The cytoskeleton and its importance as a mediator of inflammation

K R Rogers, C J Morris, D R Blake

Cellular life by its very nature requires organisation and structure. Cells must, however, also have a degree of plasticity to perform varying cellular functions. The cytoskeleton possesses the required characteristics for both these properties.

The eukaryotic cytoskeleton is a complex three dimensional lattice radiating throughout the cytosol and nucleus which is made up of three distinct types of filament (table 1). There is, however, a vast array of other associated proteins, many of which have unknown function. The protein composition of the cytoskeleton is characteristic for a specific cell or tissue type, and provides the machinery required for cellular/tissue function. Within the cytosol these filaments provide a structural and an organising role. Many organelles, for example, have a close association with the various filament types. These include the mitochondria, Golgi apparatus, and endoplasmic reticulum. An intact cytoskeleton is essential for vital cellular functions, including vesicle/organelle transport, cell-cell interaction, cell extracellular matrix interactions through association with surface receptors, cell motility, and cell cycle. Despite the structural role of the cytoskeleton it is highly dynamic as cell function/activation requires rapid modification of cellular structure.

Cytoskeleton structure/function

Microfilaments

Microfilaments are made up of actin monomers (43 kilodaltons). Actin is an astoundingly highly conserved protein and is therefore essential for cell survival. There are, however, various actin isoforms that occur in different cell types owing to phosphorylation and expression of different gene products. Three such isoforms, which can be distinguished by isoelectric focusing, are termed α, β, and γ in descending order of acidity. Actin is a globular protein but is not spherical. It has one ATP binding site and one high affinity binding site for divalent ions. Microfilament actin (F-actin) exists in equilibrium with a soluble monomeric actin (G-actin) pool and gives rise to the so-called gel-sol transition. Filament formation proceeds in two steps: nucleation and elongation. Nucleation involves the formation of an actin oligomer and is slow. It is the major variable for actin assembly in vitro, and is thought to be an important regulatory step in vivo. Recent studies using microinjection have shown that the presence of nucleation sites does not necessarily lead to filament formation (see associated proteins below). Elongation is rapid and involves the addition of monomers to the nucleation site. ATP is hydrolysed when G-actin binds to the growing end of the filament. Microfilaments form a two-start, double stranded, right handed helix with an axial repeat of 36 nm (about 13 subunits). The monomer binding constant is different for each end of the filament, which gives it a definite polarity. There are also a large number of actin binding (or associated) proteins which regulate filament structural processes (figure). Capping Some proteins bind to the ends of the filament. This effectively stops further association of actin monomers and filament elongation.

Nucleation is a major regulatory step in filament formation. Proteins exist that regulate this process. Gelsolin, for example, binds two actin monomers and hence produces a site for filament formation. (Note, however, that gelsolin can have a paradoxical function, see below.)

Monomer binding Profilin is the best known member of this group, which regulates the

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Table 1 Composition of the eukaryotic cytoskeleton

<table>
<thead>
<tr>
<th>Filament</th>
<th>Size (nm)</th>
<th>Subunit protein</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microfilaments</td>
<td></td>
<td>Actin protein</td>
<td>Structure, cell motility</td>
</tr>
<tr>
<td>Microtubules</td>
<td>25–39</td>
<td>Microtubulin</td>
<td>Intracellular transport, cell division</td>
</tr>
<tr>
<td>Intermediate filaments</td>
<td>10</td>
<td>20–30 different types</td>
<td></td>
</tr>
</tbody>
</table>

Microfilament structural processes.
number of monomers that are available for filament formation by binding them and thereby altering the equilibrium between monomer and filamentous actin.

**Securing** Some proteins bind to intact filaments and then cause them to break into two.

**Cross linking** This group forms bridges between more than one filament and can thereby form either networks—for example, filamin, or bundles—for example, villin (in stress fibres). Differential expression of these proteins will obviously have a dramatic effect on microfilament structure. It is also known that several important glycolytic enzymes (glyceraldehyde-3-phosphate dehydrogenase, aldolase, and phosphofructokinase) are associated with microfilaments. Thus microfilaments may restrict enzymes involved in energy metabolism to different compartments. Microfilaments are essential for cell structure and morphology as the drug cytochalasin b, which disrupts microfilaments, causes fibroblasts to round. In non-muscle cells they form an actin cortex on the cell periphery. This cortex is largely made up of stress fibres that have connections with the extracellular matrix through, for example, the fibronectin receptor. Microfilaments also form a power generating system to provide the force required for cell motility. Actin filaments can therefore be seen as extensive structures in the moving front of pseudopodia. Recent data have suggested a role for microfilaments in cell activation. Profilin not only binds actin but also polyphosphatidylinositol 4,5-bisphosphate (PIP₂). Phospholipase C converts PIP₂ to inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol, which are both second messengers that play a part in cell signalling. Profilin also regulates the phospholipase C conversion of PIP₂ to IP₃ and diacylglycerol. In an unstimulated cell 8:1 PIP₂:profilin complexes are present, and hence the basal production of IP₃ and diacylglycerol is low. After activation an increase in activity occurs and PIP₂ is broken down.

**MICROTUBULES**

Microtubules are hollow cylinders with internal and external diameters of 15 and 25 nm respectively. The diameter of the filament is made up of about 15 α and β tubulin monomers of molecular weights 56 000 and 54 000 which bind to form heterodimers. These proteins are highly conserved and characterised by a highly acidic C terminus with a large number of aspartic and glutamic acid residues. Each dimer contains two GTP binding sites but only one, the exchangeable (or E) site, which is located on the β monomer, contains GTPase activity. The GTP in the non-exchangeable site remains unhydrolysed throughout polymerisation. This GTPase is activated on binding to the filament. Energy is therefore used for tubule formation and ATP does affect microtubules indirectly by affecting nucleation. The wall of the cylinder is made up of linear elements termed protofilaments, which are formed from tubulin subunits aligned in rows. The most common number of protofilaments in a microtubule is 13.

Microtubule formation, as in the microfilament, occurs in two steps: nucleation, when a lag period occurs for oligomer formation, and elongation where subunits add directly to the growing polymer. Heterodimers bind to both ends of the filament, but at different rates—that is, they have different critical concentrations for dimer addition. Thus microtubules, like microfilaments, are polar. Their formation has also been linked to mitochondria where the 73 kilodalton heat shock protein and chaperonin protein are involved in oligomer formation. The in vitro assembly of microtubules is profoundly affected by two cations: magnesium and calcium. Millimolar quantities of magnesium are obligatory for filament formation, whereas even micromolar amounts of calcium are inhibitory. For this to happen, however, calmodulin must be present. Hence when the calcium concentration reaches submicromolar levels in the cell, microtubules disassemble. Microtubules radiate throughout the cytoplasm from the nucleus to the surface membrane and are extensively associated with the endoplasmic reticulum and Golgi apparatus. They, therefore, play a part in vesicle transport and endocytosis/exocytosis. Nacodazole, a microtubule disrupting agent, completely inhibits retrograde transport from the Golgi apparatus to the endoplasmic reticulum. During mitosis microtubules participate in the generation of spindle fibres from the centrioles, which are involved in movement of the chromosomes during cell division.

**INTERMEDIATE FILAMENTS**

Intermediate filaments were first discovered as 10 nm filaments and originally thought to be degradation products of the other types of cellular filament. Intermediate filaments can be classified into five groups based on the sequence homology of the proteins from which they are constructed (table 2). These groups of intermediate filament proteins, of which 20 or so are known, are highly developmentally regulated. When a cell has differentiated it has a characteristic intermediate filament protein expression. Hence mesenchymal cells express vimentin, muscle cells express desmin, nerve cells express neurofilaments, and epithelial cell express cyto-keratins. Some cells, however, possess no intermediate filaments. Intermediate filament proteins have a common basic subunit monomer structure consisting of three domains: the N terminus variable region, the central highly conserved 38 kilodalton region, and the C terminus variable region. The central domain region possesses a large number of hydrophobic amino acids, which

<table>
<thead>
<tr>
<th>Type</th>
<th>Classification of intermediate filaments</th>
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<tbody>
<tr>
<td>I</td>
<td>Acidic keratins</td>
</tr>
<tr>
<td>II</td>
<td>Neutral/basic keratins</td>
</tr>
<tr>
<td>III</td>
<td>Vimentin, desmin, and glial fibrillary acidic protein</td>
</tr>
<tr>
<td>IV</td>
<td>Neurofilaments</td>
</tr>
<tr>
<td>V</td>
<td>Lamins</td>
</tr>
</tbody>
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The most common number of protofilaments in a microtubule is 13.
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functions—namely, (a) ATP and NAD depletion; (b) Ca\(^{2+}\) influx; (c) activation of ADP polyphosphate; (d) thiol redox status; (e) the glyceraldehyde-3-phosphate by oxidation of a critical thiol.\(^{33}\)

Actin structures are disrupted during oxidative stress induced by H\(_2\)O\(_2\).\(^{34} 35\) It should be borne in mind, however, that the concentrations of H\(_2\)O\(_2\) used were high, leading to cell mortality. Nevertheless, this actin disruption caused a loss of cellular organisation with membrane blebbing and cell rounding. Of the several important cell functions affected during this process—for example, Ca\(^{2+}\) influx, ATP depletion, and thiol oxidation, all are known to affect microfilaments.

There are, however, a large number of actin associated proteins, some of which are regulated by Ca\(^{2+}\) and phosphorylation, which control microfilament structure and may be perturbed during oxidative stress, leading to microfilament disruption. We have shown that intermediate filaments are also susceptible to oxidative stress. At high concentrations of H\(_2\)O\(_2\) (100 \(\mu\)mol/l) activation of a Ca\(^{2+}\) dependent, vimentin specific proteinase occurs.\(^{36}\) This cleaves the N-terminal region which is important for filament formation. At lower concentrations (25 \(\mu\)mol/l), when no loss in cell viability occurs, the major factor seems to be the blocking of the sole cysteine in vimentin, possibly by reduced glutathione.\(^{37}\) The effect of this is to produce a collapse of these filaments around the nucleus. Furthermore, rheumatoid synoviocytes are more susceptible to this collapse than other control cells (human skin fibroblasts). Interestingly, various other stress phenomena (such as heat shock) also produce this collapse.\(^{38}\)

The effect of oxidative stress in vivo on microtubules seems to be undocumented. In vitro oxidation, however, does render tubulin incapable of forming microtubules.\(^{39}\) A number of studies have been carried out to show the effect of reduced cellular glutathione on these structures.\(^{40} - 42\) Glutathione depletion leads to complete disassembly which would, therefore, seem to involve thiol groups. It is also likely that the high susceptibility to Ca\(^{2+}\) is important. Recent work has shown that low concentrations of H\(_2\)O\(_2\) can lead to changes in gene expression through activation of the transcription factor NF-KB from its inactive cytoplasmic form. This raises the possibility that some cytoskeletal alterations are due to the presence of newly transcribed gene products within the cell.\(^{43}\)

**The cytoskeleton in inflammation**

**Oxidative Stress**

During activation of neutrophils at an inflammatory site, or after hypoxic reperfusion events, or both, reactive oxygen species are generated. Superoxide (O\(_2\)) is generated from NADH oxidase and can dismutate to form hydrogen peroxide (H\(_2\)O\(_2\)). This may then react with superoxide when catalytic iron (or another redox active metal) is present to produce the highly reactive hydroxyl radical by means of the Fenton reaction.\(^{52}\)

Oxidative stress perturbs several cellular functions, including (a) ATP and NAD depletion; (b) Ca\(^{2+}\) influx; (c) activation of ADP polyphosphate; (d) thiol redox status; (e) the glyceraldehyde-3-phosphate by oxidation of a critical thiol.\(^{33}\)

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Hypoxia/Reperfusion

In the inflamed joint abnormally high pressures are generated during exercise\(^{44}\) causing the closure of the synovial capillary beds. The joint is subjected to repeated hypoxic (ischaemic) reperfusion events.\(^{45}\) Hypoxia/reperfusion has been reviewed elsewhere, but little attention has been paid to effects on the cytoskeleton. The limited amount of data available, however, suggests that the cytoskeleton is very susceptible to perturbation during such events.\(^{46}\) It is likely that the Ca\(^{2+}\) influx, O\(_2\) generation by xanthine
oxidation, or ATP depletion are all important in this process. These effects are apt to be directed to the endothelial cells.

A CRITICAL ROLE FOR THE ENDOTHELIAL CELL CYTOSKELETON
Inflammation is associated with an increase in vascular permeability to macromolecules, particularly in the postcapillary venules.  Such permeability is thought to be the result of interendothelial cell gap formation following endothelial cell contraction.  Normal microfilament structure is required for retention of cell shape, and disruption may therefore be of particular importance in the microvascular endothelial cells. For example, inflammagens, such as histamine, neuropeptides, bradykinin, prostaglandins, leukotrienes, and thrombin, have all been shown to increase vascular permeability, and a number of them also cause changes in large vein endothelial cell shape.  Their effect is caused, at least in part, by second messenger activation, which acts on several cytoskeleton components. Calcium has a potent effect on microtubules and several microfilament associated proteins, whereas cAMP induces phosphorylation of vimentin rendering it assembly incompetent.  This results in changed cellular morphology and disruption of intercellular contacts. It is interesting to speculate that such changes are associated with the production of high endothelial venules, which are important in lymphocyte trafficking into synovial tissue.

In vivo studies have shown that the influx of polymorphonuclear leucocytes into pulmonary tissue increases when the actin cytoskeleton is rearranged.  Possibly, also the actin microfilaments regulate surface adhesion molecules such as the integrins with which they are known to be closely associated.  The importance of microfilaments in the control of cell permeability has been shown by Hecht et al., who treated cell monolayers with the toxin A of Clostridium difficile (which causes severe inflammatory enterocolitis in man) and produced an increase in transcellular transport and oedema.  Furthermore, the increase in permeability in this model is correlated with the disruption of the actin microfilaments. This correlation did not occur when permeability was induced with Ca2+ or 8-bromo-cAMP.

Other studies also indicate that cytoskeleton integrity is essential for maintenance of the endothelial intercellular tight junction and control of vascular permeability. It is therefore possible to modulate permeability by using such agents as phalloidin (a fungal toxin which stabilises and increases actin polymerisation, and cytchalasin B (which induces actin disassembly) in vivo.  Goldman et al have recently produced in vivo data showing that microfilaments are important in controlling polymorphonuclear leucocyte infiltration in a rat lung model.  In this model phalloidin decreased leucocyte infiltration induced by leukotriene B4.  Cytchalasin B had an opposite effect and this could be inhibited by phalloidin. It has also been shown that microfilaments are involved in the movement of organelles, and this function may also be restricted after actin filament disruption.

NEUTROPHIL DEACTIVATION
Activation of neutrophils by chemotactic agents induces changes, cell shape, migration, degranulation, and phagocytic responses, all of which require cytoskeletal restructuring.  In addition, superoxide production by NADPH oxidase is also regulated by microfilaments. For example, it has been shown that cytchalasin B drastically increases O2 production after stimulation with N-formyl-methionyl-leucyl-phenylalanine (fMLP), platelet activating factor, and concanavalin A. Botulinum C2 toxin (which ADP-ribosylates G actin) has also recently been shown to produce the same effect.  Interestingly, both these compounds inhibit actin polymerisation. The precise mechanism by which this occurs is unknown, though the ligand-occupied fMLP receptor associates very rapidly with the cytoskeleton and may therefore produce a desensitising effect. Association of the receptor-ligand with the microfilaments stops the signal for cell activation by termination of second messenger production. This would therefore represent a negative feedback mechanism as the production of the second messengers IP3 and diacylglycerol causes disruption in the actin cytoskeleton.

Data presented by Sarndahl show that a G protein interaction is involved.  He also suggests that a binding site for actin is produced by a conformational change when either the α or β subunits dissociate from the G protein complex. Any disruption of this feedback mechanism could induce massive production of O2 when the cell is activated owing to the fact that the cell is unable to terminate the signal produced at its surfaces. This general mechanism may also be of relevance to other receptor-ligand responses in other cells—for example, in endothelial cells.

AUTOANTIBODIES
Autoantibodies to cytoskeletal proteins occur in rheumatoid arthritis and in other connective tissue disorders, such as Sjögren's syndrome and systemic lupus erythematosus. The presence of antibodies to intermediate filament is particularly widespread; antibodies to vimentin occurring in up to 80% of patients with rheumatoid arthritis.

Use of these antibodies for diagnostic purposes is hampered by the lack of specificity as they occur in 12% of apparently normal subjects. The antibodies are of the IgG and IgM classes. The biological relevance of these antibodies remains obscure as does the mechanism by which they arise. Indeed whether they are protective or damaging is still open to speculation. Possibly, for example, they prevent the overactivation of complement by aiding opsonisation and removal of intermediate filaments. Conversely, they may direct the immune system to such filaments. Further studies on antibody subtyping may throw some light on this matter.
For example, it has been shown that antibodies to keratin are significantly higher in IgG1 and lower in IgG2. There is also a high prevalence of IgG4 possibly owing to chronic exposure to the protein antigen. There is evidence that subclasses of antibodies occur, some of which cross react with other cellular antigens, such as DNA and cardiolipin.

Sanchez et al have recently shown that a particular subset of antibodies from patients with systemic lupus erythematosus react with DNA and vimentin. These antibodies are specific for IgM and possibly, therefore, some classes only occur in particular diseases, providing a useful diagnostic test.

In rheumatoid patients the epitope with which the antibodies react is unknown, but efforts made to locate this may be rewarding diagnostically.

In acute proliferative glomerulonephritis, which occurs after streptococcal infection, cross reactive antibodies are present that react with a different epitope on type 1M and type 12M streptococcal proteins and with vimentin. In type 1M proteins the epitope has been mapped to a tetrapeptide which occurs at the N-terminal side of a helical part of the rod domain of vimentin. It is noteworthy that the epitope in the type 1M protein is also a helical coiled coil (cf structure of intermediate filaments). Interestingly, our data show that rheumatoid serum samples react with epitope(s) present within a 20 kilodalton region of the central core domain which also contains this tetrapeptide sequence. Also, autoantiserum which react with antigens in placental extracts have recently been described. On western blots, these antigens occur mainly at 48 kilodaltons with several smaller molecular weight bands which are characteristic of vimentin degradation by a Ca\textsuperscript{2+} dependent protease. Moreover, the authors claim that this reactivity is 100% specific for rheumatoid patients. If the autoantiserum were directed against vimentin it is difficult to explain the 100% specificity. One possibility is that reactivity is directed against a posttranslationally modified protein and may therefore represent a subpopulation of antibodies that react with epitopes in vimentin. If this were the case there would be obvious clinical and diagnostic implications.

Complement activation
When tissue sections or fixed cells are incubated with normal serum, binding of complement components (Clq, C4, and C3) to the intermediate filaments occurs specifically. This binding is rapid for Clq (within 10 seconds) and causes activation through the classical pathway. Accumulation of C3 takes up to several minutes. The C3 binding may be through the alternative pathway and is independent of antibodies (but see also below).

Activation of complement causes degradation of the intermediate filaments, which are highly sensitive to proteolysis. Intermediate filaments are, therefore, endogenous activators of complement. It has been shown that monocytes can bind to cells which have been previously incubated with serum and that such monocyte binding is closely associated with intermediate filament structures. The binding is inhibited by Ca\textsuperscript{2+} chelators, indicating that some of the binding may occur by receptors on the monocytes recognising C3b and C3bi. Possibly, also, there is binding through Clq as there is also a receptor (on monocytes) for this component. Hansson has shown that vimentin filaments, but not monomeric vimentin, on western blots possess high affinity saturable binding sites for IgG. This occurs through the Fc portion of the IgG molecule and most probably in the C\gamma\textsubscript{2} domain. This is independent of the autoantibodies discussed above. In endothelial cells, IgG aggregates have been shown to be closely associated with intermediate filaments in vivo.

Furthermore, intermediate filaments activate complement by formation of complexes with IgG Clq. In vivo, therefore, monocyte binding may help in the removal of exposed intermediate filaments or non-viable damaged cells by opsonisation. A prerequisite for this mechanism is damage at the plasma membrane, and viable cells would, therefore, be unaffected, producing a self regulating system. This process occurs in non-pathological tissue and therefore functions in normal cell turnover. When tissue damage occurs an increase in monocyte recruitment is required, and this probably occurs as a result of the release of chemotactic factors during complement activation. Recruitment of monocytes will obviously be particularly important

The synovial lining cell
The rheumatoid synovium is characterised by a proliferation of B type synoviocytes, which possess fibroblastic morphology and have a vast increase in the 10 nm vimentin intermediate filaments in the cytosol. The cause of this is at present unknown, but a number of circulating factors have been shown to increase vimentin expression. Vimentin is also a growth regulated gene, which is upregulated after oncogene activation. The ras oncogene when transfected into myoblasts causes the continual expression of vimentin. Two other transforming factors also increase vimentin expression: tax (p66x) protein of human T cell leukaemia virus type 1 and the SV40 T antigen. The 19 kilodalton product of the adenovirus EIB oncogene also associates with vimentin intermediate filaments and specifically disrupts this class of cytoskeleton filament.
after endothelial cell damage as there is direct contact with circulating monocytes. Overactivation of these mechanisms may cause accumulation of monocytes and tissue damage at sites of inflammation. The presence of large quantities of vimentin intermediate filaments in rheumatoid synovial cells may be important as removal of unviable cells would need a greater recruitment of monocytes, again leading to tissue destruction/inflammation.

Vitronectin has recently been shown to bind cytotkeratin intermediate filaments and it is suggested that the vitronectin stops over-activation of the complement mechanism discussed above. This is an attractive proposal, and it is intriguing to speculate that in some pathological conditions this regulatory system may be aberrant.

POSSIBLE DRUG INTERVENTION

In this review we have shown that the cytoskeleton has an important and complex role in inflammatory processes. There is, therefore, the possibility that new drugs can be developed to gain therapeutic advantage. It may be possible to reduce oedema by the use of drugs that decrease the sensitivity to Ca" influx. The problem with this approach, however, is that such drugs would have a non-specific effect, and as microfilaments are important to cellular function, toxicity might be a problem. One way to negate this would be to direct drug action to the capillary bed. This could be achieved by designing compounds which alter those microfilament associated proteins that are specifically expressed in such cells. These drugs would not, therefore, affect normal cellular function.

As discussed above, thios are important in maintaining the normal cytoskeleton. It is well documented that there is a decrease in free thiol in rheumatoid serum. We have also shown that disodium aurothiomalate, an antiarthritic drug which is thiol reactive, produces similar effects to those of hydrogen peroxide exposure—that is, a collapse in the vimentin structures around the nucleus. This drug also prevents cell proliferation and derives a therapeutic effect by inhibition of the proliferating synovial lining cell. It is also attractive to speculate that this effect is mediated through binding to critical thios in the cytoskeleton. It may therefore be advantageous to produce drugs that bind to such thios specifically.

Conclusion

The cytoskeleton is quite clearly involved in a vast array of vital cellular functions. Many of these also have a pronounced influence on the inflammatory process. This area has received little attention thus far. Future research will undoubtedly disclose new inflammatory processes influenced by the cytoskeleton. Furthermore, a better understanding of these processes will enable the design of truly new therapeutic compounds.

We thank the Arthritis and Rheumatism Council for Research for supporting this work.

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