Stages in acute inflammatory response

COX ESSAY

Key stages in acute inflammatory response (Juwon K0710483)

Mediators in inflammation and their function

Acute inflammation can well be defined as a normal response to unwanted tissue damage/injury or infections. It is characterised by erythema, oedema, hyperthermia, hyperalgesia, cell influx and loss of function. There is an accumulation of leucocytes at sites of inflammation which is thought to be linked to tissue damage at these sites due to the secretion of lysosomal enzymes and toxic oxygen radical.

Salmon A. Higgs A. (1987). Prostaglandins and leukotrienes as inflammatory mediators. British medical bulletin, Vol 43 (2), pg 285-296.

There are two major components to acute inflammatory response, namely (i) Vascular events and (ii) Cellular events. The vascular events involves vasodilatation and increase in vascular permeability; on the other hand activities in the cellular events include emigration from capillaries and post capillary venules, migration of leucocytes at the inflammation sites, removal of stimuli and activation of inflammatory cells.

Mediators of inflammation and their functions

These key events mentioned above will be enhanced by actions of mediators. Mediators in inflammation include prostaglandins, leukotrienes, vasoactive amines (such as histamine), plasma kinins (such as bradykinin), cytokines (such as tumour necrosis factors and interleukins) and complement – derived peptide mediators. The most relevant of the

polypeptide mediators jointly known as cytokines are tumour necrosis factor (TNF) which is synthesised primarily by macrophages and interleukin 1 (IL-1) which is made by various cells but likely to be produced by macrophage lineage, epithelial and endothelial cells at the early stages of inflammation. The functions of these two cytokines overlap although relative potencies with cell type and biological effect may differ. The functions of these cytokines can be observed in three main areas namely (i) defence role, (ii) repair role and (iii) metabolic role.

Histamine as a mediator of inflammation plays a major role in acute inflammatory response affiliated with mast cell degranulation. It is primarily stored and released from mast cells normally found along blood vessels. The release of histamine leads to the following responses; (i) increased microvascular permeability leading to oedema formation, (ii) increase in blood flow and volume and (iii) vasodilatation in the skin as a result of local axon reflex. The combined effect of the increased microvascular permeability and part of the hydrostatic segment of the vasodilatation response caused by histamine mainly contributes to oedema formation. The two main receptors involved in the acute inflammatory response are H1 and H2 receptors, both receptors are involved in vasodilatation while increased microvascular permeability only utilises the H1 receptor.

Histamine lacks chemotactic activity however; they may be specifically chemotactic towards eosinophils. The permeability of microcirculation is also increased by histamine allowing the movement of white blood cells into the extravascular space, the amount of white blood cells moved into the

extravascular space is however insignificant compared to other inflammatory processes.

Billingham M. (1987). Cytokines as inflammatory mediators. British medical bulletin, Vol 43 (2), pg 350-370.

The oxygenation of arachidonic acid can happen via two enzyme pathway, (I) cyclo-oxygenase pathway which produces prostaglandins and prostacyclin as its two most important mediators, and (ii) 5-lipoxygenase pathway which produces the leukotrienes. The two most important products from the cyclo-oxygenase pathway are both potent hyperalgesic and vasodilator agents, and due to their presence at inflammation sites they are thought to contribute to the characteristic features of inflammatory response (which include oedema, pain and erythema). Dienoic prostaglandins (PGE2), prostacyclin and tetraenoic leukotrienes (LTB4) are the most relevant in inflammation response. The vasodilator prostaglandins have an indirect effect on oedema formation but, synergise with mediators such as histamine and bradykinin that increase vascular permeability. The combination of prostaglandins with histamine and bradykinin also results into the afferent pain nerve ending to be more sensitised to the effects of bradykinin and histamine causing more apparent pain. PGE2 and prostacyclin also promote a state of hypersensitivity causing usually non-painful stimuli to be painful (allodynia) e. g. pain from a touch of clothing; prostacyclin is a more potent hyperalgesic agent with a short lasting effect compared to PGE2 which has a cumulative and longer lasting effect. PGE2 is also a potent pyrogenic agent that causes fever which is further promoted by an endogenous pyrogen interleukin-1. The synergism effect of PGE2 and prostacyclin with other

mediators suggest that they have a more central role in the build up of acute inflammatory response.

The most relevant leukotrienes, LTB4, is a potent chemotactic and degranulating agent that causes the accumulation of polymorphonuclear (PMN) in vivo and as a result it has a strong effect on polymorphonuclear (PMN) functions, also due to this strong effect on circulating polymorphonuclears and synergism with vasodilator prostaglandins, there is a rise in plasma exudates. It is important to note that the actions of LTB4 on polymorphonuclears are stereospecific and are unique to just LTB4s.

Salmon A. Higgs A. (1987). Prostaglandins and leukotrienes as inflammatory mediators. British medical bulletin, Vol 43 (2), pg 285-296.

The activation of complement system enhances migration of leukocytes and killing of pathogens by phagocytosis, release of toxic products and acute inflammation. Complement system activation mainly involves the cleavage of third (c3) and fifth (c5) compliment to give derivatives c3a and c5a along with other respective metabolites; both c3a and c5a are anaphylatoxins because they release histamine from mast cells and basophil, they also stimulate smooth muscle contraction. The histamine released will enhance supply of complement systems at the inflammatory site as a result of increasing microvascular permeability.

Peptides derived from complement c5 such as c5a enhances neutophil-endothelial interaction in vivo and as a result there is accumulation of neutrophils accompanied by oedema formation, however, c5a exerts its most important effect on leukocytes. As to the action of c5a on leucocytes, in vitro

studies suggest aggregation, degranulation to release enzyme, chemotaxis, increased adhesion to endothelial cells and oxygen radical generation. Individuals deficient in activated c3 generally are susceptible to recurrent pyrogenic infection due to the lack of complement-c3b which is needed for defence immune adherence and phagocytosis. Studies have suggested that loss of activated complement system in humans decreases the ability to trigger an acute inflammatory response to infections; this will result into decreased likelihood of pathogens been killed and eliminated.

Jose J. (1987). Complement-derived peptide mediators of inflammation, British Medical Bulletin. Vol 43 (2), pg 336-349.

Bradykinin is a potent inflammatory mediator that can cause vasodilatation, pain and increase in microvascular permeability. This mediator is known to stimulate the synthesis of arachidonic acid (a key substrate of lipooxygenase) which helps to mediate its proinflammatory actions.

Nakao. S. (2000) et al. Bradykinin potentiates E2 release in the human gingival fibroblasts pretreated with interleukin-1ß via Ca2+ mobilization. pg 247-253.

Atherosclerosis

Our understanding of atherosclerosis is that it’s this disease that involves simply passive accumulation of lipids in the artery; furthermore in addition, it is also an inflammatory disease involving a number of factors and stages. Each stage of this disease from initiation to termination involves inflammation; inflammatory response is enhanced in this disease as the homeostatic functions are altered. The inflammation of the endothelial walls

in the artery attracts leucocytes and monocytes which penetrates the intima resulting into predisposition of the artery wall to lipid vasculitis. Another event that happens is the migration of the T cells into the intima where it secretes cytokines which are responsible for promoting inflammatory response, which also further enhances the proliferation of smooth muscle cells. Inflammatory mediator can also weaken the protective cap of the atheroma resulting into thrombosis and a possible appearance of acute coronary syndrome such as myocardial infarction and angina pectoris.

A particular circulating cytokine called IL-6 has been spotted as a marker of inflammation in atherosclerotic plaques, increased serum level of this cytokine has been observed in response to acute myocardial infarction and angina pectoris. IL-6 regulates the expression of other inflammatory cytokines and also stimulates platelet aggregation. Another inflammatory marker involved in atherosclerosis is C-reactive protein (CRP) which activates complement cascade, regulates inflammation and mediate phagocytosis. Furthermore, it is a sensitive but nonspecific marker of tissue inflammation.

As we have learnt previously in this discussion that COX-2 is involved in inflammation and with atherosclerosis been an inflammatory disease, it should spring to mind that the treatment would involve the inhibition of this COX-2. This leads me on my next part of this discussion which is treatment of atherosclerosis using COX-2 inhibitors.

Paoletti. R et al. (2004). Inflammation in atherosclerosis and implications for therapy. Journal of the American heart association. Vol 109, pg 20-26

The use of COX-2 inhibitors in treating atherosclerosis

COXIBs such as celecoxib, rofecoxib and valdecoxib are selective COX-2 inhibitors that can be used to treat atherosclerosis. They inhibit the action of COX-2 by disrupting microsomal PGE synthase-1, the main gene that synthesise PGE2. However, COX-2 inhibitors can also have the detrimental effect of inhibiting synthesis of prostacyclin, which is a mediator that can restrain some endogenous mediators from having adverse cardiovascular effect.

Funk. C. D. Fitzgerald. G. A. (2007). COX-2 inhibitors ad cardiovascular risk. J Cardiovasc Pharmacol. Vol 50 (5), pg 470-479.

Novel mediators and drugs

Novel mediators

A group of endogenous chemical mediators called proresolving lipids are proposed novel mediators involved in acute inflammation, they include lipoxins, resolvins and protectins. These mediators control the magnitude and duration of inflammation and are biologically synthesised in the subsiding phase of acute inflammation; the biological synthesis of this mediators is an active process. Even though the anti-inflammatory actions of these lipid mediators help stop potent chemoattractants and also infiltration of neutrophils, they do so in a non-inflammatory manner for instance, activation of mononuclear cell infiltration by lipoxins without having to stimulate the release of pro-inflammatory cytokines. Their other actions include promoting the uptake of apoptotic polymorphonuclears and clearance on mucosal surfaces.

- Lipoxins

These are lipooxygenase derived from enzyme catalysed reaction of arachidonic acid, and are released during acute inflammatory response. Lipoxins act specifically to reduce the attraction of polymorphonuclears, chemotaxis as well as adhesion to inflammation site; lipoxins are principally a “ braking” signal for polymorphonuclears and tissue injury enhanced by polymorphonuclears.

The derivatives of lipoxins such as LXA4 and LXB4 were the first set of proresolving lipid mediators to be recognised. Lipoxins are primarily made during vascular and mucosal cell-cell interactions; they can also be made through interaction between platelets and leukocytes (platelet-leukocytes interaction). The generation of lipoxins can be affected by aspirin resulting into aspirin triggered lipoxins via the cyclo-oxygenase pathway; the acetylation of the COX-2 inhibits the actions of the enzyme by changing the chirality of the enzyme’s product and the generation of the aspirin triggered lipoxins as shown in Figure 2.

Serhan. C. N. (2008). Controlling the resolution of acute inflammation: A new genus of dual anti-inflammatory and proresolving mediators. Vol 79 (9), pg 1520- 1526.

Apoptosis of cells take place during inflammation; the remains of these dead cells are cleared by macrophages that received signals from lipoxins as part of the suppression process of inflammation. Inflammatory cytokines such as IL-1ß can also induce expression of other anti-inflammatory mediators such as lipoxins which enhances suppression of inflammation.

- Resolvins

Resolvins are another new group of compounds (endogenous) discovered in the suppression of inflammation. There are two types, resolvins-D and resolvins- E, which are made from docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) respectively. Recent evidence has shown that resolvins exhibit anti-inflammatory actions by blocking the synthesis of inflammatory mediators, and also by controlling the movement of leukocytes to inflammation sites. For instance, resolvins blocks transmigration and infiltration of polymorphonuclear, they also help to lower expression of cytokines on microglia cells.

- Protectins

This group of compounds are also recently discovered in suppression of inflammation. They have similar actions to resolvins in that they also help to stop polymorphonuclear infiltration. They help to reduce cytokine expression on glial cells although they are made on these cells.

Novel Drugs

There are quite a few downsides to the use of COX-2 inhibitors including, inhibition of prostacyclin synthesis due to lack of aspirin like anti-platelets action, disabling one of the primary defences of the endothelium against hypertension, platelet aggregation and atherosclerosis, they also enhance an imbalance between vasoconstriction and vasodilatation in favour of vasoconstriction. All these associated biological actions can increase the risk of cardiovascular activities such as stroke, myocardial infarction and heart failure in individuals using COX-2 inhibitors. NEJM REF. As we have learnt in the discussion above that COX-2 is the cyclo-oxygenase involved in inflammation, and drugs such as rofecoxib, valdecoxib and celecoxib are

currently used to reduce inflammatory response. Furthermore, there is the need for more potent COX-2 inhibitors as the present ones lack anti-thrombotic which can result into renal and cardiovascular inabilities adding to their gastrointestinal irritation problem (main side effect).

The tendencies of NSAIDs to cause gastric irritation vary, and the two mechanism by which this gastric irritation happens are (i) the inhibition of cytoprotective COX-1 in the stomach and secondly, (ii) direct physical effect and ion trapping mechanism.

Reports have suggested that conversion of carboxylic acid group of some NSAIDs into amides and esters as they will be more selective towards the inhibition of COX-2 enzymes, and taking into consideration the side effects caused by the COXIBs and the time scale to develop a new drug, some common NSAIDs were converted into p-aminophenol derivatives. However, p-aminophenol has previously been discovered as an analgesic and antipyretic agent, but only the N-acetylated derivati0ve, which is paracetamol, is the most suitable therapeutically. NSAIDs (containing carboxylic acid) were then use to replace the acetyl group by substitution method; this substitution should bring about three advantages. The first advantage should be that at physiological pH, nonhydrolysable amide linkage will block the free carboxylic acid group in the NSAIDs, and as a result the local contact mechanism that was partially responsible for the gastric irritation (caused by the NSAIDs) will be prevented. Furthermore, these new derivatives should be more selective to inhibition of COX-2 as reported, which can further reduce ulcerogenicity in patients using NSAIDs.

Finally they should show enough antipyretic effect like paracetamol due to the structural resemblance between these new derivatives and paracetamol.

Yadav. M. R et al. 2006. Synthesis of new chemical entities from paracetamol and NSAIDs with improved pharmacodynamic profile. Bioorganic and medicinal chemistry 14. pg 8701-8706.