Disease Markers 26 (2009) 181–188
DOI 10.3233/DMA-2009-0629
IOS Press

A systematic review of studies examining inflammation associated cytokines in human abdominal aortic aneurysm samples

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Abstract. *Objectives:* Inflammation is critical in abdominal aortic aneurysm (AAA) but there is no current consensus on which inflammation related cytokines are important. The aim of this review was to systemically assess previous studies investigating the relative expression of inflammation associated cytokines within human AAA samples.
Methods: The MEDLINE database was searched for studies which simultaneously examined an array of different inflammation associated cytokines in aortic samples in order to identify those associated with AAA. Focused searches were then conducted for further studies assessing relative concentrations of these cytokines in aortic samples in relation to AAA. Appropriate studies were assessed by two reviewers independently.
Results: Eighteen studies were included. A number of different cytokines have been consistently found to be upregulated within AAA by comparison to aortic samples removed from patients without cardiovascular disease, however findings relative to samples of aortic athero-thrombosis were less consistent. TNFA and INFG appear to be the most consistently associated with AAA in studies using both normal and atherosclerotic controls. Cautious interpretation of these data is recommended due to a number of methodological problems.
Conclusions: This systematic review suggests that TNFA and INFG are the most consistently upregulated cytokines in large AAAs. Further studies utilizing larger populations, new proteomic techniques and better patient matching are required.

1. Introduction

Abdominal aortic aneurysm (AAA) is estimated to be responsible for approximately 5,000 deaths per year in England and Wales [1]. At present there are a number of deficiencies in the management of this condition. AAAs are usually defined by maximum infrarenal aortic diameter $\geqslant$ 30 mm, and monitored by regular diameter measurements. Additional markers are required which reflect the biology of the individual AAA and which can be used, along with anatomical and clinical information, to guide detection of clinical important AAAs which are likely to expand and rupture [2].

AAAs are believed to release a range of biomarkers into the circulation which could potentially be useful in diagnosing or guiding management [3–5]. Interleukin 6 (IL6) for example has been measured at increased concentrations within the iliac arteries compared to the proximal aorta in subjects with AAA, consistent with its release from the aneurysm [5]. The identification of biomarkers upregulated specifically within AAAs may suggest suitable markers to aid in diagnosis, improve prognostic ability and target treatment.

Previous histological studies have demonstrated that transmural inflammation is a common finding in samples of larger AAAs [6]. Whilst a large array of inflammation related cytokines have been linked with AAA

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there is currently no consensus on which cytokines are specifically associated with this condition [7–11]. We carried out a systematic review to identify inflammation associated cytokines which were up or down regulated within human AAA samples.

2. Methods

2.1. Search strategy

Our aim was to review previous studies comparing the relative expression of soluble inflammation modulating cytokines in human AAA and control samples. Identification of studies for inclusion in this review was carried out in 2 stages. We searched the MEDLINE database using the terms "abdominal aortic aneurysm" and "tissue" or "sample" and "cytokine", limits human. A total of 93 papers were identified from this search, and the corresponding abstracts were read to identify those studies appropriate for inclusion. From these 93 studies a total of 13 met the inclusion criteria [10,12, 14–17,20–25,27]. The inflammatory cytokines identified from these papers were Interleukin 1 Beta (IL1B), Interleukin 6 (IL6), Interleukin 8 (IL8), Interleukin 10 (IL10), Interleukin 12 (IL12), Tumour Necrosis Factor Alpha (TNFA), Prostaglandin E2 (PGE2), Interferon Gamma (INFG), Transforming Growth Factor Beta (TGFB1), Osteoprotegerin (also known as tumor necrosis factor receptor superfamily, member 11 B; TNFRSF11B) and Chemokine CC motif ligand 2 (CCL2, more commonly known as monocyte chemotactic protein 1, MCP-1). In order to ensure a thorough search was performed, individual searches were then carried out for these specific cytokines. The MEDLINE database was searched using the terms "abdominal aortic aneurysm" and the name of the cytokine identified from stage one. Thus a search for "IL6" and "abdominal aortic aneurysm" for example was carried out, along with searches for the other identified cytokines. A total of 239 papers were identified from these searches and the corresponding abstracts were read to identify those studies appropriate for inclusion. This two stage search strategy identified 2 new papers not previously included [9,19].

2.2. Inclusion and exclusion criteria

Only studies which compared levels of the cytokine of interest in full thickness AAA samples taken from intact AAAs to that in aortic control samples were included in this review. While some studies also included data on cytokines in samples from ruptured AAAs, we felt that comparisons between the cytokine profile of ruptured and intact samples would be confounded by the likely additional markers of the pathological process of aortic rupture.

We excluded papers for a number of reasons, including those examining levels of cytokines in animal models (N = 3), those that did not include comparison between aortic and control samples (N = 74) and those that were not related to recognised inflammation modulating cytokines, such as proteases (N = 3). Numbers given relate to numbers of papers excluded by each criteria, applied in order of priority. In order to focus discussion of our findings, in tabular presentation of our results we have only included cytokines assessed for association with AAA in at least three studies [9, 10,12,13,15–28].

2.3. Data extraction

The following information was recorded from each study where available: Number of patients providing AAA and control samples; diameter of AAA; type of controls (athero-thrombosis and normal); source of control sample (organ donor, patients undergoing aortic bypass, post-mortem); whether the control sample was obtained pre or post-mortem; whether patients and controls were matched for other risk factors, such as age and gender; techniques used to assess cytokine expression (measured directly within aortic sample or based on secretion of cytokine from sample in explant culture); methods used to quantify cytokines of interest (quantitative or non-quantitative RNA assessment, Western blotting, protein array, ELISA, bioassay); cytokine expression value in AAA and control aortic samples; statistical comparison of relative cytokine expression reported (p value). Each study was assessed by two reviewers independently and disparities resolved by re-review of the study. Tables were subsequently developed to summarize the study design and cytokine results. Since a large range of different outcome measures and quantification techniques were employed, relative expression between AAA and control samples were ultimately reported in terms of fold change relative to the control sample. We thus present the relative expression of the cytokines of interest compared to normal aortic controls and samples of athero-thrombosis separately.

Table 1
Summary of included studies

Ref.	Aortic diameter of cases (cm)	# AAA	# control	Control type	Outcome	Sample[a]	Method	Covariant matched
9		6	7	Normal[c]	mRNA	Tissue	Expression array	Gender & Age
21	6.2 (3.5–11)[h]	8	8	AOD[b]	mRNA/Protein	Tissue	Q-RT-PCR ELISA	Gender & Age
22	5.8 ± 1.8[e]	3	3	Normal[b]	mRNA	Tissue	Q-RT-PCR	Yes
10	$5.0 - 10.0$	32	14	Normal[c]	Protein	Tissue	ELISA	No
12	7.5 (5.6–9.3)[h]	10	9	Normal[c]	Protein	Tissue	Protein array	No
13	5.7 ± 0.3[e]	4	4	Normal[c]	mRNA	Tissue	Expression array	No
15	> 5.0	14	7	AOD[b]	mRNA	Tissue	Q-RT-PCR	No
17	Open surgery	7	2/3[d]	AOD[b]/Normal[c]	Protein	Tissue	ELISA	N/A
18	6.7 ± 1.1[e]	17/14[f]	11/12[g]	AOD[b]	mRNA/Protein	Tissue	Q-RT-PCR/ Immunoassay	No
19	6.4(5.5–9.3)[i]	25	15	Normal[c]	Protein	Tissue	ELISA	No
20	Open surgery	19	5/5	AOD[b]/Normal[c]	mRNA	Tissue	Q-RT-PCR	No
23	> 5.9	8	5	Normal[c]	Protein	Tissue	ELISA	N/A
16	> 4.5	13	14/16	AOD[b]/Normal[b]	Protein	Secretion	Biological Functional assay	N/A
24	Open surgery	12	4/6	AOD[c]/Normal[c]	Protein	Secretion	ELISA	N/A
25	Open surgery	7	4/4	AOD[b]/Normal[c]	Protein	Secretion	ELISA	N/A
26	Open surgery	15	5/6	AOD[b]/Normal[c]	Protein	Secretion	ELISA	No
27	Open surgery	20	4	Normal[c]	Protein	Secretion	ELISA	N/A
28	Open surgery	10	10	Normal[c]	Protein	Secretion	ELISA	N/A

AAA = abdominal aortic aneurysm; AOD = aortic Occlusive Disease. Q-RT-PCR = Quantitative Reverse Transcriptase Polymerase Chain Reaction. [a]Studies assessed outcome measures directly within aortic samples or by measuring secretion in explant culture. Control samples were obtained. [b]pre-mortem or [c]post-mortem. [d]Both control types were combined for comparison with AAA. [e]Mean ± Standard Deviation. [f]17 AAA samples were used to measure mRNA levels, 14 samples were used to measure protein levels. [g]The number of controls used to measure relative levels of cytokines was 11 except for measurements of IL6 & IL8 for which 12 controls were used. [h]Mean (Range). [i]Median (Range)

3. Results

3.1. Description of studies

A total of 18 studies were selected based on our exclusion and inclusion criteria and are summarized in Table 1 [9,10,12,13,15–28]. A median (range) of 13 [3–32] patients with AAA and 6 [2–16] control subjects were included in these studies. The control samples used included those obtained from patients with aortic atherosclerosis, organ donors and subjects undergoing post-mortem. In 7 studies [15–17,20,21,25,26] aortic atherosclerotic samples were obtained from patients undergoing surgical revascularization for lower limb ischemia while in 2 studies atherosclerotic tissue was taken from pre-mortem organ donors [18] or from autopsy [24]. In 15 studies control samples were defined as normal aged aorta and obtained from live [16] or cadaveric organ donors [9,10,12,13,17,19,20,23–28], or from the macroscopically normal neck of an AAA [22].

3.2. Matching of cases and controls

The majority of studies were unable to match risk factors in the patients who provided AAA and control samples and no adjustment for this was made in subsequent statistical analyses [10,12,13,15,18–20,26]. In 7 studies no information on patients' risk factors was reported [16,17,23–25,27,28]. In one study [22] cytokine expression was compared between the body and macroscopically normal neck of AAA samples thereby adjusting for a whole range of variables which may alter between patients (such as age, gender, atherosclerotic risk factors and medication). In a second study assessing the secretion of cytokines from explant samples, patients with AAA or aortic atherosclerosis had non significant differences in age and gender, but other risk factors were not reported [21]. Finally, one microarray study matched cases and controls for age, gender and ethnicity [9].

3.3. Assessment techniques

The methods used to assess cytokine levels varied in a number of ways. Seven studies measured RNA expression within AAA samples using quantitative polymerase chain reaction (PCR) [15,18,20–22] or expression array [9,13]. Thirteen studies measured protein expression in aortic samples using immunoassay [18], ELISA [10,17,19,21,23–28], protein array [12], or biological functional assay [16]. Two studies assessed both RNA and protein [18,21]. The methods used to

quantitate the cytokines of interest also varied. Twelve studies [9,10,12,13,15,17–23] measured either RNA or protein directly from aortic samples, while 6 studies assessed cytokine concentrations in conditioned media taken from aortic explants [16,24–28].

3.4. Cytokines examined and their relative concentration in AAA samples

While a range of different cytokines have been assessed for their relation to AAA, interleukins were by far the most commonly investigated. Other cytokines assessed included TNFA, INFG, PGE2 and CCL2. As shown in Table 2, the expression of IL1B was greater in AAA relative to normal aortic samples in 6 of 7 studies [9,10,12,17,23,26,27]. IL1B expression was not consistently associated with AAA by comparison to aortic atherosclerotic samples [17,18,21,26]. Two studies reported greater expression of IL1B in AAA samples [17,18], one identified greater concentrations in aortic atherosclerotic samples [21] and one reported no significant differences [26]. The study identifying greater concentrations of IL1B in atherosclerotic samples was the only one to report matching of gender and age for the subjects included [21].

Relative expression of IL6 was significantly greater in AAA samples by comparison to normal aortic samples in 4 of 5 studies [10,12,16,25,27]. IL6 expression was more variably associated with AAA by comparison to atherosclerotic samples [15,16,18,21,25]. Two studies reported higher IL6 expression in AAA samples [15,18], 2 reported greater expression in aortic atherosclerotic samples [16,21] and one study reported no significant differences [25].

Relative IL8 expression was reported to be greater in AAA samples than normal controls in 7 of 8 studies [9,10,12,13,19,22,24,27]. Only one study reported significantly higher concentrations of IL8 in AAA samples by comparison to aortic atherosclerosis [18]. No consistent association of IL10 and AAA was identified, despite a protein array study reporting its upregulation [12,18,21,27]. No consistent association of IL12 with AAA was reported [9,18,21,27].

Relative TNFA expression was reported to be increased in AAA compared to normal aortic samples in 5 of 7 studies (Table 3) [9,10,12,17,20,23,26]. Similar upregulation of TNFA was reported in 4 of 5 studies comparing expression in AAA and aortic atherosclerotic samples [15,17,18,20,21]. One study however reported lower expression of TNFA in AAA compared to aortic atherosclerotic samples [21]. INFG was reported to be upregulated within AAA relative to atherosclerotic samples in 2 of 3 studies [18,21,25]. The study reporting no association between INFG and AAA was the only study to report matching gender and age between cases and controls [21]. Three studies reported increased secretion of PGE2 from AAA compared to normal aortic samples [16,27,28]. Three studies reported upregulation of CCL2 in AAA compared to normal aortic samples [9,12,24]. Two studies reported significantly greater CCL2 levels in AAA compared to aortic atherosclerotic samples [18,24].

4. Discussion

Recruitment of a range of inflammatory cells is consistently demonstrated in AAA samples [8–11,29,30]. Many different cytokines are known to control adhesion, migration and the function of inflammatory cells and have therefore been a significant focus in AAA research [3–6,31]. This systematic review identified a large number of studies assessing expression of such cytokines in AAA, atherosclerotic and normal aortic samples [9,10,12,13,15–28]. Our findings suggest that the cytokines IL1B, IL6, IL8, TNFA, PGE2 and CCL2 are upregulated in AAA compared to normal aortic samples [9,10,12,13,16,17,19,20,22–28]. Many of these cytokines however appear to be non specific for AAA, thus we found no consistent differences in the expression of IL1B, IL6, IL8 and IL10 between AAA and aortic atherosclerotic samples [15–18,21,24–26]. The identification of cytokines specific to AAA as compared to occlusive atherosclerosis is of particular interest. Such specific cytokines might be able to be used to highlight the mechanistic differences between occlusive and aneurysmal disease and thereby improve diagnosis, monitoring and treatment of AAA.

We did identify 3 cytokines with some evidence to support their specificity to AAA. Seven of 10 studies reported upregulation of TNFA in AAA when compared to both aortic atherosclerotic and normal aortic samples [9,10,12,15,17,18,20]. A smaller number of studies also suggested a consistent upregulation of INFG and CCL2 in AAA compared to aortic atherosclerotic samples [18,19,24,25]. Insufficient studies were identified comparing the expression of PGE2 in AAA relative to atherosclerotic tissue; thus although this cytokine appears to be upregulated in AAA compared to normal tissue the specificity of this relative to AAA could not be determined [16,27,28].

Table 2
Relative expression of interleukins in AAA samples

Reference	Total number of cases & controls	Relative expression compared to AOD	p value	Relative expression compared to normals	p value
IL1B					
27	24			1.5	NS[b]
9	13			1.6	< 0.01
23	13			1.9	< 0.05
17	10			4.0	< 0.05
10	46			7.2	< 0.01
26	21			9.8	0.05
12	19			Upregulated	< 0.01
21	16	0.4	< 0.05		
26	20	1.6	NS[b]		
17	9	4.0	< 0.05		
18 (Protein)	26	10.2	< 0.01		
18 (mRNA)	28	12.4	< 0.01		
IL6					
27	24			3.2	NS[b]
25	11			5.3	< 0.05
16	29			7.7	0.02
12	19			15.0	< 0.01
10	46			18.7	< 0.01
16	27	0.36	0.03		
21	16	0.7	< 0.05		
25	11	2.1	NS[b]		
18(mRNA)	28	29.9	< 0.01		
15	21	60	0.02		
18 (Protein)	26	> 100	< 0.01		
IL8					
27	24			1.1	NS[b]
9	13			1.4	< 0.01
12	19			4.3	0.002
22	6			4.8	< 0.01
24	18			5.6	< 0.05
10	46			7.2	< 0.01
13	8			11	Significant[c]
19	40			28.1	< 0.01
24	16	2.3	NS[b]		
18(mRNA)	28	21.1	0.003		
18(Protein)	26	> 100	< 0.01		
IL10					
27	24			1.05	NS[b]
12	19			Upregulated	0.002
18(mRNA)	28	1.4	0.55		
21	16	2.0	< 0.05		
IL-12					
9	13			1.3	< 0.01
21 (mRNA)	16	0.7	NS[b]		
18 (Protein)	26	1.0	NS[b]		

Reported is the relative expression in or secretion from AAA samples as compared with that from aortic atherosclerosis (AOD) or normal aortic samples. [b]NS means not significant. [c]Stated to be significant but statistical testing not reported. Where possible the fold difference in expression has been calculated relative to the control sample (AOD or normal). In some studies it was not possible to report relative expression since cytokine concentrations were below detectable limits. In these cases upregulation or downregulation relative to the control sample has been stated.

There is ongoing controversy as to the contribution of different T-cell subsets such as T-helper type 1 (TH-1) and T-helper type 2 (TH-2) in AAA [4,8–11,21,25, 32–34]. This systematic review suggests that the TH-1 cytokines TNFA and INFG are the most consistently identified T cell cytokines upregulated in AAA (Table 3). Unlike the large array of cytokines upregulated in AAA compared to normal aortic samples, TNFA and INFG have also been found to be upregulated in AAA as compared to atherosclerotic samples in a

Table 3
Relative expression of other cytokines in AAA samples

Reference	Total number of cases & controls	Relative expression compared to AOD	p value	Relative expression AAA compared to normals	p value
TNFα					
9	13			1.5	< 0.01
20	14			1.5	< 0.05
10	46			1.6	< 0.01
26	21			1.8	NS
23	13			3.03	NS
17	10			86[b]	< 0.01
12	19			Upregulated	< 0.01
21	16	0.7	< 0.05		
15	21	1.3	< 0.01		
20	14	2.9	< 0.05		
18(mRNA)	28	3	NS		
17	9	86[b]	< 0.01		
18 (Protein)	26	Upregulated	< 0.01		
INF-γ					
16	29			Unchanged	NS
25	11			1.4	< 0.05
21	16	1.1	NS		
25	11	1.8	< 0.05		
18 (mRNA)	28	265	< 0.01		
18 (Protein)	26	Upregulated	< 0.01		
PGE2					
27	24			2.9	< 0.05
16	29			28.9	< 0.01
28	20			39.6	< 0.01
16	27	0.8	NS		
CCL2					
19	40			9.4	< 0.01
24	18			11.8	< 0.05
12	19			13.7	0.003
18 (Protein)	26	1.8	NS		
18 (mRNA)	28	2.8	< 0.05		
24	16	8.6	< 0.05		

Reported is the relative expression in or secretion from AAA samples as compared with that from aortic atherosclerosis (AOD) or normal aortic samples. [b]In this study 2 patients with atherosclerotic disease and 3 normal controls were combined as a control group. Where possible the fold difference in expression has been calculated relative to the control sample (AOD or normal). In some studies it was not possible to report relative expression since cytokine concentrations were below detectable limits. In these cases upregulated or not upregulated relative to the control sample has been stated.

number of studies.

Many of the studies assessing the relationship between cytokines and AAA are based on the rationale that such information will be useful in targeting medication therapy to treat small AAAs. At present this and other studies do not clearly identify singular cytokine pathways which can be targeted. Another potential value of identifying specific AAA associated cytokines is for their use in diagnosis and prognosis. It is possible that cytokines upregulated within AAA will be released into the circulation and therefore act as blood borne markers for the diagnosis and subsequent monitoring of AAA progression. Currently a limited number of studies have measured circulating cytokines in relation to AAA [3–5,35,37]. IL6 has been the most investigated, with one study demonstrating that circulating IL6 and IL1B were significantly higher in patients with AAA than in those with coronary heart disease or normal controls [4]. A further 3 studies have also found significantly elevated levels of IL6 in AAA patients compared to normal controls [3,5,35]. Consistent with these reports, 4 of the 5 studies reviewed here reported higher concentrations of IL6 in AAA samples compared to normal aorta [10,12,16,25,27]. IL6 however was not specific to AAA and was also upregulated in some aortic atherosclerotic samples [16,21]. Thus in terms of diagnosis IL6 may only be of value in screening populations with low incidence of occlusive atherosclerosis.

Circulating levels of TNFA and INFG have also been demonstrated to be higher in patients with AAA than

in normal controls in some studies [3,4,9]. These findings for TNFA are consistent with our review of cytokine expression in aortic samples. Four of the 6 studies included in the current report found higher concentrations of TNFA in AAA compared to normal aortic samples [9,10,12,20,23,26]. In contrast to IL6, TNFA appeared relatively specific to AAA as it was also upregulated in aneurysmal relative to atherosclerotic specimens in 4 of 5 studies [15,17,18,20,21]. A smaller number of studies in this review reflected the findings seen for circulating levels of INFG [18,25]. Further studies are required to investigate circulating levels of biomarkers, such as those we have highlighted to be most consistently associated with AAA based on aortic samples.

This review of previously published data illustrates a number of limitations with previous studies. With the exception of three studies [9,21,22], matching of the risk factors for patients and controls was not reported. Many factors such as age, sex, smoking, diabetes and medication may have contributed to reported differences in cytokine levels. Given the different disease processes being compared (AAA, athero-thrombosis or absence of macroscopic aortic disease) risk factors would be expected to be different between cases and controls. Ideally large studies are required in which differences in risk factors are clearly documented and adjusted for in statistical analyses. Another consideration in studies of this type is the source of control aortic samples. The identified studies reported obtaining atherosclerotic samples from individuals undergoing aortic bypass [15–17,20,21,25,26] and also from autopsy cases [24]. It is likely that severity of atherosclerosis would be significantly greater in those requiring surgery. Similarly, there is significant variability in the source of normal control aortic samples used, with some investigators reporting the use of samples taken from patients after death [9,10,12,13,17,19,20,23–28] and other studies obtaining samples from live organ donors [16,22]. Many of these identified factors may have contributed to the variation in outcomes reported in different studies.

One possible way of reducing the difficulties in obtaining adequately matched and identically sampled AAA and control samples is to use macroscopically normal aortic tissue from patients undergoing AAA repair. This approach was used in one of the studies included in this review [22]. This technique is not beyond criticism however since there is some evidence to support global vascular changes in patients with AAA [38]. This method however is probably the most practical approach for obtaining matched controls.

In conclusion, this systematic review confirms that a large number of inflammation associated cytokines are upregulated within AAA samples. The TH-1 associated cytokines TNFA and INFG have currently been the most specifically associated with AAA as opposed to atherosclerosis in general. Further larger studies, with better matching of cases and controls, and employing newer proteomic based techniques are required to better identify cytokines specifically associated with AAA.

Funding

Funding from the National Institute of Health, USA (RO1 HL080010-01) and NHMRC (project grant 540403/540404/540405) supported this work. JG and PEN hold Practitioner's Fellowships from the NHMRC, Australia (431503/458505).

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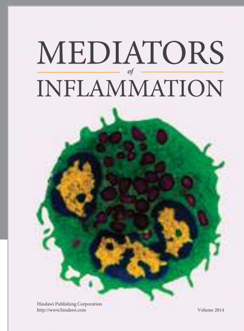

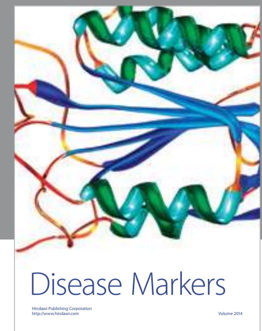

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