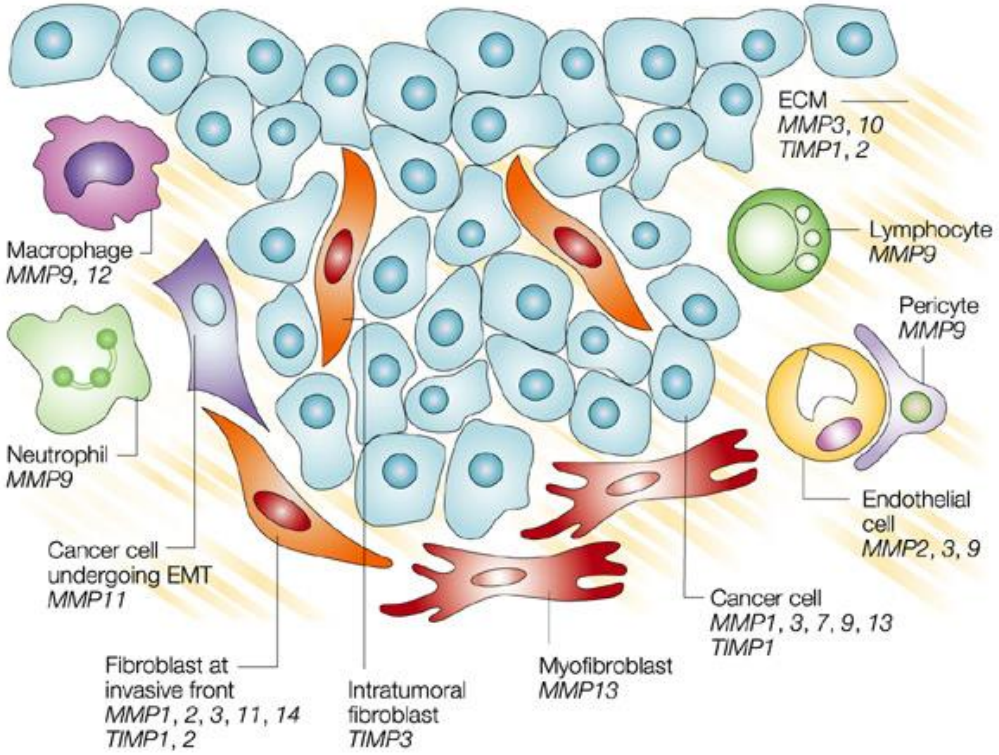
Multiple studies on different cancers and MMPs

MMPs are implicated in tumor growth

Research is looking to see if they could be markers for specific cancers

Or can be involved in improving outcomes

ie: TIMP2 may play a role in inhibiting ovarian cancer proliferation, invasion and chemoresistance

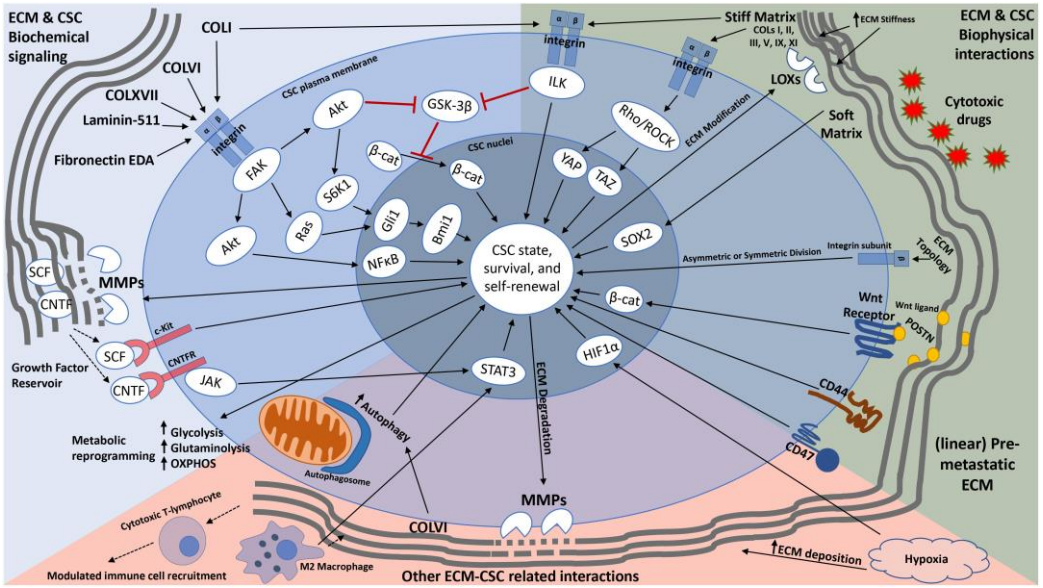


MMP-14 is the driving force behind extracellular matrix and tissue destruction during cancer invasion and metastasis

Cancer cells can imbed in the ECM and remodel it

Most MMPs have consistently increased gene expression across all cancers, while several MMPs have consistently decreased expression in several cancer types

Again, the goal is to use this information for biomarkers and perhaps influence outcomes by using specific MMPs or TIMPs

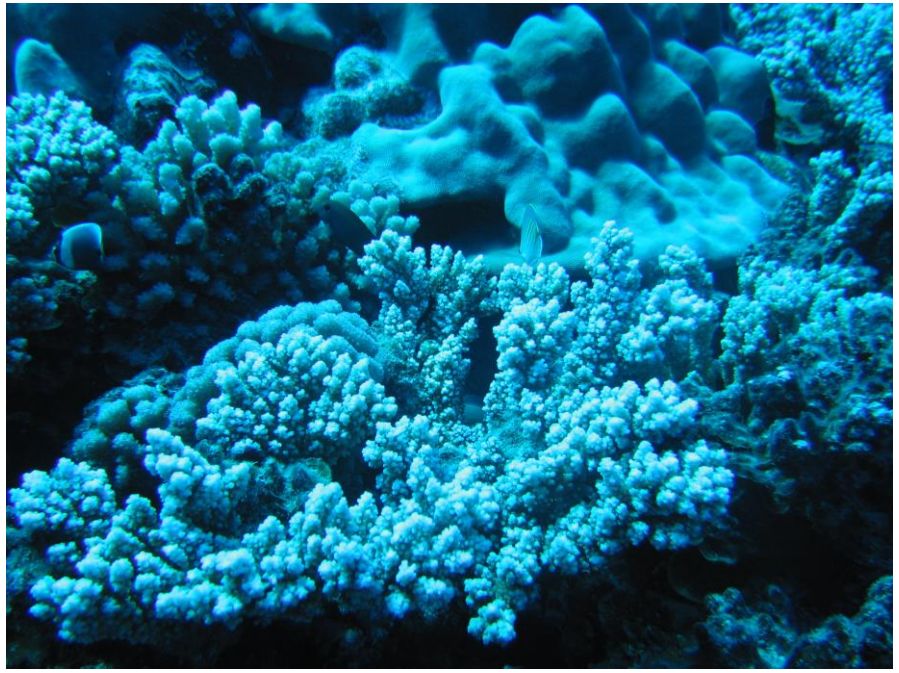


Researchers have been trying to develop MMP inhibitors

Like many other medical interventions, we have to consider that inhibiting would only be of benefit if in excess and could cause issues if MMPs were lowered too much

Current research is looking at isolating natural substances

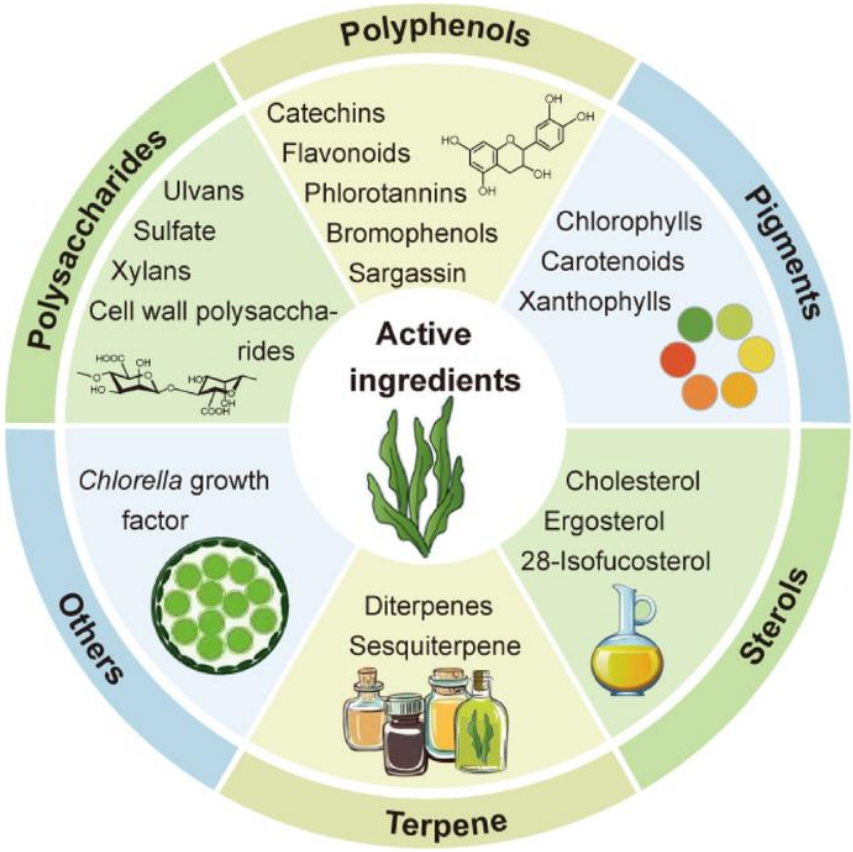
One substance is Sinulariolide (acetate) - found in coral and it may decrease MMP2 and MMP9 and increase TIMP1, TIMP2



Several diterpenes, polyphenols, polysaccharides, and flavonoids, found in many plants are being studied and found to have an effect on MMPs and TIMPs

The goal of the research is to create products that can target specific MMPs or TIMPs to be increased or decreased

And most of the research is for potential cancer therapies



Rosemary

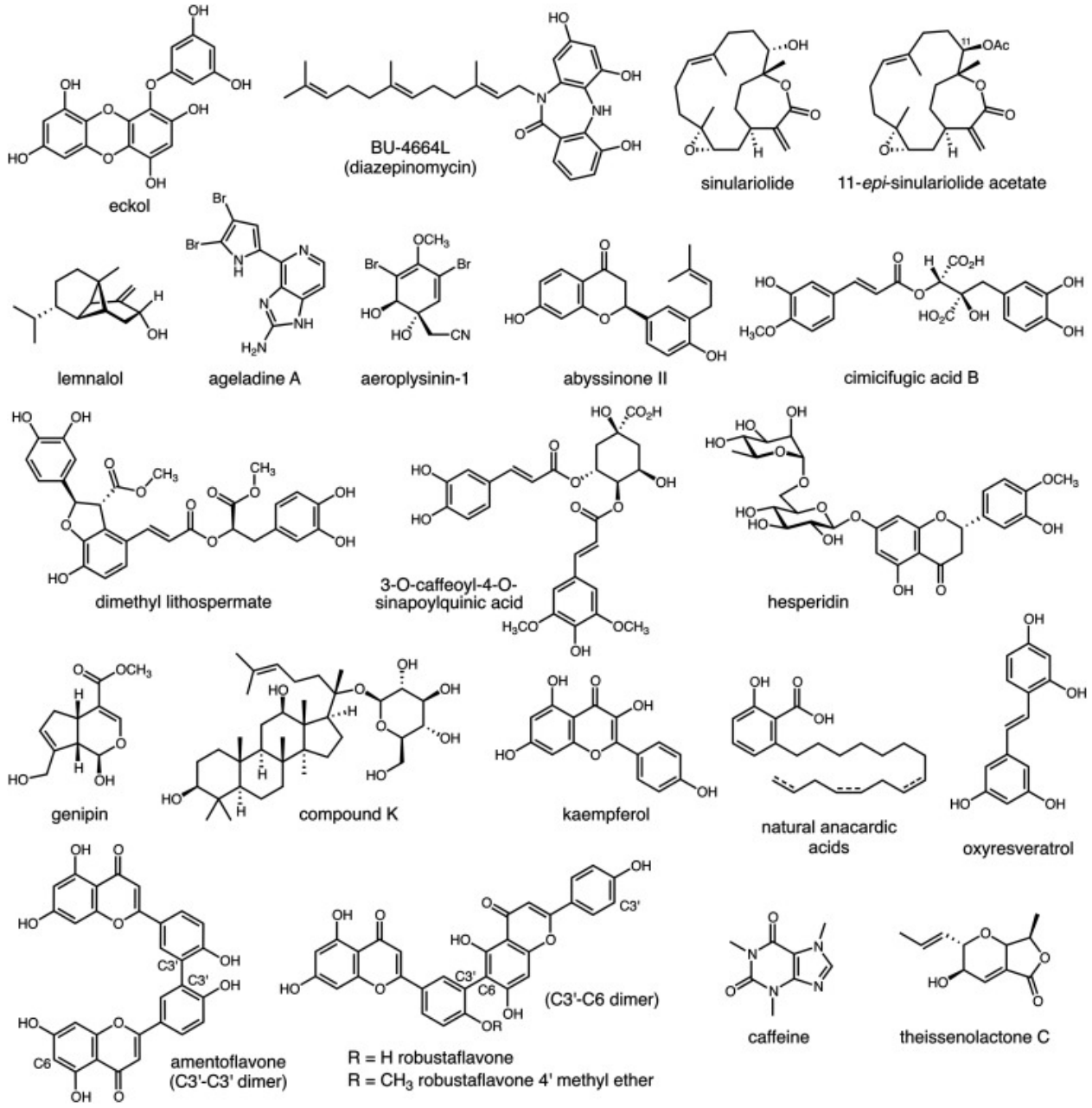
Seminar – many years ago – rosemary helped inhibit excess MMPs

Looked for the research – hard to find

One study found carnosic acid (rosemary, sage)– a diterpene decreased MMPs found to increase photoaging from UV exposure by supporting extracellular matrix and reducing ROS

Rosemary contains diterpenes, polyphenols, and flavonoids – all of which have been mentioned to help balance MMPs

Also supports decreased oxidative stress and inflammation in the GI tract


eckol
BU-4664L
(diazepinomycin)
sinulariolide
11-epi-sinulariolide acetate
lemnalol
ageladine A
aeroplysinin-1
abyssinone II
cimicifugic acid B
dimethyl lithospermate
3-O-caffeoyl-4-O-
sinapoylquinic acid
hesperidin
genipin
compound K
kaempferol
natural anacardic
acids
oxyresveratrol
amentoflavone
(C3'-C3' dimer)
R = H robustaflavone
R = CH3 robustaflavone 4' methyl ether
(C3'-C6 dimer)
caffeine
theissenolactone C

Hesperidin has the potential to inhibit pro-inflammatory cytokines and inhibit MMP-1, 3, and 9

Found in lemons, limes, mandarins, oranges, grapefruits

Ginseng-derived compound K – Major compound found in Panax Ginseng

Suppresses MMP-1

Kaempferol: Inhibits cell invasion and migration by inhibiting MMP-2 function

Found in green leafy vegetables, berries, apricots, peaches, kiwi, watermelon

Kaempferol decreases MMP3 which has been connected to increased tumor invasion and low prognoses

Caffeine can inhibit MMP2 and MMP9

Anacardic Acid – phenolic compound found in cashews, cashew apples

Ginkgolic Acid (Ginko giloba)

Both can inhibit MMP2 and MMP9

All of these phytonutrients show that there are answers in nature

But not enough for specific outcomes

What Can We Do?

Balance inflammatory pathways to prevent chronic inflammation

Support the liver – due to its relationship with the immune system, hormones, and the gut

Balance hormones and ensure proper detoxification

Support gut health – getting rid of dysbiosis and consuming prebiotic foods to build gut bacteria

Most of these substances are known to be anti-cancer or antioxidants

With this research, we are starting to see how they help by how they influence MMPs and TIMPs

In the future, research will give us answers

Because we now know about MMPs and TIMPs, we will have a better understanding to assess the information