INFLAMMATION IS RELATIVELY LINKED TO CANCER AND PLAYS A SIGNIFICANT ROLE IN TUMOR FORMATION AND PROGRESSION

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INTRODUCTION

Inflammation, is relatively linked to cancer and it has a significant aspect in tumor formation and its progression. Chronic inflammleads to carcinogenesis by the stimulation of tumor cell proliferation, angiogenesis, and metastasis while diminishing responsiveness to the immune system as well asanti-cancer agents. A microenvironment highly rich in inflammatory cells, growth factors, and chemicals that promotes DNA damage, leads to long-term and enhances cell proliferation and its survival, increasing the risk of cancer. Several epidemiological studies have indicated a significant relationship between inflamm and cancer. Tumor cells grow similarly to inflammatory cells in terms of phenotype because they produce cytokines, chemokines, and their receptors. Chronic synthesis of these inflammatory mediators can induce tissue and DNA damage, resulting in the accumulation of mutations in Ep while accelerating their proliferation. Mutated cells extend to release cytokines and attract inflammatory cells, contributing to angiogenesis, migration, and metastasis by creating a cancer inflammatory microenvironment. Many anti-inflammatory medicines, particularly NSAIDs, can impair the tumour microenvironment by decreasing cell migration and increasing apoptosis and chemosensitivity.Long-term NSAID medication was associated with a low risk of initial or recurring malignancies.

INFLAMMATION

Inflamm is a natural response to microbial pathogen infection and wound healing. Activated endothelium, macrophages, and mast cells located in the tissues recruit neutrophils to inflammatory regions by releasing appropriate mediators in response to tissue damage. Neutrophils are the first effectors of inflammation, and they are recruited via a four-step process that includes activation of P-, L-, and E-selectins to promote cell rolling along the vascular endothelium, activation of leukocyte integrins, neutrophil freezing on the vascular endothelium, and transmigration to the inflammatory sites.

[**ABBREVIATIONS :**Inflamm - INFLAMMATION ; Ep - EPITHELIAL CELLS]

NOMENCLATURE

The suffix 'itis' is commonly used to signify the nomenclature of an inflammatory lesion. Thus, inflamm of the appendix is referred to as appendicitis.

ETIOLOGY

There are many factors responsible for inflamm in an individual:

NON-INFECTIOUS FACTORS

- **Physical:** Physical injury, ionizing radiation, trauma, Burn, foreign bodies,
- **Chemical:** Alcohol, fatty acids, glucose, chemical irritants, toxins
- **Biological:** Cell injury
- **Psychological:** Exhilaration

INFECTIOUS FACTORS

Viruses,Bacteria and other microbes.

CLASSIFICATION OF INFLAMMATION

Inflammmay be classified as- 1. Acute and 2. Chronic

ACUTE INFLAMMATION

Acute inflammation is the body's initial response to harmful stimuli, and it is characterised by an increase in the flow of plasma and leukocytes (especially granulocytes) from the circulation into the injured tissues.

PROLONGED INFLAMMATION

Chronic inflammation is long-term inflammation. This causes a progressive shift in the kind of cells present at the site of inflammation, such as mononuclear cells, and is characterised by the inflammatory process's simultaneous destruction and repair of tissue. Moving leukocytes from the circulation into tissue boosts the inflammatory response.

SYMPTOMS

Inflammation symptoms differ depending on whether the reaction is immediate or persistent. The abbreviation "PRISH" summarises the consequences of acute inflammation. They are as follows:

- **Pain**:Chemicals that stimulate nerve endings are produced, increasing the sensitivity of the region.
- **Swelling**: This is due to a fluid build-up.
- **Redness**:This occurs because the capillaries in the area are filled with more blood than usual.
- **Heat**: More blood rushes to the afflicted region, making it warm to the touch.
- **Immobility**: There may be some loss of function in the inflamed area.

These five acute inflamm markers only apply to skin inflamms. Chronic inflammatory symptoms can be beneficial in a variety of ways. Examples include fatigue, fever, mouth sores, rash, chest discomfort, joint and stomach pain.

PATHOPHYSIOLOGY AND MOLECULAR MECHANISM OF INFLAMMATION

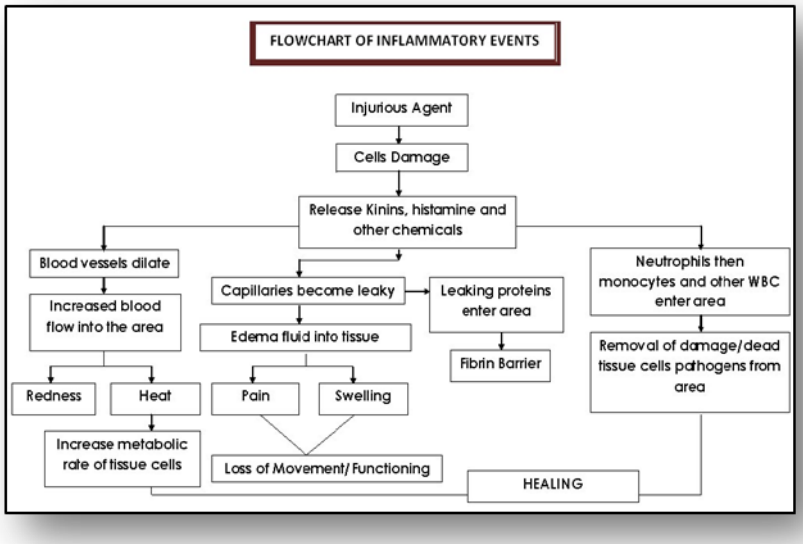

FIG – 1: <u>PATHOPHYSIOLOGY OF INFLAMMATION</u>

Initially, host cells detect inflamm through transmembrane receptors called pattern-receptors, which are produced by both innate and adaptive immune cells.

Theydothisbyidentifyingstructuresconservedinmicroorganismsknownaspathogen-associatedmolecularpatterns(PAMPs)andendogenouschemicalsderivedfrominternaldamageknownashazard-associatedmolecularpatterns(DAMPs)..Thesecondstepinvolvesmaturationof IL-1bycaspase-1-mediatedcleavageofpro-IL-1.Thisrequiresa'caspase-1-activating'high-molecular-weightcomplexknownastheinflammasome.

MembersoftheNK-κBfamilysharestructuralsimilaritywiththeretroviraloncoproteinv-RelattheN-terminusknownastheRelhomologyregion(RHR),formingstablehomodimersandheterodimers.Itpromotesthegenerationofamomers.Inresponsetostimulation,NK-κBdimersarereleasedintoherIBcytoplasmandtranslocatetothenucleus,wheretheytriggerspecificgeneexpression.InadditiontoNK-κB,severalothertranscriptionfactorsplayimportantrolesinselectiveactivationofinflammatorygenes.

Activatorprotein-1(AP-1),tonameafew,isaheterodimerofthebasicleucinezipperproteinsc-Junandc-Fos.Cyclic-AMP(cAMP)ResponseElementBindingProtein(CREB),cAMPinducer.E2F,atranscriptionfactoractivatedbytheadenoviralE1Aproteininadenovirus-

infectedcells.Serumresponsefactor(SRF)andrelatedternarycomplexfactor(TCF)involvedinserumin ductionofFostranscription.**"Figure-1"**showsaschematicdiagramofthepathophysiologyofinflammation.

INFLAMMATION AND CANCER

Severalepidemiologicalandclinicalstudieshaveshownassociationsbetweeninflammationan dcancer.Forexample,ulcerativecolitisandCrohn'sdiseasemayincreasetumorrisk,whereasanti-colitisdrugsmayminimizethisprocess.
Additionally,microbialagentsorchemicalirritantsoftencauseinflammation.Forexample,Helicobacte rpyloriinfectionorHepatitisBand virusescanpredisposetocancer.

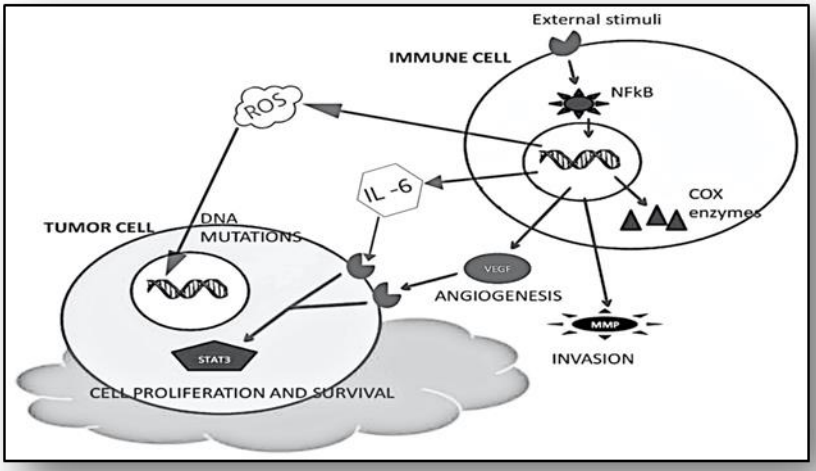

FIG – 2: INFLAMMATION AND CANCER

AvarietyofinflammatoryandcarcinogenicagentscanactivatethetranscriptionfactorNF-kB.IL-6andgrowthfactorsinduceSTAT3activationleadingtocellproliferationandsurvival,whereasmetallop roteasesdegrademembranesubstratesandpromotecellinvasion.Inaddition,macrophagessecretenum erousreactiveoxygenspecies(ROS)andantimicrobialmutagens.TheycauseDNAalterationsthatinduc epersistenttissuedamageandcontributetotumorigenesis.Thesecytokinesreleasedatthetumorsitearei ntrinsicsignalsforlymphocyterecruitment,buttheirimportanceintumorprogressionisunknownmutan tcellscancreateatumorinflammatoryenvironmentenrichedwithmacrophages,neutrophils,eosinophil s,dendriticcells,mastcellsandlymphocytes,allofwhichplayimportantrolesininflammatorymalignan

cies.increase.Tumor-associatedmacrophages(particularlyTAMs)contributetoangiogenesisandpromotetumorgrowthbysecretingspecificfactorssuchascytokinesandgrowthfactors,endothelin-2,andurokinase-typeplasminogenactivatorthatsuppressimmuneresponses.canfacilitateprogress.**“Figure -2”**showsaschematicdiagramofinflammationandcancer.

THE ORIGINS AND TYPES OF INFLAMMATION IN CANCER

Inflammationmayplayanimportantroleincancer,fromtheonsetofthemalignantphenotypetometastaticprogression**"Figure-3"**andmetastasesindistantplaces**"Figure-4"**.

INFLAMMATION ARISING FROM INFECTION, AUTOIMMUNITY OR THE ENVIRONMENT

Therearemanyexamplesofinflammationthatcontributetotheonsetofcancer,including(1)infectiousagentsthatdirectlycausecancer,e.g.felineleukemiavirus,orinflammatoryviruses,eg.:Helicobacterpylori causesmucosal-associatedlymphoma(MALT)orgastriccarcinomainhumans;(2)immune-mediateddiseasesthatpromotechronicinflammation,e.g.inflammatoryboweldiseaseIBDandcoloncancer;(3)subclinicalinflammation,forexample:obesitycausesinflammationandleadstolivercancer;(4)environmentalcarcinogens,e.g.smokepollution.

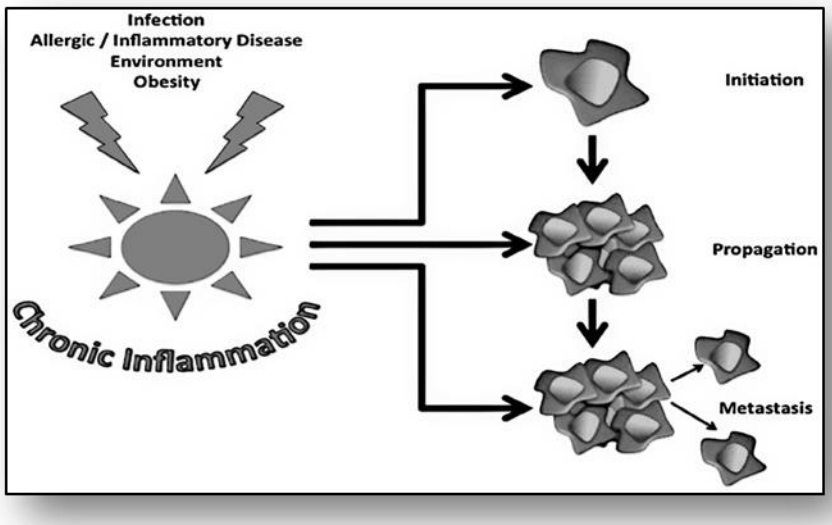

FIG –3: ROLE OF INFLAMMATION IN CANCER

INFLAMMATION ARISING FROM TUMOURS

Themicroenvironmentmaintainsapersistentinflammatorystateoncetumorsareestablished.Tumorselicitaninnateinflammatoryresponseandproto-tumoralmicroenvironmentsupportedbymacrophageinfiltrationandregulatedbychemicalmediatorssuchasinterleukinsIL-8andIL-10.CellInfiltration,Cytokines,Chemokines:(1)Itisproangiogenicandpromotesangiogenesisincancer; (2)actasagrowthfactorfortumorcells;(3)promotesepithelial-to-mesenchymaltransition(EMT).

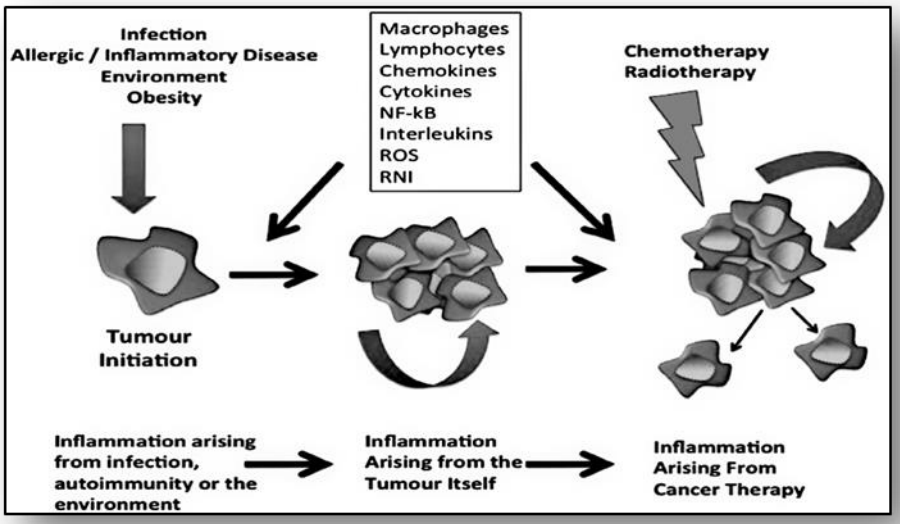

FIG – 4: ORIGIN OF CANCER RELATED INFLAMMATION

INFLAMMATION ARISING FROM CANCER THERAPY

Contrarytopopularbelief,standardcancertreatments(chemotherapyandradiationtherapy)maypromotetumordevelopmentbyincreasinginflammation.Chemotherapyandradiationcandamagecellsandcauseinflammation-inducingnecrosis. **"Figure - 5"**showsaschematicdiagramoftumour initiation through the effects on DNA.

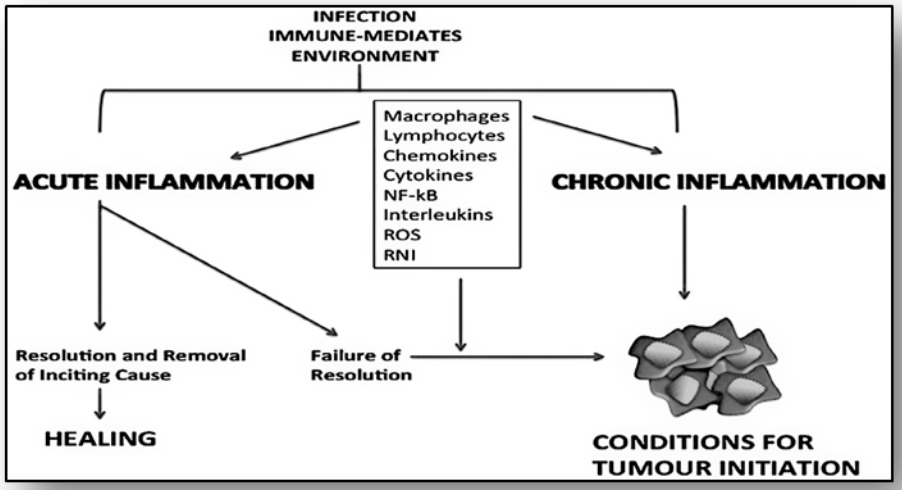

FIG – 5: TUMOUR INITIATION THROUGH THE EFFECTS ON DNA

THE KEY MEDIATORS OF INFLAMMATION

Therearetwomechanismsthatlinkinflammationandcancer. Exogenousandendogenous("Figure - 6").Uponactivation,NF-kBsecretesinflammatorymediators,growthfactors,andmetalloproteasesthatcontributetotheestablishmentoftheinflammatorytumormicroenvironment.Forexample,cytokines,growthfactors,anddifferentiationfactorsinvolvedinregulatingimmunecellproliferationanddifferentiationcontributetocancerbyactivatingcellproliferationandinhibitingandinhibitingapoptosisofdamagedcellsthroughdifferentmolecularsignalingcascades.

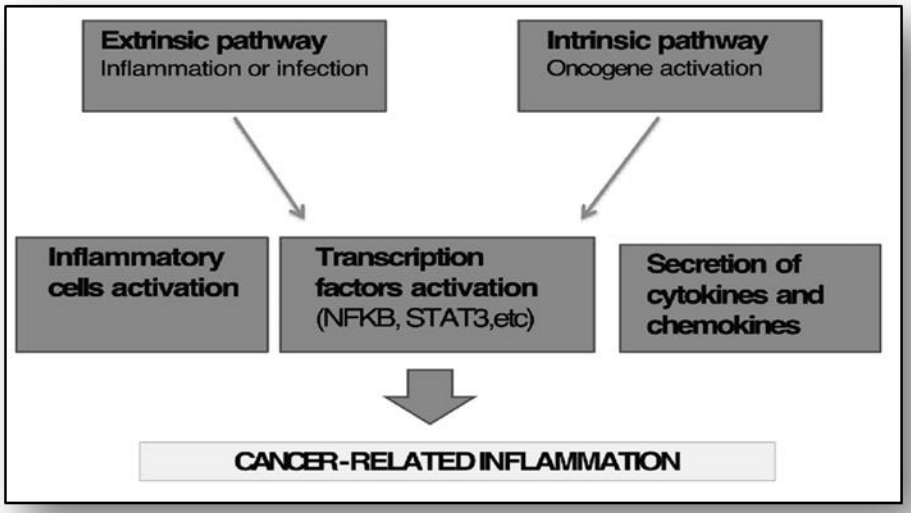

FIG – 6 :LINK BETWEEN INFLAMMATION AND CANCER

TUMOR NECROSIS FACTOR ALPHA (TNF-ALPHA)

Itcanalsosuppresstheexpressionofadiponectin,glute-4,PPAR-,andperilipininadipocytes.StudieshaveshownthatTNF-αproducesadditionalpro-inflammatorycytokinessuchasIL-1andIL-8inherCaco-2orHT-29celllines.

1. HISTAMINE

Histamine is a vasodilator, smooth muscle constrictor, and stimulator of vascular permeability, respiratory mucus, and stomach acid production.

2. LEUKOTRIENES

The biologic combination, also known as the anaphylactic slow-reacting substance, is made up of leukotriene (LT) C4 and its derivatives, LTD4 and LTE4.

3. PROSTAGLANDINS

Prostaglandins are another type of arachidonic acid-derived molecule that mediates allergic responses. Human mast cells produce PGD2 after being triggered by the Ig-E receptor or a calcium ionophore.

4. CYTOKINES AND CHEMOKINES

Cytokines such as IL-1, -2, -4, -5, -6, and GM-CSF impact the development of allergic inflamm by influencing the activity of inflammatory cells such as eosinophils, macrophages, B cells andT cells.

5. iNOS AND NO SECRETION

iNOSisanenzymethatinterfereswithNOproductionandisoverexpressedinvariationsofchronicinflammatoryandcancerprocesses.ActivationofiNOSbyproinflammatorycytokinesorNFkBcausesDNAdamage,reducesDNArepair,andpromotescancerdevelopment.

6. LOX AND COX PATHWAYS

5-LOXhasbeendetectedinhumanoranimalcancercelllinessuchasbrain,breast,colon,kidney,mesothelium,esophagealmucosa,pancreas,andprostate,andmostoftheseinvestigationsalsoincreased5-LOXproducts.I'mhere.Arecentstudyshowsthat5-LOXexpressioninpapillarythyroidcarcinoma(PTC)promotescarcinogenesisthroughinductionofmetalloproteinases(MMPs).Theseenzymesareoftwotypes:

•**COX-1,**isconstitutivelyexpressedinmanycellsandisprimarilyinvolvedinthephysiologicalproductionofprostanoids.

•**COX-2,**Itsexpressionisofteninducedincellsininflammatoryconditions.

7. JAK/STAT PATHWAY

TheSTAT3(signaltransducerandactivatoroftranscription3)proteinisaconstitutivetranscriptionfactorpresentinavarietyofhumancancers,includingmultiplemyeloma,leukemia,lymphoma,breastcancer,prostatecancer,andsquamouscellcarcinomaoftheheadandneck.

8. CREB SIGNALING PATHWAY

Cell survival, neuron growth, and metabolism all rely on CREB. For example, CREB-mediated gene expression is necessary for nerve growth factor (NGF)-induced cell survival, which improves sympathomimetic neuron survival by activating downstream target genes.

THE ROLE OF INFLAMMATION IN TUMOUR INITIATION AND MAINTENANCE

Tumor products have an impact on inflammatory conditions; immunosuppressive cytokines allow immune evasion and the recruitment of tumor-promoting inflammatory cells such as myeloid-derived suppressor cells, regulatory T cells, and tumor-promoting (M2) macrophages **"Figure -7"**. The tumour microenvironment is a complex network of interactions between tumour cells, supporting stroma, and inflammatory cells that collaborate to maintain the malignant phenotype **"Figure - 8"**. Cancer and inflammation are intricately linked **("Table - 1").**

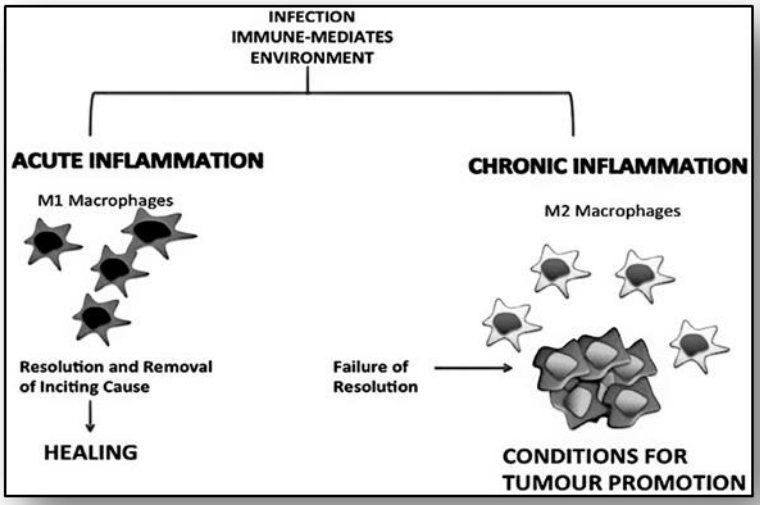

FIG – 7 : <u>TWO ENDS OF A PHENOTYPIC SPECTRUM OF MACROPHAGES</u>

BRIDGING CANCER AND INFLAMMATION

Afterexposuretopathogens,innateandspecificimmuneresponsescanworktogethertoeliminatethesourceofinfectionandavoidadditionaltissuedamageduringacuteinflammation.Thisnotonlyprolongsimmunecellinfiltration,butalsoleadstotheformationofreactiveoxygenspecies(ROS),reactivenit

rogenspecies(RNA),andmacrophagemigrationinhibitoryfactor(MIF),allofwhichcancauseDNAdamage.

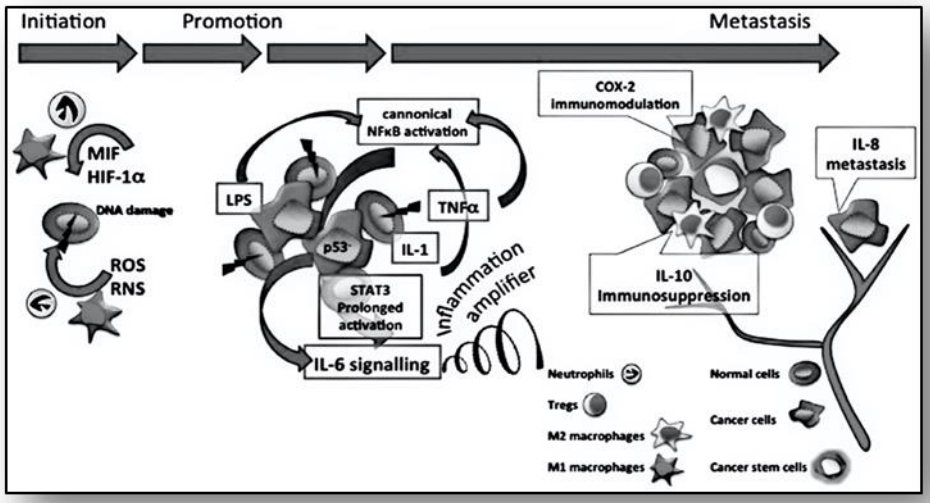

FIG – 8 : SUMMARY OF THE CELLS AND MEDIATORS WITHIN THE TUMOUR MICROENVIRONMENT

▶ CENTRAL ROLE OF NF-κB

NF-κBisimportantinregulationoftheimmuneresponsetoinfection,anditsdysregulationhasrelatedtoillnessessuchasautoimmunityandcancer.Thismolecule'scriticalinvolvementincancermaybesummarisedasfollows:(1)constitutiveNF-κBexpressionhasbeenidentifiedinmanycancertypes,supportingitsroleinpromotingthecancerphenotype;(2)dysregulationoftheNF-κBpathwayhasdocumentedinhaematologicalmalignanciesandlymphoma;theselymphoidmalignanciesfeatureaberrantNF-κBactivation,whichpromotestumorigeniccellsurvival,protectsagainstapoptosisandfavoursoncogenesis;(3)ConstitutiveNF-κBactivationisacharacteristicofchronicinflammatoryillness,whichisconnectedtoanelevatedriskofcancer.; (4)TheprimarycauseofdysregulationoftheNF-κBsignallingpathwayinhumannon-lymphomaHodgkin's(NHL)includeschromosomalabnormalities(e.g.EpsteinBarrvirus,humanT-

cellleukaemiavirus-1);(5)Up-regulationofanti-apoptoticBcl-2familyproteinsasaresultofpersistentactivationoftheNF-κBpathway;(6)Thedevelopmentofresistanceinthecytotoxiceffectsofchemotherapeuticdrugsisaserious barriertocurrentcancertherapy.Manychemotherapeuticdrugsthatinducep53-mediatedapoptosisalsoactivateNF-κB.

NF-κBinhibitionincreasestheeffectivenessofanticancerdrugsanddecreasetheincidenceofresistancetothesetreatmentsinnumerousinvivoandinvitromodels,makingNF-κBaprospectivetherapeutictargetinoncology.Thus,theNF-κBsignalingpathwayisinvolvedincomplexinteractionswithmanycancersignalingpathways(proteinkinases,c-JunN-terminalkinase,STAT3,andtranscriptionfactorssuchasp53),potentiallyConcernshavebeenraisedaboutitsuse.UseofNF-κBinhibitorsforcancertreatmentwithunforeseensideeffects.

INFLAMMATION AS TARGET FOR CANCER PREVENTION

Sinceinflammationcanpredisposetotumorigenesis,targetinginflammationandmoleculesinvolvedininflammatoryprocesses(COX-2cyclooxygenase2,NF-kB,VEGF)maybebeneficialforcancerpreventionandtreatmentmethod**("Table–1")**.

1. NSAIDs

CancerpreventionbyNSAIDsworksbyinterferingwiththeeicosanoidsystem.NSAIDsarelesstoxicthanconventionalchemotherapy,havenon-specificeffects,andcanreducetumorigenesisbyinteractingwiththetumor'sinflammatorymicroenvironment.Severalstudieshaveshownthatanti-inflammatorydrugscanimproveapoptosisandsensitivitytostandardtreatmentswhilereducinginvasionandmetastasis,leadingthemtopromisingalternatives.forcancertreatment.

2. CORTICOSTEROIDS

Corticosteroidsareeffectiveinreducingthesideeffectsofchemotherapyandradiationtherapy,andsomestudieshaveshownsignificantbenefitsinfightingcancer,eitheraloneorincombination.Dexamethasonetherapyenhancedtheantitumorefficacyofconventionaldrugsinvariousanimalcancermodels.

TABLE – 1 : PREVENTIVE AND ANTICANCER EFFECTS OF ANTI-INFLAMMATORY DRUGS

SL NO.	DRUG	EFFECT
1	ASPIRIN	Induced activation of NF-kB pathway in colon cancer cells,Preventive effect on bladder cancer,breast cancer,colorectal cancer,esophageal cancer,lung cancer
2	COLECOXIB	Induced apoptosis in prostate cancer cells,Preventive effect on bladder cancer,breast cancer,colorectal cancer,esophageal cancer,lung cancer, cervix cancer, neuroblastoma
3	DEXAMETHASONE	Induced cell death in multiple myeloma mediated by miR-125b expression, Preventive effect on breast cancer,rectal cancer,multiple myeloma
4	IBUPROFEN	Inhibited activation of nuclear β-catenin in human colon adenomas,Preventive effect on breast cancer
5	PIROXICAM	Prevented colon carcinogenesis by inhibition of membrane fluidity and canonical Wnt/β-catenin signaling,Preventive effect on colorectal cancer
6	SULINDAC	Induced activation of NF-kB pathway in colon cancer cells,Preventive effect on breast cancer

ANTI-CANCER EFFECTS OF ANTI-INFLAMMATORY AGENTS

Severalpreclinicalandclinicalstudieshaveshownthatacombinationofchemotherapeuticanda nti-inflammatoryagentsimprovespatientprognosis.Althoughthemechanismofactionbehindtheanti-cancereffectsofanti-inflammatorydrugsisunknown,threemajorpossibleprocesseshavebeencharacterized.

I. CHEMOPROTECTION

Thesideeffectprofileofstandardanticancertherapiesisoneofthedifficulties.Chemotherapyoft encausestoxicitytoboththeTumorandvariousnormaltissues,reducingthepatient'squalityoflife.Somes tudieshaveshownthatcombiningconventionaltreatmentswithanti-inflammatorydrugscanreducethesideeffectsofchemotherapy.Forexample,inpatientswithmetastatic prostatecancer,combinedtreatmentwithcelecoxibanddocetaxelreducedmyelotoxicity,

whereascelecoxibcombinedwithFOLFIRI(folinicacid,fluorouracil,andirinotecan)orcapecitabinediarrhea.TheGECO(gemcitabine-coxib)studyevaluatedtheeffectofcelecoxibincombinationwithgemcitabineinpatientswithNSCLCandfoundthat3monthsofcelecoxibtreatmentimprovedqualityoflife.Anotherglucocorticoid,budesonide,hasbeenusedincombinationwithirinotecantoreduceepisodesofdiarrhea.

II. ALTERATIONS IN PHARMACOKINETICS OR METABOLISM

Anti-inflammatorydrugscanalterthepharmacokineticsofotherdrugs.Glucocorticoidsdonotaffectplasmapharmacokinetics,butaltertheabsorptionofgemcitabineorcarboplatinfromthespleenandbonemarrow,increasingthenumberofdrugsreachingthetumor.

Inaddition,anti-inflammatorydrugsmayaffectchemotherapymetabolism.Forexample,rofecoxibactsasaCYP1A2inhibitorcausingchangesintheconcentration,half-life,andclearanceofotherdrugsmetabolizedbyCYP1A2.DexamethasoneincreasesherCYP2D6activity,whichcelecoxibdecreases,impairingtheefficacyoftheCYP2D6substratetamoxifen.DiclofenacinhibitsDMXAAglucuronidationbyinhibitingitsmetabolismandincreasingplasmaconcentrations.

III. CHEMOSENSITIZATION

Inadditiontotheabilityofanti-inflammatoryagentstoreducethetoxicityofconventionaltreatmentsbyalteringmetabolism,thebeneficialanticancereffectsofcombinationsofanti-inflammatoryandchemotherapeuticagentsarelikelyduetochemo-sensitizationofanti-inflammatoryagents.Thing.Severalpreclinicalstudieshaveshownthatcelecoxibisadditiveorsynergisticinvitrowhencombinedwithetoposide,doxorubicin,vincristine,oririnotecan.Notably,celecoxibincombinationwithirinotecanordoxorubicinsuppressedtumordevelopmentinaneuroblastomaratmodel.Furthermore,celecoxibsensitizedprostatecancercellstodocetaxelinvitroandinvivoandsensitizedgliomastoradiation.MultiplestudieshaveshownthatNSAIDspromoteapoptosisinmultipletumortypesbydirectlyactingontheNF-kBpathway.AspirinandsulindaccanbindtoNF-kBinthenucleolusandinhibittranscriptionofNF-

kBtargetssuchascytokines,growthfactorsandadhesionmolecules.Celecoxibenhancedtheantitumoreffectofdoxorubicinbyincreasing IkBexpressionanddecreasingNF-kBactivity.Dexamethasonealsoinhibits theNF-kBpathway.

Anti-inflammatorydrugscankillcancercellsbyinterferingwithproteinsinvolvedinprogrammedcelldeath.Forexample,celecoxibenhancedtheefficacyofdocetaxelbyactivatingcaspasesandPARPwhilereducingXIAPactivity.AspirinreducesNF-kBactivitybyinhibitingcaspasesandpro-apoptoticproteins,possiblyinterferingwiththeproteasome.AccordingtoDittmannetal.Cancercellscanbeexposedtoradiationbysuppressing EGFRinaCOX-2-independentmanner.

NOVEL ANTI-INFLAMMATORY DRUGS WITH ANTI-CANCER ACTIVITY

Severalclinicalstudieshavebeenconductedevaluatingtheuseofanti-inflammatorydrugsincombinationwithchemotherapyregimensforcancerpreventionandtreatment,andanti-inflammatorydrugshaveshownpromisingefficacyandtoxicityresults.

1. ANTI-CANCER AGENTS BASED ON COX-2 INHIBITORS

SeveralstudiesevaluatingtheuseofCOX-2inhibitorsincancertherapyhaveshownthattheantitumoreffectsoftheseagentsareindependentoftheirabilitytoinhibitCOX-2.

2. NO-DONATING NSAIDS

NO-donatingNSAIDsareNSAIDanalogueswithfewersideeffects.Thesedrugsretaintheactiveingredientthatproducestheanti-inflammatoryeffectandareattachedtoNOviaaspacer.NO-NSAIDscontainingaromaticspacersweremorepotentthanthosecontainingaliphaticspacers.Onceproduced,NOprotectsthegastrointestinaltractfromdamagecausedbyactivedrugsbyreducinggastrointestinaltoxicity. NO-donatingcompoundsweremadebymodifyingdiclofenac,naproxen,aspirin,sulindac,andibuprofen.SeveralNO-

donatingNSAIDscausedapoptosis,growthinhibition,orcellcyclearrestinvariousformsofcancerinvitroandinvivo. AllpreclinicalstudiesofNO-donatingNSAIDshaveshownhigherefficacythanNSAIDs,butfurtherstudiesareneededtofullyrealizetheirpotentialincancerprevention. NO-ASA(NO-acetylsalicylicacid)showedsynergisticoradditivebenefitsincombinationwithoxaliplatinor5-fluorouracilincoloncancermodelsandreducedcancerriskininducedpancreaticcancermodels.

3. NATURALPRODUCTS

Grapes/redwine(resveratrol),garlic(variouschemicals),andcurrypowderareallanti-inflammatoryfoodsornaturalproducts(curcumin).Producedanticancereffectsoncancercellsorxenografts.Thesechemicalsactasanti-inflammatoryagentsbyinhibitingVEGForCOXenzymesorbytargetingNFKB,MAPK,andJNKsignalingpathways,andtheiractivitycontributestotheiranticanceractivity.

Garliccompoundshavebeenshowntoenhancetheanticancereffectsofcytarabineandfludarabineinmyeloidleukemiacellsandimprovethesensitivityofprostatecancercellsandxenografttumorstodocetaxelwithfewersideeffects.

4. LOX INHIBITORS

Manyresearchershaveproposed5-LOXinhibitors(Zileuton,ZYflo,ABT-761),FLAPinhibitors(MK-886)usedpharmacologicaltoolssuchasLTA4hydrolaseandLTsantagonists(zafirlukastandmontelukast)blockcellproliferation.Anti-LTstherapiesthatincreaseandinduceapoptosisshowpromiseforcancerpreventionandtreatment,butfewclinicalstudieshavebeenconductedtoevaluatetheefficacyof5-LOXinhibitorsinantitumortherapy.TreatmentwithLOXinhibitorsdramaticallyinhibitedcellproliferationinseveralpancreaticcelllines.Invivoexperimentsusingathymicmiceshowedthat LOXinhibitorssuppresstumorgrowthandhavepotentialapplicationsinthepreventionandtreatmentofpancreaticcancer.Goshfoundthatinhibitionofhis5-LOXbyherMKAP1,aFLAPinhibitor,causedapoptosisinLNCaPandPC3celllines.5-LOXinhibitorsinducedapoptosisinesophagealcancercells,whereas12-LOXinhibitorsshowedanti-proliferativeandpro-

apoptoticeffectsongastriccancercells.Finally,severalexperimentswithhematopoieticcellsshowedthattheinhibitor5-LOXAA861causedapoptosisintheleukemiacelllineP388.

5. EMBELINANDITSDERIVATIVES

Embelinisabenzoquinonederivativethatcanimpairarachidonicacidmetabolism.Itsstructureconsistsofa2,5-dihydroxy-1,4-benzoquinonepolarcorelinkedatthe3-positiontoalonghydrophobicalkylchainthatconferssolubilityinpolarphasesandallowsthemoleculetocrosscellbarriers.Ithasbeen.CollaborativeresearchwithprofessorOliverWerz(UniversityofJena,Germany)showedthatthismoleculecaninhibitboth5-LOXandmPGES-1activitywithIC50values of0.06and0.2μM,respectively.Chronicstructureofthemembraneisimportantforinhibitoryeffects.Thismoleculehasbeenshowntobeabletoblockenzymeswithoutgoingthroughthehydroquinonereduction pathway.Dockingexperimentsshowedthatembelindoesnotbehavelikeaniron chelator,butfitswithitsnon-decylatedchainintothehydrophobicchannelwheretheiron-catalyzedoxygenationprocessofAAnormallytakesplace.Thebenzoquinoneringformshydrogenbondswiththreeaminoacids(Gln363,Gln557,andTyr181)tomaintaincontactbetweenenzymemolecules.Twowatermoleculesthatco-crystallizewiththecomplexandformhydrogenbondswithtwoaminoacids,Asn425andThr364,facilitatetheinteractionbetweenembelinand5-LOX.Recentstudieshaveshownthatemberinanditsderivativeshaveantioxidantproperties.**"Figure - 9"**showsaschematicdiagramofanticancer effects of embelin.

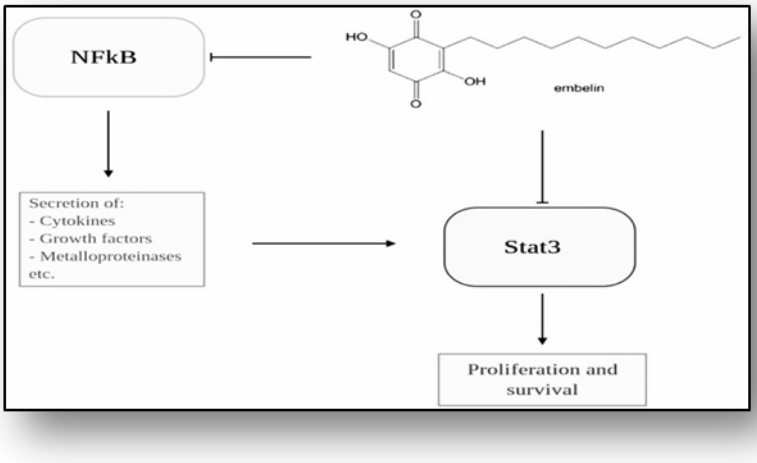

FIG – 9: ANTICANCER EFFECTS OF EMBELIN

CONCLUSION

Inflammationiscloselyassociatedwithcancerandplaysanimportantroleintumorgrowthandprogression.Therefore,thereisaneedtotargetinflammationaloneorincombinationwithchemotherapeuticagentsforcancerpreventionandtreatment.Manyanti-inflammatorydrugscanbeusedasadjunctstoconventionaltherapy,butfurtherresearchisneededtofully exploitthepotentialofanticanceragents.Earlydetectionandtreatmentofchronicinflammationcanhelp preventcancerfromdeveloping.Widespreadoff-targeteffectsandtoxicitylimittheuseofFDA-approvedanti-inflammatorydrugsincancertherapy.Abetterunderstandingofthecriticalroleofinflammationincancer isneededtodevelopmoreeffectivealternativetherapies.

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