Aus dem Institut für Laboratoriumsmedizin
der Ludwig-Maximilians-Universität München
Direktor: Univ.-Prof. Dr. med. Daniel Teupser

Molecular Signatures in Abdominal Aortic Aneurysms

Dissertation
zum Erwerb des Doktorgrades der Naturwissenschaften (Dr. rer. nat)
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

vorgelegt von
Bernd H. Northoff

aus
Münster

2023

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Betreuerin:	Prof. Dr. med. Dr. rer. nat. Lesca Miriam Holdt
Zweitgutachter:	Prof. Dr. rer. nat. Jürgen Bernhagen
Dekan:	Prof. Dr. med. Thomas Gudermann
Tag der mündlichen Prüfung:	24. März 2023

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Abbreviations

Common Abbreviations

AAA ..... Abdominal aortic aneurysm

AOD ..... aortic occlusive disease

C_T ..... Cycle threshold

CAD	Carotid artery disease
CHD	Coronary heart disease
$CI_{95\%}$	95% confidence interval
DEA	Differential expression analysis
eAAA	Elective abdominal aortic aneurysm
ESVS	European Society for Vascular Surgery
GEO	Gene Expression Omnibus
GRCh37	Genome Reference Consortium human build 37
GRCm38	Genome Reference Consortium mouse build 38
GSEA	Gene set enrichment analysis
GWAS	Genome-wide association study
IA	Intracranial aneurysm
iAAA	Intermediate abdominal aortic aneurysm
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} revision
IEL	Internal elastic lamina
lAAA	Large abdominal aortic aneurysm
MeSH	Medical Subject Headings
MMP	Matrix metalloproteinase
NA	Not available
OR	Odds ratio
P	P value
PAA	Popliteal artery aneurysm
PAD	Peripheral artery disease
PCA	Principal component analysis
PVAT	Perivascular aortic adipose tissue
qRT-PCR	Quantitative real-time polymerase chain reaction
rAAA	Ruptured abdominal aortic aneurysm
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SNP	Single nucleotide polymorphism
TIMP	Tissue inhibitor of matrix metalloproteinases
VSMC	Vascular smooth muscle cells

Abbreviations of Murine AAA Models

AngII model ..... Angiotensin-II perfusion model
$CaCl_2$ model ..... Calcium chloride model
ePPE model ..... External periadventitial elastase model
PPE model ..... Porcine pancreatic elastase perfusion model

Chemicals, Genes and Proteins

ABHD16B ..... Abhydrolase domain containing 16B
ADAMTS8 ..... ADAM metallopeptidase with thrombospondin type 1 motif 8
ADAMTS9 ..... ADAM metallopeptidase with thrombospondin type 1 motif 9
AngII ..... Angiotensin II
ANGPTL2 ..... Angiopoietin like 2
ANGPTL4 ..... Angiopoietin like 4
ANRIL ..... Antisense non-coding RNA in the INK4 locus
Apoe ..... Apolipoprotein E
ATOH8 ..... Atonal bHLH transcription factor 8
BAPN ..... β-Aminopropionitrile
C20orf181 ..... Chromosome 20 open reading frame 181
CCL4L1 ..... C-C motif chemokine ligand 4 like 1
CDKN1A ..... Cyclin dependent kinase inhibitor 1A
CDKN2B ..... Cyclin dependent kinase inhibitor 2B
CDKN2B-AS1 .... CDKN2B antisense RNA 1
CELSR2 ..... Cadherin EGF LAG seven-pass G-type receptor 2
CHRNA3 ..... Cholinergic receptor nicotinic alpha 3 subunit
CHRNB4 ..... Cholinergic receptor nicotinic beta 4 subunit
CRISPLD2 ..... Cysteine rich secretory protein LCCL domain containing 2
CRP ..... C-reactive protein
CXCL8 ..... C-X-C motif chemokine ligand 8
CXCR1 ..... C-X-C motif chemokine receptor 1
CXCR2 ..... C-X-C motif chemokine receptor 2
DAB2IP ..... DAB2 interacting protein
ERG ..... ETS transcription factor ERG
FAS ..... Fas cell surface death receptor
FBN1 ..... Fibrillin 1
FCGBP ..... Fc gamma binding protein
GAL3ST4 ..... Galactose-3-O-sulfotransferase 4
GDF7 ..... Growth differentiation factor 7
GFPT2 ..... Glutamine-fructose-6-phosphate transaminase 2
HIF-1α ..... Hypoxia inducible factor 1 subunit alpha

HILPDA ..... Hypoxia inducible lipid droplet associated
HSP90AB3P ..... Heat shock protein 90 alpha family class B member 3, pseudogene
IL-6 ..... Interleukin 6
IL-8 ..... Interleukin 8
IL6R ..... Interleukin 6 receptor
JAK2 ..... Janus kinase 2
Ldlr ..... Low density lipoprotein receptor
LEP ..... Leptin
LINC00540 ..... Long intergenic non-protein coding RNA 540
LINC00861 ..... Long intergenic non-protein coding RNA 861
LINC02103 ..... Long intergenic non-protein coding RNA 2103
LINC02775 ..... Long intergenic non-protein coding RNA 2775
LIPA ..... Lipase A, lysosomal acid type
LOX ..... Lysyl oxidase
LPA ..... Lipoprotein(a)
LRP1 ..... LDL receptor related protein 1
MCP-1 ..... Monocyte chemoattractant protein-1
MEPE ..... Matrix extracellular phosphoglycoprotein
MMP-2 ..... Matrix metallopeptidase 2
MMP-9 ..... Matrix metallopeptidase 9
Nfe2l2 ..... Nuclear factor, erythroid derived 2, like 2
PCIF1 ..... Phosphorylated CTD interacting factor 1
Pcsk9 ..... Proprotein convertase subtilisin/kexin type 9
PDGF-D ..... Platelet-derived growth factor D
PFK15 ..... 1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one
PPAR ..... Peroxisome proliferator-activated receptor
PSRC1 ..... Proline and serine rich coiled-coil 1
PTGS2 ..... Prostaglandin-endoperoxide synthase 2
PURPL ..... P53 upregulated regulator of p53 levels
RNU6-1032P ..... RNA, U6 small nuclear 1032, pseudogene
RPS4XP18 ..... Ribosomal protein S4X pseudogene 18
SMYD2 ..... SET and MYND domain containing 2
SORT1 ..... Sortilin 1
SRPX2 ..... Sushi repeat containing protein X-linked 2
STAT3 ..... Signal transducer and activator of transcription 3
STC1 ..... Stanniocalcin 1
Tgf-β ..... Transforming growth factor beta
TRIB1 ..... Tribbles pseudokinase 1
VEGF ..... Vascular endothelial growth factor
ZNF335 ..... Zinc finger protein 335
ZPR1 ..... ZPR1 zinc finger

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Publication I:

Gäbel G, Northoff BH, Weinzierl I, Ludwig S, Hinterseher I, Wilfert W, Teupser D, Doderer SA, Bergert H, Schönleben F, Lindeman JHN, Holdt LM. Molecular Fingerprint for Terminal Abdominal Aortic Aneurysm Disease. *J Am Heart Assoc*. 2017 Nov 30; 6(12).

DOI: 10.1161/JAHA.117.006798

Publication II:

Gäbel G*, Northoff BH*, Balboa A, Becirovic- Agic M, Petri M, Busch A, Maegdefessel L, Mahlmann A, Ludwig S, Teupser D, de Waard V, Golledge J, Wanhainen A, Wågsäter D, Holdt LM, Lindeman JHN. Parallel Murine and Human Aortic Wall Genomics Reveals Metabolic Reprogramming as Key Driver of Abdominal Aortic Aneurysm Progression. *J Am Heart Assoc*. 2021 Sep 7; 10(17)

*G. Gäbel and B.H. Northoff contributed equally as co-first authors.

DOI: 10.1161/JAHA.120.020231

Publication III:

Kokje VBC, Gäbel G, Dalman RL, Koole D, Northoff BH, Holdt LM, Hamming JF, Lindeman JHN. CXCL8 hyper-signaling in the aortic abdominal aneurysm. *Cytokine*. 2018 Aug; 108:96-104.

DOI: 10.1016/j.cyto.2018.03.031

Publication IV:

Kokje VBC, Gäbel G, Koole D, Northoff BH, Holdt LM, Hamming JF, Lindeman JHN. IL-6: A Janus-like factor in abdominal aortic aneurysm disease. *Atherosclerosis*. 2016 Aug; 251:139-146.

DOI: 10.1016/j.atherosclerosis.2016.06.021

Publication V:

Doderer SA, Gäbel G, Kokje VBC, Northoff BH, Holdt LM, Hamming JF, Lindeman JHN. Adventitial adipogenic degeneration is an unidentified contributor to aortic wall weakening in the abdominal aortic aneurysm. *J Vasc Surg*. 2018 Jun; 67(6):1891-1900.e4.

DOI: 10.1016/j.jvs.2017.05.088

1 Introduction

1.1 Clinical Relevance and Epidemiology of Abdominal Aortic Aneurysms

1.1.1 Clinical Relevance

Abdominal aortic aneurysm (AAA) formation is a complex disease of the aortic wall characterized by local dilatation of the abdominal aorta caused by segmental weakening[6]. An AAA is defined by the Society for Vascular Surgery[7] and the European Society for Vascular Surgery (ESVS)[8] as the enlargement of the abdominal aorta to $\geq$ 30 mm. This threshold, quantified by imaging techniques, such as ultrasonography, computed tomography angiography or magnetic resonance imaging, correspond to the excess of two standard deviations above the mean diameter for men[9–11] and is widely used in current research[12–15], although the aortic diameter is known to vary depending on age, sex and height[16]. Thus, the ESVS discusses[8] a lower threshold for women[17] and Asian population[18] in their guideline. To account for individual variation in the diameter, other researchers suggest as criteria for AAA the use of the infrarenal to suprarenal diameter ratio[19,20] or normalizing of the aortic diameter to body surface area[21]. Also absolute diameters ranging from 25 mm[22] to 40 mm[23] were used as threshold in several studies.

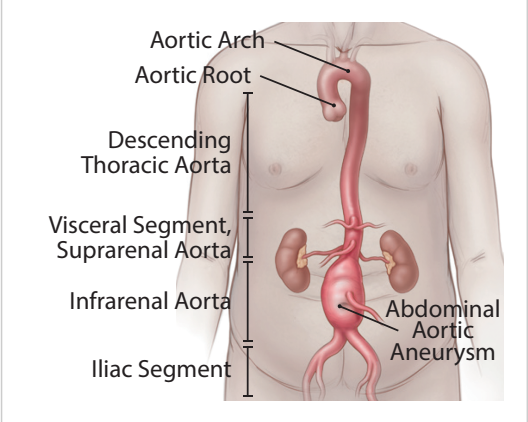

Figure 1: Scheme of an abdominal aortic aneurysm and aortic segments. *Abdominal aortic aneurysms are caused by weakening and dilatation of the infrarenal aorta, located between the visceral and iliac segment of the aorta. Figure adapted from Schanzer et al., 2021*[24].

The progressive dilatation of the aorta, which is usually asymptomatic, has the potential to result in a fatal aortic rupture. Since the risk of aortic rupture increases with larger diameters[25–34], clinical risk assessment relies on the diameter[8] to consider the balance between the patient's operative risk and the risk of aneurysm rupture. While the risk of rupture is low for AAAs $<$ 50 mm, the risk increases substantially by a diameter of 60 mm[35]. The relative risk of rupture was shown to increase by 1.39 per 1 cm diameter with 95 % confidence interval ranging from 1.11 to 1.73 ($CI_{95\,\%} = [1.11,\ 1.73]$) in a prospective multicenter cohort study[33].

Since AAA often remains asymptomatic until rupture, AAA is also associated with a high mortality rate. A population based retrospective study in Finland revealed a mortality rate of 79.1 % for patients with ruptured AAAs, whereby 52.5 % of all patients died prehospital[36].

Although more than hundred targets have been proposed to limit aneurysm growth, there is currently no established pharmacological treatment for aneurysm stabilization[37,38].
To avoid the risk of fatal rupture, AAA surgical repair should be performed when aortic diameters expand to $\geq 50\,\text{mm}$ in women[8] and $\geq 55\,\text{mm}$ in men[8,31,39]. Surgery is currently the exclusive prophylactic intervention for larger aneurysms and is performed either by open surgical repair or endovascular aortic aneurysm repair, depending on AAA specific features and patients' characteristics[14,35].

1.1.2 Epidemiology

Diseases of the cardiovascular system (ICD-10: I100-I199), which include AAA, were the leading cause of death in Germany with 356,616 affected persons in 2015 and a mortality rate of 437 deaths per 100,000 inhabitants[40]. Of these cases, 3,725 individuals (2,322 males and 1,403 females) died as a result of aortic aneurysms and aortic dissections (ICD-10: I71).
Although the prevalence of AAA per 100,000 inhabitants decreased slightly in Western Europe from 269 in 1990 ($\text{CI}_{95\,\%} = [248,\ 291]$) to 244 in 2010 ($\text{CI}_{95\,\%} = [223,\ 265]$)[41], AAA rupture is still an important cause of death in adults. While the global prevalence and incidence of AAA have declined between 1990 and 2010, regional assessments revealed increases in prevalence in many regions of the world[41]. Thus, the prevalence of AAA depends on the population studied. AAA prevalences ranging from 1.7 % to 12.7 % with a median of 5.0 % were reported[42].

1.1.3 Genetic Risk Factors

Abdominal aortic aneurysm is a complex disease, associated with multiple environmental and genetic risk factors. Twin studies attributed 70 % of AAA variance to genetic effects ($\text{CI}_{95\,\%} = [0.33,\ 0.83]$), while 30 % of AAA variance could be explained by non-shared environmental factors ($\text{CI}_{95\,\%} = [0.17,\ 0.46]$)[43]. These genetically determined risk factors include male sex[44–49] and ethnicity[41].
Individuals with an affected first-degree relative have an estimated 11.6-fold increased risk of developing an AAA compared to individuals without family history[50].
Genome-wide association studies (GWAS) were used to identify genomic variations associated with AAA formation[51–60]. To date, 33 variants at 28 loci were associated with AAA[61] (Table 1) at genome-wide significance ($P = 5 \times 10^{-8}$)[62] with odds ratios (ORs) ranging from 0.79 at rs7936928[57] to 2.78 at rs193181528[57] and risk allele frequencies ranging from 0.07 at rs118039278[57] to 0.98 at rs11591147[53], as listed in the GWAS catalog[61] for the trait abdominal aortic aneurysm (Experimental Factor Ontology ID: EFO_0004214, accession date: 2022-01-10).
The most significant genetic association with AAA diagnosis was found for genomic variants at the Chr9p21 locus, located near the genomic region of the long-noncoding ribonucleic acid (RNA) *ANRIL* / *CDKN2B-AS1*. Substitution of major allele G by risk allele A at rs10757274 revealed $\text{OR} = 1.24$ ($\text{CI}_{95\,\%} = [1.20,\ 1.29]$) with $P = 2 \times 10^{-33}$[63]. Association of other genetic variants located in the Chr9p21 locus at rs2383207 ($\text{OR} = 1.27$, $P = 2 \times 10^{-8}$)[52] and rs7866503

($OR = 1.26,\ P = 2 \times 10^{-13}$)[55] have been identified by independent GWASs. The pleiotropic Chr9p21 locus haplotype block has also been associated with other diseases of the arteries, such as coronary artery disease (CAD)[64–69], peripheral artery disease (PAD)[70–72] and stroke[73–79]. Genomic variants at this locus were shown to *cis*-regulate expression of *ANRIL*[71,80,81] and *CDKN2B*[82] and also *trans*-regulate a broad range of additional genes[83,84]. These factors regulate cellular functions such as adhesion, apoptosis and proliferation as well as controlling ribosomal RNA processing and protein translation[85].
Additional pleiotropic loci are known to be associated with inflammation (*IL6R*), lipid metabolism (*LRP1*, *Ldlr*, *PSRC1-CELSR2-SORT1*, *DAB2IP*, *LIPA*, *Pcsk9* and *LPA*), extracellular matrix remodeling (*PCIF1-ZNF335-MMP-9*) and vascular development and angiogenesis (*SMYD2* and *ERG*)[63].

1.1.4 Environmental Risk Factors

Firstly described in 1958 by Hammond and Horn[44], many studies have associated smoking as a major risk factor for AAA formation[44–49]. Also, in recent cohort-based and case-control studies, the odds of AAA formation were at least 2.75 times higher for smokers ($OR \geq 2.75$)[23,86–90], and thus one of the strongest risk factors. Additionally, old age has also been recognized as a major risk factor for AAA in these studies. The risk of AAA was also shown to be associated with cardiovascular disease, hypertension and increased cholesterol and triglyceride levels[23,86–91]. In contrast, diabetes has been associated with a reduced risk of AAA development ($OR = 0.54$, $CI_{95\%} = [0.44,\ 0.65]$)[92].

Table 1: Genetic loci associated with AAA in genome-wide studies. *List of genetic variants associated with AAA with genome-wide significance ($P < 5 \times 10^{-8}$) and sorted by position. Strength of association is given by P value and effect size by odds ratio and corresponding 95% confidence interval as listed in the GWAS catalog (accession date: 2022-01-10)[61]. AAA, abdominal aortic aneurysm; $CI_{95\%}$, 95% confidence interval; CAD, carotid artery disease; CHD, coronary heart disease; GRCh37, Genome Reference Consortium human build 37; GWAS, genome-wide association study; IA, intracranial aneurysm; NA, not available; OR, odds ratio; P, P value; PAD, peripheral artery disease; SNP, single nucleotide polymorphism.*

Mapped gene	SNP	GRCh37 position	*P*	OR	$CI_{95\%}$	GWAS catalog study accession	Other diseases the locus has been associated with[63]
CELSR2, *PSRC1*	rs602633	1:109,278,889	7.00E-09	1.14	[1.09, 1.19]	GCST003877	CHD and dyslipidaemia[56]
IL6R	rs12133641	1:154,455,807	5.00E-13	1.14	[1.10, 1.18]	GCST003877	Asthma and CHD[56]
SMYD2, *LINC02775*	rs1795061	1:214,235,937	9.00E-11	1.131	[1.09, 1.17]	GCST003877	
Pcsk9	rs11591147	1:55,039,974	6.00E-11	1.58	[1.38, 1.82]	GCST011495	CHD and dyslipidaemia[57]
GDF7	rs7255	2:20,679,060	9.00E-13	1.1	[1.07, 1.13]	GCST011496	Barrett's oesophagus and oesophageal adenocarcinoma[93]
ATOH8	rs113626898	2:85788308	9.00E-09	2.71	[1.93, 3.82]	GCST90038468	
HSP90AB3P, *MEPE*	rs10023907	4:87851383	2.00E-08	1.09	[1.06, 1.12]	GCST011496	
LINC02103, *PURPL*	rs116390453	5:27996901	4.00E-09	2.51	[1.84, 3.4]	GCST90038468	
LPA	rs118039278	6:160564494	4.00E-18	1.28	[1.21, 1.35]	GCST011495	Aortic stenosis, CHD and dyslipidaemia[57,94]
CDKN1A	rs3176336	6:36681039	1.00E-10	1.1	[1.07, 1.13]	GCST011496	Breast cancer[95]
LINC00861, *TRIB1*	rs10808546	8:125483576	1.00E-10	1.1	[1.07, 1.13]	GCST011496	Dyslipidaemia[96]
DAB2IP	rs7025486	9:121660124	5.00E-10	1.21	[1.14, 1.28]	GCST000727	CHD, PAD and pulmonary embolus[52]
	rs10985349	9:121662964	2.00E-11	1.17	[1.12, 1.23]	GCST003877	
ANRIL / *CDKN2B-AS1*	rs7866503	9:22091925	2.00E-13	1.26	[1.20, 1.32]	GCST003683	CHD and IA[76]
	rs10757274	9:22096056	2.00E-33	1.24	[1.20, 1.29]	GCST003877	
	rs2383207	9:22115960	2.00E-08	1.27	NA	GCST000727	
JAK2	rs193181528	9:5059543	3.00E-08	2.78	[1.93, 3.99]	GCST90038468	
LIPA	rs1412445	10:89243047	1.00E-10	1.1	[1.07, 1.13]	GCST011496	
ZPR1	rs964184	11:116778201	5.00E-19	1.18	[1.14, 1.23]	GCST011496	Dyslipidaemia[97]
ADAMTS8	rs7936928	11:130409273	8.00E-09	0.79	[0.72, 0.85]	GCST90038468	
	rs4936098	11:130410772	7.00E-16	1.13	[1.10, 1.16]	GCST011496	
LRP1	rs1466535	12:57140687	5.00E-10	1.15	[1.10, 1.21]	GCST001312	Aortic dissection, migraine, diabetes, blood pressure and dyslipidaemia[56,98,99]
LINC00540	rs9316871	13:22287782	5.00E-10	1.15	[1.10, 1.15]	GCST003877	
FBN1	rs595244	15:48548638	1.00E-08	1.35	[1.25, 1.45]	GCST003683	
CHRNA3, *CHRNB4*	rs55958997	15:78623530	9.00E-14	1.12	[1.09, 1.16]	GCST011495	Lung cancer[100]
CRISPLD2	rs35254673	16:84885919	3.00E-08	1.09	[1.06, 1.13]	GCST011496	
RNU6-1032P, *RPS4XP18*	rs8087799	18:22605468	2.00E-09	1.21	[1.15, 1.27]	GCST003683	
	rs4401144	18:22613705	4.00E-14	1.11	[1.08, 1.14]	GCST011496	
Ldlr	rs6511720	19:11091630	8.00E-14	1.24	[1.18, 1.32]	GCST003877	CAD and CHD[56]
Apoe	rs429358	19:44908684	1.00E-15	1.17	[1.12, 1.21]	GCST011496	Alzheimer's disease and CHD[57,101]
PCIF1	rs58749629	20:45942678	2.00E-17	1.223	[1.17, 1.28]	GCST003877	CHD[56,102]
C20orf181, *ABHD16B*	rs73149487	20:63849998	8.00E-09	1.26	[1.16, 1.36]	GCST011495	
ERG	rs2836411	21:38447907	6.00E-09	1.113	[1.07, 1.15]	GCST003877	

1.2 Pathogenesis of Abdominal Aortic Aneurysms

1.2.1 Comparison of Healthy Aortic Wall and Aneurysms

Tissue remodeling in aortic aneurysms is characterized by destruction of the structural and cellular components of the vessel wall (Figure 2). The intima consists of a layer of endothelial cells, connective tissue and an internal elastic membrane (internal elastic lamina, IEL). The IEL is a thin, flexible barrier consisting of elastic fiber with a variable number of fenestrations for diffusion of molecules through the intima to the media [103]. The media, which represents the thickest and most variable layer of the aorta, consists of several layers of circumferentially oriented vascular smooth muscle cells (VSMC), surrounding elastic fibers and connective tissue. The extracellular matrix of this layer consists of proteins, such as proteoglycans, glycoproteins, glycosaminoglycans and collagens. The media is delimited by the external elastic lamina. The outer adventitia consists of fibroblasts, collagen and elastic fibers in a loose connective tissue and contains the vasa vasorum, lymphatics and innervations. The network of elastic and collagen fibrils is primarily responsible for the elastic properties of the aortic wall [104,105]. The precise structural composition of the aortic wall varies along the length of the aorta and thereby influences key mechanisms of aneurysm formation, such as vessel mechanics, protease profiles, cell-signaling pathways and atherosclerotic plaque deposition [106].

In comparison to healthy tissue, aortic tissue of AAA samples is characterized by immune driven weakening of the aortic wall through invasion of inflammatory cells [107], and complex tissue remodeling of the aortic wall. Aneurysms show decreased VSMC density in the media, associated with increased VSMC apotposis [108–110] and replicative senescence [111]. AAAs are also characterized by fragmentation of the elastic fibres and a decreased concentration of elastin [112,113]. In several studies, the occurrence of AAAs was also associated with the presence of atherosclerotic alterations of the aorta [114].

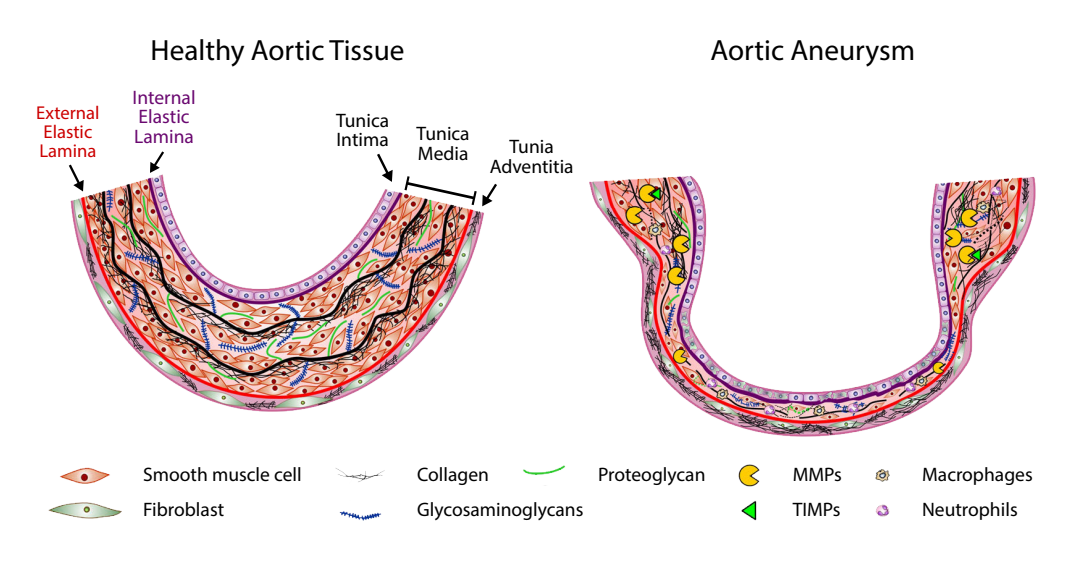

Figure 2: Cross section of the aortic wall of healthy aortic tissue versus aortic aneurysms. *Adverse remodeling of the aortic wall induces dilatation and aneurysm formation by endothelial damage, loss of smooth muscle cells and degradation of extracellular matrix. Figure adapted from Jana et al., 2019 [105]. MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases.*

1.2.2 Immune-driven Weakening of the Aortic Wall

A major hallmark of AAA formation is extensive active chronic inflammatory changes in tissue sections of AAAs, which were firstly described in 1972[107]. In accordance with these findings, many studies have documented the accumulation of mononuclear cells, such as T and B lymphocytes, plasma cells, monocytes, and natural killer T cells[115–119] in the aortic wall, while normal aortic tissues are not affected by inflammatory cell infiltrates[115]. Immune cells are able to access the aortic wall from periadventitial lymph nodes or from vessels of the vasa vasorum in the adventitia[120], and are embedded mainly in the adventitia and in the media of AAA samples[121]. The presence of immune-related antigens[122] and the expression of pro-inflammatory cytokines and transcription factors[118,123–125] by these infiltrated cells, and also by cells of the arterial wall, indicate local inflammation in these lesions. The pro-inflammatory response in AAA was also characterized by increased levels of interleukin 6 (IL-6), interleukin 8 (IL-8)[126] and C-reactive protein (CRP)[127,128]. Thus, AAA can be characterized on the molecular level as an inflammatory response with extensive upregulation of pro-inflammatory cytokines, inducing VSMC apoptosis and dysfunction as well as destruction of the aortic media (Figure 3).

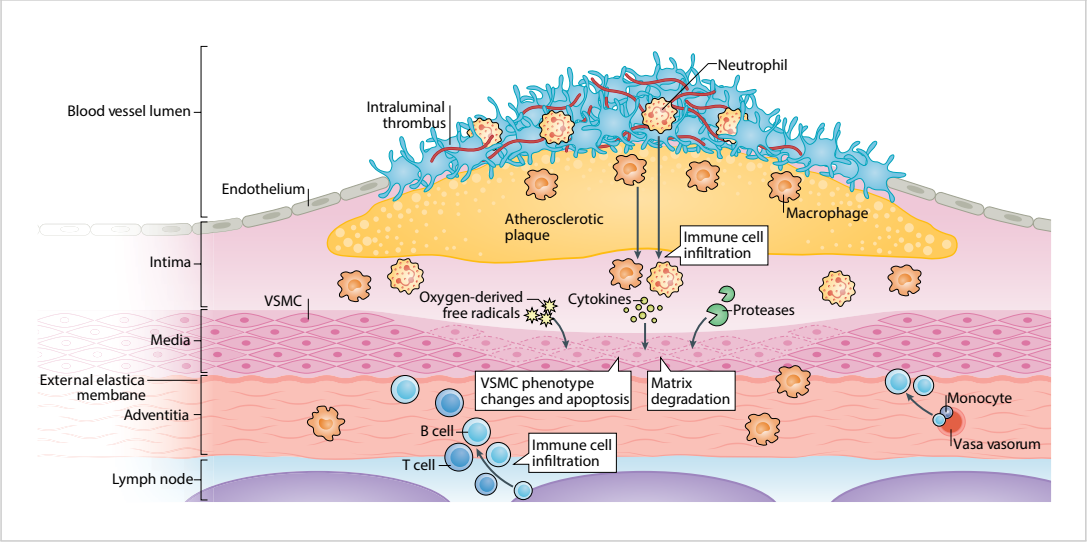

Figure 3: Potential effects of inflammation in AAA pathogenesis. *Innate immune cells infiltrate the aortic wall and induce inflammatory response strengthened by expressed cytokines, such as apoptosis and phenotypic changes of vascular smooth muscle cells. Finally, infiltration reduces matrix-producing and matrix-repair capacity of the media, and induces fragmentation of the microfibrils of the media, leading to loss of wall elasticity. Togehter these effects may cause medial thinning and aortic weakening. Figure adapted from Golledge, 2019[120].*
VSMC, Vascular smooth muscle cells.

Currently, it remains unclear whether a specific immune response incites AAA lesion formation, or whether inflammatory cells accumulate in response to some other injury[129].
Additionally, there are conflicting reports about the role of autoimmunity[130,131] and infectious agents including *Chlamydia*[132–138], *Mycoplasma pneumoniae*[133], *Borrelia burgdorferi*[139], human cytomegalovirus[140], herpes simplex virus[141] and further bacteria[142] in the initiation and progression of AAA development.

1.2.3 Tissue Remodeling and Proteolytic Modulations

Dissections of aortic aneurysms comprise increased levels of proteases, such as matrix metalloproteinases (MMPs), cathepsins, chymase and tryptase, neutrophil-derived serine elastase and serine protease of the plasmin pathway[143].

MMPs are a class of zinc-dependent endopeptidase proteins mediating changes in extracellular matrix, which are known to modulate angiogenesis[144] as well as cardiovascular diseases[145] by remodeling elastin and collagen. MMPs are known to be modulated by reactive oxygen species (ROS)[146], which are locally increased in AAA segments, as well as inflammatory cytokines, growth factors, glucocorticoids or retinoids[147]. The gelatinases MMP-2 and MMP-9 were shown to be highly expressed in human AAA tissue compared to healthy aortic tissue[148–150]. Also the ratio of MMP expression to endogenous tissue inhibitors of MMPs (TIMPs) was found to be higher in AAA samples[151].

These proteolytic enzymes destruct components of the extracellular matrix, disrupt the structural integrity of the aortic wall and lead to aortic dilation[152,153]. However, the underlying functional mechanisms of both MMPs in AAA formation remain controversial[154].

Media thinning is also caused by apoptosis of VSMCs, another hallmark of AAAs[108,109]. Apoptosis of VSMCs is induced by the release of ROS by inflammatory cells and VSMCs during inflammatory processes and thus increasing oxidative stress within the vessel wall[155–157]. VSMC apoptosis is also known to be mediated by the FAS and perforin pathways, initialized by cytotoxic mediators of macrophages and T lymphocytes[109], and by PTGS2[158].

1.2.4 Pathological Impact of Adipose Tissue

Perivascular aortic adipose tissue (PVAT) is thought to be the differentiated continuation of the vascular adventitia, consisting of adipocytes, microvasculature, stromal cells and inflammatory cells[159]. PVAT of the abdominal aorta mainly contains white adipose tissue[160,161], which is known to secrete various hormones, cytokines and enzymes modulating inflammation, metabolism, and vascular homeostasis[162,163]. Crosstalk of the metabolic active PVAT and the adventita allows the PVAT to modulate the vascular tone[164,165], endothelium-dependent relaxation[166], vessel wall thickness[167], angiogenesis[168,169] and inflammation[170].

Thus, dysfunctional PVAT is suspected to promote AAA progression. Inflammatory cells, mainly T lymphocytes, are known to migrate from the PVAT to the vascular wall[171] and to promote the release of pro-inflammatory factors. PVAT is also known to secrete CRP and inflammatory cytokines such as MCP-1[172], which are also known to accelerate aneurysm formation. Secretion of ANGPTL2 by PVAT regulates expression of MMPs[173]. Furthermore, PVAT-mediated expression of additional factors like LEP, PDGF-D and VEGF are also known to modulate AAA formation by promoting inflammation, neovascularization and vascular remodeling[171].

An increase of adipocytes was also observed in ruptured aortas compared to non-ruptured aortas after perfusion of triglycerides in the adventitial vasa vasorum in an animal model[174]. In parallel, the amount of triglycerides in the human adventitia, a major component in adipocytes, was also found to be positively correlated with the AAA diameter[174]. Thus, an abnormal appearance of adipocytes in the vascular wall is also suggested to be involved in AAA rupture[174].

1.2.5 Atherosclerotic Alterations in Patients with Abdominal Aortic Aneurysms

In several studies, the formation of AAAs was considered to be an end-stage manifestation of complicated atherosclerosis[175,176] since a majority of AAAs arise in association with severe atherosclerotic degeneration. Histological analyses indicate that arterial narrowing by atherosclerotic plaque formation causes haemodynamic alterations and lead to changes in VSMC phenotypes. As a result, released MMPs induce weakening of the aortic wall and AAA formation by remodeling extracellular matrix and medial thinning to normalize the luminal diameter and haemodynamic stress[114,177].

In contrast, several studies show that patients with advanced atherosclerosis do not develop AAA and vice versa, leading to the conclusion, that AAA and atherosclerosis are two separate pathological entities with distinct risk profiles[178–181]. These findings are supported by notable differences in clinical manifestation, localization, inflammation and risk factors of AAA and atherosclerosis (Table 2). Additionally, AAAs occur extremely rare in typical vessels of atherosclerosis, such as the carotid or external iliac arteries.

Recent findings support the hypothesis of a parallel development of AAA and atherosclerosis in contrast to a causal dependency[182]. The joint occurence of atherosclerosis and AAA could be traced back on shared environmental and genetic risk factors, such as smoking, hypertension and family history[6]. However, a causal role of atherosclerosis for AAA cannot be ruled out and needs further investigations[114,182].

Table 2: Characteristics of abdominal aortic aneurysm and atherosclerosis. *Comparison of pathological characteristics and risk factors of abdominal aortic aneurysm and atherosclerosis. Table adapted from Peshkova et al., 2015[183].*
VSMC, vascular smooth muscle cells.

Characteristics	Abdominal Aortic Aneurysm	Atherosclerosis
Clinical manifestation	Vessel rupture	Vessel occlusion
Affected area of the vessel wall	Media and adventitia	Intima
Location of inflammation	Transmural	Intima and media
Proliferation of VSMC	Apoptosis of VSMC	Proliferation of VSMC
Elastin destruction	Progressive elastin destruction resulting in media degradation	Slight destruction of elastin in the plaque area
Key risk factors	Age Smoking Hypertension Male sex	Age Smoking Hypertension Dyslipidemia Diabetes

1.3 Mouse Models of Abdominal Aortic Aneurysms

1.3.1 Mouse Models in Translational Research

To analyze the underlying pathophysiological mechanisms of AAA formation, three mainly used inducible mouse models have been established: the AngII model[184], the PPE model[185] and the $CaCl_2$ model[186]. However, each model mimics only parts of human AAA formation and growth. Models relying on spontaneous AAA formation are also limited by low penetrance of AAA development and high variation of local distribution[187].
More recently, the use of organoids and organs-on-a-chip technology that mimic complex human tissues and diseases might replace the translational usage of these *in-vivo* models[188], however today no corresponding models are available for AAA development.

1.3.2 AngII Model

The prevailing method to induce abdominal aneurysm formation in mice is based on a combination of subcutaneous infusion of angiotensin II (AngII) with parallel induction of hyperlipidemia, called Angiotensin-II perfusion model (AngII model)[184,189–195].
AngII is known to be a regulatory factor of the wall structure and function during vascular remodeling[196]. AngII is considered to induce the pro-inflammatory phenotype of human vascular smooth muscle cells[197], to modulate vascular cell migration and decrease vascular smooth muscle apoptosis[198] and to alter extracellular matrix composition by promoting the expression of MMPs[199].
AngII infusion promotes slight AAA formation in normocholesterolemic mice. This effect was enhanced significantly by inducing hypercholesterolemia via *Ldlr* deficiency[184,200], *Apoe* deficiency[189] or an adeno-associated viral mediated infection with a mouse *Pcsk9* gain-of-function mutation[201]. However, AAA formation in normocholesterolemic mice with AngII infusion was also enhanced by long-term high-fat diet in the absence of hypercholesterolemia[202], neutralization of Tgf-β[203–206], disrupted cross-linking of extracellular matrix proteins induced by β-Aminopropionitrile (BAPN)[207], and genetic deficiency of the stress-responsive transcription factor *Nfe2l2*[208].
The AngII model reflects essential features of human AAA, including leukocyte infiltration into the smooth muscle-rich medial layer and transmedial dissection causing rapid luminal expansion within the first seven days of AngII infusion, followed by inflammatory processes, causing intramural thrombus formation and elastin degradation and profound remodeling causing fibrotic changes containing several types of inflammatory cells[189,209]. The AngII model is also promoted by important risk factors of human AAAs, including male sex and cigarette smoke[189–195,210]. In contrast to humans, the aortic aneurysm usually appears in the suprarenal region of mice in the AngII model, while human AAAs occur more often in the infrarenal region[189].
Differences in the embryological backgrounds of the affected regions of the aorta in mice are thought to be responsible for species differences[106,211].
Modulation of the renin–angiotensin system in humans by angiotensin-converting enzyme inhibitors revealed contrary effects on AAA growth and rupture[212,213].

1.3.3 PPE Model

The murine porcine pancreatic elastase perfusion model (PPE model) is based on a temporary ligature of a defined segment of the abdominal aorta between the level of the left renal vein and the bifurcation, followed by perfusion of type I porcine pancreatic elastase into the lumen of the infrarenal aorta by a syringe pump[185]. After the 5-minute period of perfusion with 100 mmHg, whereby the aorta typically dilates about 50 to 70 %, ligations are removed and mice are allowed to recover up to 14 days[185].
The perfusion results in a degradation of the medial elastic lamellae, with subsequent inflammatory response, followed by temporal dilatation of the whole aortic wall[214], unlike the luminal expansion of the AngII model[120]. The observed temporal aneurysm formation, which is limited to the segment infused with elastase, is also associated with an inflammatory cell production of MMP-9[185].
The PPE model is limited by the acute aortic injury causing a regression of dilatation after a maximum of 8 weeks. Thus, prolonged effects of drugs on AAA cannot be analyzed. Furthermore, the PPE model is technically difficult compared to the AngII model.

1.3.4 $CaCl_2$ Model

The commonly used $CaCl_2$ model induces aneurysm formation in the infrarenal abdominal aorta of wildtype mice by infusion of calcium chloride or the related compound calcium phosphate[186,215,216]. However, the degree of induced aortic dilatation is relatively mild[120] and causes more vascular wall thickening[214]. In accordance to human AAA, the $CaCl_2$ model causes calcification, inflammatory cell infiltration, oxidative stress, neovascularization, elastin degradation and vascular smooth muscle cell apoptosis[215]. Limitations of this model are the absence of aortic thrombus, atherosclerosis and rupture which are classical features of human AAA[215] and the acute injury preventing the study of prolonged effect of potential therapeutic interventions[120].

1.3.5 Modifications of Mouse Models of Abdominal Aortic Aneurysms

The external periadventitial elastase application model (ePPE model) is a modification of the PPE model based on extraluminal treatment with porcine pancreatic elastase[217]. The PPE model and the ePPE model are comparable with respect to aneurysm growth rate, but extraluminal induction preserves endothelial cell function and elastic fibers[217]. The ePPE model induces also acute inflammatory infiltrates, whereas intraluminal elastase perfusion induces chronic inflammation with angiogenesis and endothelial destruction[217].

The lysyl oxidase inhibitor BAPN increases AAA development and rupture induced by the AngII model[207,218] and the ePPE model[219,220] by reducing blocking crosslinking of elastin and collagen and thus reducing matrix stability. The sole application of BAPN is also used as model for thoracic aortic dissection[221].

1.4 Transcriptomic Insights in Diseased Tissue

1.4.1 Role of RNA Transcripts

The transcriptome is defined as the complete set of present RNA molecules or transcripts in an individual cell or cell population under specific conditions. RNA molecules serve as templates for translation to proteins and are also known to have widely varying functions in complex regulatory processes as well[222]. Thus, the transcriptome is characterized by a broad level of diversity including protein-coding genes as well as a vast number of non-coding sequences with important impacts on development and diseases[223–226].
Technological progress of the last 25 years enabled the quantitative and qualitative analyses of RNA molecules at the genome-wide level, termed transcriptomic profiling. These analyses have become one of the most commonly used method to unravel pathophysiological mechanisms and to identify novel disease biomarkers.

1.4.2 Transcriptomic Expression Profiling

The development of quantitative real-time PCR (qRT-PCR) in 1996[227] allowed the fast and reliable quantification of single transcripts. This method bases on the nuclease degradation[228] of dual-labeled fluorogenic hybridization probes[229–231] by the 5' nuclease activity of *Taq* polymerase during the extension phase of PCR[227]. The release of the quenching dye and the corresponding increase in fluorescent emission reflects a quantitative measurement of the input target sequences indicated by the cycle threshold (C_T). This method enabled a fast, accurate, sensitive and cost-effective quantification of low sample input. Thus, qRT-PCR is generally deemed as the 'gold standard' method for measuring expression levels of transcripts[232].
Hybridization-based methods of microarrays overcame the limited number of targets that could be measured in a single qRT-PCR and enabled the parallel quantification of tens of thousands of targets[233–235]. This technological progress of arrayed probes on solid surfaces enabled the analysis of large sets of patterns and relationships of transcripts by measuring fluorescent labels of hybridized target molecules and allowed to associate their expression with functionally important states of the samples. However, this high-throughput method is also limited by the design of the probes and thus the ability to quantify only clearly defined transcripts. This limitation implies also the requirement upon existing knowledge about genome sequences. The quantification is biased by the dynamic range of detection and possibility of cross-hybridization[236].
The development of the next generation sequencing technology enabled a novel high-throughput method for quantifying the abundance of RNA molecules, called RNA-Seq[237,238]. Based on massive parallel sequencing of RNA molecules, RNA-Seq is able to detect and quantify novel RNA transcript variation and is not limited to known transcripts in contrast to microarrays. This enables the detection of novel transcript isoforms, splice variants, chimeric gene fusions as well as nucleotide variants. Due to the depth of sequencing, RNA-Seq is also able to quantify accurately an increased dynamic range of expression[237–239] compared to microarrays.

1.4.3 Transcriptomic Signatures

One major approach to unravel the genetics of complex diseases is comparing the expression of transcripts at different conditions, such as samples of healthy and diseased tissues, to identify differentially expressed genes[240,241]. The zero hypothesis H_0 of the corresponding statistical test claims that there is no statistically significant difference in read counts between experimental conditions. Since the measurand of expression depends on used quantification platforms and algorithms, differential expression analyses (DEAs) make use of different normalization and statistical testing algorithms. While the gene expression is measured as fluorescence intensities by microarrays, abundances in RNA-Seq experiments are frequently measured by counts of sequenced reads. DEA algorithms also take the distribution, including mean and variance estimation strategies, as well as filtering steps and the experimental design into account (Table 3). Due to high-dimensionality of transcriptomic data, *P* values should be adjusted for multiple testing by controlling the false-discovery rate, e.g. by using Benjamini-Hochberg procedure[242]. Alternatively, the type I error can also be controlled by the family-wise-error-rate using the more conservative Bonferroni procedure[243] or the Holm procedure[244].

Table 3: Characteristics of statistical tools for differential expression analyses.

Tool	Distribution of expression values	Test statistics
DESeq2[245]	Negative binomial distribution, with dispersion estimated by the DESeq2 method	Wald's test for generalized linear model
edgeR[240]	Negative binomial distribution using empirical Bayes estimation of the dispersion	Exact test
glm edgeR[240]	Negative binomial distribution, with dispersion estimated by the edgeR method	Likelihood ratio test for generalized linear model
limma[246]	Normal distribution, based on $\log_2$ transformation	Moderated *t*-statistic for linear model
limma-voom[247]	Normal distribution, based on voom transformation	Moderated *t*-statistic for linear model

However, the informative value of single genes identified by DEAs is limited[248]. Small changes in the expression of single genes are biologically difficult to interpret and may also be overlooked although they might have important effects on pathways. Results of DEAs strongly depend on statistical models and included predictors which may cause over- and underfitting of the models. Correcting for multiple testing may also weaken the DEA in consideration of small effects of each gene. Furthermore, DEAs are known to be poorly reproducible[249].

Gene set enrichment analyses (GSEAs) are a popular method to overcome these limitations[248]. The aim of this method is to determine, whether an *a priori* defined set of genes[250], e.g. of a biological process, shows statistically significant, concordant differences between two compared conditions. The computed enrichment score reflects the degree to which the defined gene set is overrepresented at the extremes of a ranked list of analyzed genes of two conditions[248]. However, this statistical approach takes known directions of effects not into account, which limits the explanatory power.

Comparing the observed direction of gene expression change with the expected direction of known effects in biological pathways, enables the computation of activation states by the usage of molecular networks[251], as implemented in the Ingenuity Pathway Analysis software. The computed z-score reflects the relation of increased predictions versus decreased predictions for each analyzed biological pathway and gives thereby the predicted activation state of the pathway. Thus, downstream analysis of transcriptomic quantification enables better understanding of biological processes and pathways predicted to be perturbed by differential expression of transcripts, and thus to identify molecular signatures.

1.4.4 Transcriptomic Analyses of Abdominal Aortic Aneurysms

Transcriptome-wide analyses of AAA samples and aortic controls are still rare. This might be due to limited availability of samples and technical and bioinformatical requirements for the analyses. In previous studies, three series of transcriptome-wide expression analyses of clinical AAA tissues (Table 4) with the keywords *abdominal aortic aneurysm* and the Medical Subject Headings (MeSH) term *aneurysm* were published in the Gene Expression Omnibus database (GEO, accession date: 2022-02-23)[252–254].

Table 4: Transcriptomic data of human AAA in the Gene Expression Omnibus database.
Previous transcriptome-wide expression series of AAA tissues in GEO (accession date: 2022-02-23). GEO, Gene Expression Omnibus; † Used in this thesis; § Generated in this thesis.

GEO accession	Samples	Technique	Year	Reference
GSE7084	Aneurysms (n = 6 individuals, n = 3 pools) Control aorta (n = 7 individuals, n = 3 pools)	Microarray	2007	[255,256]
GSE47472	Necks of aneurysms (n = 14) Control aortas (n = 8)	Microarray	2013	[257]
GSE57691†	Aneurysms with small aortic diameter (n = 20) Aneurysms with large aortic diameter (n = 29) Patients with aortic occlusive disease(n = 9) Control aortas (n = 10)	Microarray	2015	[258]
GSE98278§	Stable Aneurysms (n = 31) Ruptured Aneurysms (n = 17) Aneurysms with intermediate size (n = 15) Aneurysms with larger size (n = 16)	Microarray	2018	[1]

The first transcriptome-wide analyses of AAA tissue in 2007 revealed modulation of immunological pathways[255] and the complement cascade[256]. However these analyses were limited by a small number of samples. The study by Biors et al., 2014[257] focused on the transcriptomic changes located at the neck of human AAAs and revelead modulation of pathways related to immunity. The study by Biors et al., 2015[258] compared changes of small AAAs, large AAAs and aortic occlusive disease (AOD) relative to control aortas. The analyses of small and large AAAs confirmed modulation of immune-related pathways, while AOD showed distinct pathogenic mechanisms. However, none of these studies analyzed transcriptomic changes in ruptured AAAs as well as the directions of modulations of pathways.
Additionally, several studies have also analyzed the role of noncoding RNAs in AAA[259], which is however not the focus of this thesis.

1.5 Research Rationale and Aims

1.5.1 Identification of Molecular Changes causing Rupture in Patients with Abdominal Aortic Aneurysms

Development of AAA harbours the risk of fatal aortic rupture and death[6]. Current guidelines for AAA treatment recommend surgical interventions to avoid the risk of rupture, when the risk of rupture outweighs the risk of intervention and perioperative morbidity[7,8]. To this end, the decision on clinical risk assessment in AAA relies currently fully on the diameter of the aortic wall[7,8], since molecular mechanisms responsible for AAA rupture, which are distinct from AAA progression[260], are mainly unknown.

Thus, it was the aim of the study to identify transcriptomic changes associated with (1) expansion of the dilatation and (2) rupture of affected vessels. Based on an integrative analysis of these transcriptomic signatures and patients characteristics, a gene set of modulated transcripts uniquely involved in the rupture should be identified. Additionally, these finding may also provide novel targets for stabilizing growing abdominal aortic aneurysms.

1.5.2 Comparison of Modulated Pathways in Patients and Mouse Models

Currently, the majority of preclinical studies are based on three inducible mouse models of AAA formation: AngII model[184], PPE model[185] and $CaCl_2$ model[186]. Each of these models mimics certain aspects of AAA development and growth[120,214]. Based on these preclinical models and current knowledge on AAA pathogenesis, a large number of potential targets for inhibiting AAA formation and progression were identified[120,261]. However, clinical trials failed to translate these findings into clinical success[38]. Due to the lack of translatability of preclinical findings, it was the aim of the study to identify parallel and divergent functional pathways modulating AAA in clinical samples compared to the murine AngII model as well as to the murine PPE model to improve abilities of translational research.

1.5.3 Analyses of Inflammatory Pathways in Abdominal Aortic Aneurysms

Abdominal aortic aneurysms are hallmarked by an invasion of the adventitia caused by a prominent inflammatory infiltrate and transmural inflammation[115]. The infiltration of inflammatory cells is known to be induced by chemotactic proteins, such as the pro-inflammatory chemokine IL-8, encoded by *CXCL8*. Previous studies had demonstrated that IL-8 was highly expressed in the aneurysm wall[262] and that IL-8 modulates protease expression[263] and angiogenesis[264–266]. In parallel, the chemokine IL-6 was also shown to be strongly upregulated in AAAs compared to other vascular diseases[126]. IL-6 is a versatile pro-inflammatory cytokine modulating the immune response, haemopoiesis and the acute phase response[267]. However, IL-6 is also known to modulate the regulation of metabolic, regenerative and neural processes[268] depending on the signaling pathway.

Thus, it was the aim to study the role of IL-8 and IL-6 in AAA development by analyzing corresponding signaling pathways in human AAA dissections and to validate these finding in

translational studies by pertubating the affected pathways in a murine AAA model.

1.5.4 Analyses of Adipogenic Degeneration in Abdominal Aortic Aneurysms

Although inflammatory and proteolytic effects on AAA development and growth have been well studied[6,269,270], the underlying pathophysiological mechanisms are not completely understood. Since the translation of these preclinical findings to medical interventions in clinical trials has failed, additional modulators might play an important role in AAA development.
To this end, AAAs were compared to closely related human popliteal artery aneurysms (PAA), which are known to have a low propensity to rupture[271]. Due to an enrichment of adipocyte clusters in the adventitia of AAA samples, it was the aim to analyze the transdifferentiation of resident mesenchymal cells of the aortic wall into adipocytes as a potentially novel modulator of AAA.

2 Publications

2.1 Publication I

Gäbel G, Northoff BH, Weinzierl I, Ludwig S, Hinterseher I, Wilfert W, Teupser D, Doderer SA, Bergert H, Schönleben F, Lindeman JHN, Holdt LM. Molecular Fingerprint for Terminal Abdominal Aortic Aneurysm Disease. *J Am Heart Assoc*. 2017 Nov 30; 6(12).

DOI: 10.1161/JAHA.117.006798

2.1.1 Journal Citation Report

Journal Citation Report I: *Year specific citation rate, journal impact factor and journal's category rank. Source: Journal Citation Reports (https://jcr.clarivate.com/jcr/home)*

Journal, Year:	Journal of the American Heart Association, 2017	
Citations:	9,057	
Journal impact factor:	4.450	
Percentile of journal impact factor:	72.27	(CARDIAC & CARDIOVASCULAR SYSTEMS - SCIE)

2.1.2 Personal Contributions

As co-author of the paper, I was responsible for generating, analyzing and interpreting transcriptomic expression data based on qRT-PCRs and microarray data.
To identify candidate gene sets, I have identified differentially expressed transcripts by comparing samples of ruptured and stable AAAs as well as by comparing samples of AAAs with large and intermediate aortic diameters on a transcriptome-wide scale. To this end, I have analyzed more than 47,000 transcripts, measured by Illumina HumanHT-12 v4 BeadChips arrays, using the statistical software R[272] and the limma package[247]. These analyses included quality filtering and normalizing raw data, statistical testing and correcting obtained results for multiple testing. In addition, I have performed quality controls for raw data and plausibility checks for the results, such as principal component analyses (PCAs).
Furthermore, I was also involved in validating these genes in an independent cohort and in analyzing their expression levels in degenerative and dissected thoracic, infrarenal aortic and popliteal aneurysms as well as in blood and vascular cells by qRT-PCR. To this end, I have analyzed expression data, conducted statistical tests and computed correlations of expression data with phenotypes using statistical software R[272].
Based on transcriptome-wide expression analyses, I have identified activated pathways and upstream regulators of modulated networks using Ingenuity Pathway Analysis software[251].
I have also visualized these results using statistical software R[272], reviewed and approved the article. Finally, I have contributed to the peer review process of the article.

2.2 Publication II

Gäbel G*, Northoff BH*, Balboa A, Becirovic-Agic M, Petri M, Busch A, Maegdefessel L, Mahlmann A, Ludwig S, Teupser D, de Waard V, Golledge J, Wanhainen A, Wågsäter D, Holdt LM, Lindeman JHN. Parallel Murine and Human Aortic Wall Genomics Reveals Metabolic Reprogramming as Key Driver of Abdominal Aortic Aneurysm Progression. *J Am Heart Assoc*. 2021 Sep 7; 10(17):e020231.

*G. Gäbel and B.H. Northoff contributed equally as co-first authors.

DOI: 10.1161/JAHA.120.020231

2.2.1 Journal Citation Report

Journal Citation Report II: *Year specific citation rate, journal impact factor and journal's category rank. Source: Journal Citation Reports (https://jcr.clarivate.com/jcr/home)*

Journal, Year:	Journal of the American Heart Association, 2020	
Citations:	26,962	
Journal impact factor:	5.501	
Percentile of journal impact factor:	99.88	(CARDIAC & CARDIOVASCULAR SYSTEMS - SCIE)

The Journal Citation Report for 2021 is not yet available (accession date: 2022-02-23).

2.2.2 Personal Contributions

As shared first author, I was co-responsible for conception and design of this paper and solely responsible for transcriptomic analyses as a fundament of this paper.
To this end, I have performed transcriptome-wide expression analyses of human AAAs and the murine AngII model based on public available microarray data[1,193,258]. These analyses included quality filtering, normalization of raw data and DEA using the statistical software R[272] and the limma package[247].
In addition, I have analyzed expression profiles of the murine PPE model based on newly generated RNA-Seq data. These analyses included quality filtering of sequenced reads, mapping the filtered reads to the murine reference genome GRCm38 using segemehl software[273], quantification of transcripts by counting the mapped reads using featureCounts[274], followed by DEA using DESeq2[245] and the statistical software R[272].
Furthermore, I have performed quality controls, such as PCAs, at different stages of analysis. I have also performed pathway analyses using Ingenuity Pathway Analysis[251] and validated theses results by GSEA using the R package fgsea[275]. Finally, I have identified, compared and interpreted top modulated pathways in human AAAs and murine AAA models.
I have contributed to writing the manuscript, to the final approval and to the peer review process of the article.

2.3 Publication III

Kokje VBC, Gäbel G, Dalman RL, Koole D, Northoff BH, Holdt LM, Hamming JF, Lindeman JHN. CXCL8 hyper-signaling in the aortic abdominal aneurysm. *Cytokine*. 2018 Aug; 108:96-104.

DOI: 10.1016/j.cyto.2018.03.031

2.3.1 Journal Citation Report

Journal Citation Report III: *Year specific citation rate, journal impact factor and journal's category rank. Source: Journal Citation Reports (https://jcr.clarivate.com/jcr/home)*

Journal, Year:	Cytokine, 2018	
Citations:	9,645	
Journal impact factor:	3.078	
Percentile of journal impact factor:	55.35	(BIOCHEMISTRY & MOLECULAR BIOLOGY - SCIE)
	41.71	(CELL BIOLOGY - SCIE)
	46.52	(IMMUNOLOGY - SCIE)

2.3.2 Personal Contributions

As co-author of this paper, I was responsible for transcriptomic data analysis and interpretation. For this purpose, I have compared transcriptome-wide expression levels of genes in samples of full thickness aortic walls from patients with stable AAA and infrarenal control aortas, which were generated in previous studies[1,258]. To this end, I have processed raw array data of 47,231 hybridization probes, including quality control and normalization, to identify differentially expressed transcripts using the statistical software R[272] and the limma package[247]. Based on these data, I have identified pathways which were activated in AAA samples using Ingenuity Pathway Analysis software[251]. Finally, I have interpreted the results of transcriptomic profiling and pathway analyses. Furthermore, I have visualized affected pathways, critically reviewed the manuscript and approved the article.

2.4 Publication IV

Kokje VBC, Gäbel G, Koole D, Northoff BH, Holdt LM, Hamming JF, Lindeman JHN. IL-6: A Janus-like factor in abdominal aortic aneurysm disease. *Atherosclerosis*. 2016 Aug; 251:139-146.

DOI: 10.1016/j.atherosclerosis.2016.06.021

2.4.1 Journal Citation Report

Journal Citation Report IV: *Year specific citation rate, journal impact factor and journal's category rank. Source: Journal Citation Reports (https://jcr.clarivate.com/jcr/home)*

Journal, Year:	Atherosclerosis, 2016	
Citations:	22,724	
Journal impact factor:	4.239	
Percentile of journal impact factor:	84.92	(PERIPHERAL VASCULAR DISEASE - SCIE)
	71.03	(CARDIAC & CARDIOVASCULAR SYSTEMS - SCIE)

2.4.2 Personal Contributions

As co-author of the paper, I have analyzed the modulation of the IL-6 signaling pathway in samples of full thickness aortic wall from AAA patients and infrarenal control aortas based on transcriptome-wide expression analyses using Illumina HumanHT-12 v4 BeadChips arrays. To this end, I have pre-processed raw data of arrays by quality filtering of 47,231 hybridization probes as well as transforming and normalization of intensity levels of each probe, reflecting the expression level of each transcript. After quality control of these data, I have identified differentially expressed genes, as implemented in package limma[247] of the statistical software R[272]. Furthermore, I have analyzed modulated pathways using Ingenuity Pathway Analysis software[251]. In addition, I have interpreted and visualized these results. Finally, I have reviewed the manuscript and approved the article.

2.5 Publication V

Doderer SA, Gäbel G, Kokje VBC, Northoff BH, Holdt LM, Hamming JF, Lindeman JHN. Adventitial adipogenic degeneration is an unidentified contributor to aortic wall weakening in the abdominal aortic aneurysm. *J Vasc Surg*. 2018 Jun; 67(6):1891-1900.e4.

DOI: 10.1016/j.jvs.2017.05.088

2.5.1 Journal Citation Report

Journal Citation Report V: *Year specific citation rate, journal impact factor and journal's category rank. Source: Journal Citation Reports (https://jcr.clarivate.com/jcr/home)*

Journal, Year:	Journal of Vascular Surgery, 2018	
Citations:	26,542	
Journal impact factor:	3.243	
Percentile of journal impact factor:	68.46	(PERIPHERAL VASCULAR DISEASE - SCIE)
	81.53	(SURGERY - SCIE)

2.5.2 Personal Contributions

As co-author of this article, it was my task to add transcriptomic data to confirm associations of fatty degeneration and aortic rupture. To this end, I have analyzed transcriptome-wide expression levels of more than 47,000 transcripts in samples of AAA patients with stable and ruptured aortic walls as well as in samples of infrarenal control aortas, which were generated in previous studies[1,258] using Illumina HumanHT-12 v4 BeadChips arrays. I have identified modulated pathways based on differentially expressed genes, which I have computed before using the package limma[247] of the statistical software R[272]. In addition, I have interpreted results in the context of the paper. Finally, I have illustrated results, revised the manuscript and finally approved the article.

3 Summary

3.1 Main Findings

3.1.1 Molecular Signatures of Aneurysm Progression and Rupture

Today, pathophysiological processes in AAA development, growth and ultimate rupture are still not completely understood[120]. To identify genes and molecular pathways associated with AAA progression and rupture, we have performed transcriptomic expression analyses of clinical AAA samples[1].

In a first step, transcriptomic profiling of ruptured AAAs (rAAAs) versus elective AAAs (eAAAs) revealed a set of 48 differentially expressed transcripts. In parallel, 30 differentially expressed transcripts were identified by comparing large AAA with aortic diameters $> 70\,\text{mm}$ (lAAAs) versus intermediate AAAs with aortic diameters $\leq 55\,\text{mm}$ (iAAAs) in the same cohort. In a second step, we validated 10 of the overlapping differentially expressed transcripts in an independent cohort of patients with rAAA and eAAA using qRT-PCR analyses. While five of these transcripts (*ANGPTL4*, *HILPDA*, *LOX*, *SRPX2* and *FCGBP*) correlated with the aortic diameter, the other five genes (*ADAMTS9*, *STC1*, *GFPT2*, *GAL3ST4* and *CCL4L1*) were exclusively associated with AAA rupture. Furthermore, downstream analyses of all modulated transcripts revealed that the HIF-1α signaling pathway was a major upregulated network in AAA progression and rupture, which could be confirmed by immunohistochemical stainings.

In summary, our study revealed specific expression profiles for AAA growth and rupture, involving HIF-1α signaling.

3.1.2 Comparative Analyses of Clinical Aneurysms and Mouse Models

Although preclinical studies of AAA in murine models have identified several targets that limited AAA development, a lack of translatability has prevented the move from bench to bedside[38]. Thus, we aimed to identify differences and similarities of human AAA with the inducible murine AngII model as well as with the inducible PPE model[2].

While our histological comparisons showed clear differences, our transcriptome-wide analyses also revealed comparable modulations of molecular pathways in human and murine aneurysms in addition to distinct pertubations. Clinical samples showed the strongest modulation in metabolic pathways, which were also observed in the AngII model and lacking in the PPE model. Comparable activation was also observed for pathways associated with the adaptive immune response in clinical samples and the AngII model. Pathway analyses of the PPE model indicated a transient modulation of inflammation, corresponding to our histological findings. We then validated the effects of metabolic reprogramming on AAA progression, by treating AngII-infused mice with the glycolysis inhibitor PFK15, resulting in reduced aortic dilatation and aneurysm formation.

In conclusion, our study has identified modulated molecular pathways of human AAA and two inducible murine AAA models. Clinical AAA samples and the AngII model showed remarkable similarities in metabolic responses, which were confirmed by a translational intervention study of metabolic pathways in the AngII model.

3.1.3 Impact of Inflammatory Pathways in Abdominal Aortic Aneurysm

Although the cytokines IL-8 and IL-6 had previously been associated with AAA progression [126], their functional role in AAA development remained unclear. We have therefore conducted additional studies to analyze the impact of these cytokines on inflammatory pathways in AAA.

In a first study [3], we have validated the increased RNA and protein expression of the pro-inflammatory chemotactic cytokine IL-8 in human AAAs compared to aortic control tissue. Our transcriptome-wide expression analyses of aneurysm walls and infrarenal control aortas indicated the activation of the IL-8 signaling pathway in AAA as one of the top enriched pathways in AAA, which was also validated by phosphorylation analyses of downstream factors of the IL-8 signaling pathway. Additionally, inhibiting IL-8 signaling in the murine PPE model by administering the CXCR1/CXCR2 inhibitor DF2156A, revealed a reduction of aneurysm growth compared to control mice at day 14, while growth was comparable at day 7.
In summary, this suggests IL-8 as a novel target for stabilization of growing AAAs.

In a second study [4], we have also analyzed the role of the versatile cytokine IL-6 in AAAs. Our expression analyses of IL-6 confirmed increased mRNA and protein expression in human AAAs compared to atherosclerotic controls. Transcriptomic profiling indicated the activation of the IL-6 signaling pathway in aneurysm wall samples compared to samples of infrarenal control aortas. We were also able to verify the activation of this pathway by phosphorylation analyses of the downstream target STAT3. However, the administration of Il-6 neutralizing antibodies in a translational study of the murine PPE model revealed contrasting effects. While the injection of antibodies starting at the day before elastase infusion caused increased mortality due to aortic rupture, a delayed injection of antibodies starting at day 4 after elastase infusion decreased AAA progression and prevented rupturing.
In conclusion, this cannot rule out an impact of IL-6 signaling in AAA formation.

3.1.4 Role of Adipogenic Signatures in Abdominal Aortic Aneurysm

Originating from a histological comparison of human AAAs and PAAs, whereby PAAs are known to have a low risk for rupture [271] although they are closely related to AAAs [152], we have studied the role of adipocyte aggregations in the adventitia, which was found to be an exclusive characteristic of AAAs [5].
In addition to the histological analyses, we found higher RNA expression of known modulators of transdifferentiation of resident mesenchymal cells into adipocytes in AAAs compared to atherosclerotic control aortas. *In-vitro* experiments also showed increased fat accumulation in AAA-derived adventitial mesenchymal cells after culturing in adipogenic culture medium compared to cells of control aortas. Furthermore, transcriptome-wide expression analyses in rAAAs and eAAAs identified 5 of the 11 most upregulated genes in rAAAs to be adipocyte related. These findings were strengthened by additional pathway analyses, which showed modulation of adipogenesis and PPAR signaling in ruptured versus nonruptured AAAs.
In summary, our study has identified adipocyte accumulation in the adventitia and related adipogenic degeneration as a novel contributor to aortic wall weakening of AAAs.

3.2 Own Contribution

To unravel the molecular signature of AAAs, I have analyzed the transcriptome of clinical and murine AAA samples as well as corresponding control samples, based on the use of qRT-PCRs as well as high-throughput technologies, such as microarrays and RNA-Seq. Based on bioinformatics and statistical analyses, I performed transcriptome-wide expression profiling, including differential expression analyses, gene set enrichment analyses and pathways analyses. To this end, I have analyzed newly generated data as well as publically available data. My personal contributions to each publication are provided in chapter 2 in more detail.

In summary, my conducted transcriptome-wide expression analyses in samples of clinical end-stages of AAAs, such as large and ruptured AAAs, compared to samples of early-stages of AAAs, gave novel insights into AAA progression and rupture by identifying differentially expressed genes as well as modulated molecular pathways[1]. Transcriptomic profiling of microarray and RNA-Seq data helped also to get a better understanding of modulated molecular pathways in murine AAA models compared to human AAAs[2]. Finally, my transcriptome-wide expression analyses were able to unravel the impact of inflammatory[3,4] and adipogenic[5] pathways in AAA disease.

In conclusion, these transcriptomic analyses gave novel insights and a better understanding of human AAAs, enabled the identification of novel targets, and helped to improve translational research of murine AAA models.

4 Zusammenfassung

4.1 Wichtigste Erkenntnisse

4.1.1 Molekulare Signaturen von Abdominellen Aortenaneurysmen

Bis heute sind die pathophysiologischen Mechanismen von der Entstehung bis zur Ruptur des abdominellen Aortenaneurysmas (AAA) nicht vollständig bekannt[120]. Daher war es unser Ziel, modulierte Gene und Signalwege in humanen AAA zu identifizieren[1].
In transkriptom-weiten Analysen haben wir durch den Vergleich von rupturierten und elektiven AAA, sowie dem Vergleich von großen AAA mit einem Durchmesser $> 70\,\text{mm}$ und intermediären AAA mit einem Durchmesser $\leq 55\,\text{mmn}$ gemeinsame differentiell exprimierte Transkripte identifiziert, von denen wir zehn Transkripte in einer unabhängigen Kohorte von rupturierten und elektiven AAA mittels qRT-PCR validieren konnten. Dabei zeigten fünf Transkripte eine Korrelation mit dem Durchmesser der Aorta, während die weiteren fünf Transkripte ausschließlich mit der Ruptur assoziiert werden konnten. Weiterführende Analysen der Transkriptomdaten zeigten eine Aktivierung des HIF-1α Signalweges sowohl in großen, als auch in rupturierten AAA. Zusammenfassend konnten wir spezifische Expressionsprofile für das Wachstum und die Ruptur von AAA ermitteln, die eine Aktivierung des HIF-1α Signalweges aufzeigten.

4.1.2 Vergleich von humanen Aneurysmen und Mausmodellen

In früheren Studien wurden eine Vielzahl an möglichen Molekülen zur Behandlung des AAAs in Mausmodellen identifiziert, die in klinischen Studien jedoch keinen Erfolg zeigten[38]. Unsere Studie sollte daher durch den Vergleich von humanen AAA mit dem AngII Mausmodell, sowie dem PPE Mausmodell, gemeinsam und unterschiedlich modulierte Signalwege identifizieren[2].
Unsere Transkriptomanalysen zeigten vor allem eine starke Aktivierung von metabolischen Signalwegen in humanen AAA, die ebenfalls im AngII Modell, nicht aber im PPE Modell gefunden werden konnte. Humane AAA und das AngII Model zeigten weiterhin eine Aktivierung des adaptiven Immunsystems, während das PPE Model vor allem eine transiente Entzündungsreaktion auf der Ebene des Transkriptoms zeigte. In einer translationalen Studie haben wir die Aktivierung der metabolischen Signalwege in AAA durch die Applikation des Glykolyse-Inhibitors PFK15 im AngII-Modell überprüft, die eine reduzierte Ausprägung der AAA zu Folge hatte.
Diese Studie hat sowohl gemeinsam als auch differentiell modulierte Signalwege in humanen AAA und den zwei betrachteten Mausmodellen aufgedeckt. Die zentrale Rolle der Aktivierung von metabolischen Signalwegen in humanen AAA und dem AngII-Modell konnte sowohl auf der Ebene des Transkriptoms, als auch in einer murinen Interventionsstudie gezeigt werden.

4.1.3 Einfluss von Inflammatorischen Signalwegen auf Aortenaneurysmen

Eine erhöhte Expression der Zytokine IL-8 und IL-6 wurde bereits in früheren Studien mit der Ausprägung von AAA assoziiert[126]. Ziel unserer Analysen war es daher, den Einfluss dieser Zytokine auf die Ausbildung der AAA genauer zu untersuchen[3,4].

In einer ersten Studie[3] konnten wir die erhöhte Expression des Zytokins IL-8 in AAA im Vergleich zu Kontrollproben der Aorta bestätigen. Unsere Transkriptomanalysen zeigten ebenfalls

eine starke Aktivierung des IL-8-Signalweges in AAA im Vergleich zu infrarenalen Aorten. Unsere weiteren translationalen Untersuchungen im PPE Modell zeigten, dass eine Inhibition des IL-8-Signalweges durch den CXCR1/CXCR2 Inhibitor DF2156A zu einer Reduktion des Aneurysmenwachstums am Tag 14 führte.
Unsere Studie zeigte damit das Potential des IL-8-Signalweges, als neues Target für die Stabilisierung von AAA zu fungieren.

In einer zweiten Studie[4] konnten wir ebenfalls die erhöhte Expression des Zytokins IL-6 in AAA im Vergleich zu Kontrollproben der Aorta bestätigen. Auch hier zeigten die Transkriptomanalysen eine Aktivierung des IL-6-Signalweges in AAA im Vergleich zu infrarenalen Aorten. Eine translationale Interventionsstudie mit IL-6 neutralisierenden Antikörpern zeigte bei einer frühen Applikation des Antikörpers jedoch eine Zunahme der Ruptur, während eine spätere Applikation der Antikörper eine Reduktion des AAA Wachstums aufzeigte.
Zusammenfassend kann unsere Studie einen Einfluss des IL-6-Signalweges auf AAAs nicht ausschließen.

4.1.4 Adipogene Signaturen in Abdominellen Aortenaneurysmen

Frühere Studien haben gezeigt, dass Popliteaaneurysmen ein deutlich geringeres Risiko der Ruptur als AAA aufweisen[271]. Ausgehend von einem histologischen Vergleich der beiden Aneurysmatypen, haben wir eine AAA-spezifische Akkumulation von Adipozyten in der Adventitia gefunden und analysiert[5].
Ergänzend zu den histologischen Ergebnissen, konnten wir auch eine erhöhte RNA Expression von Modulatoren der Transdifferenzierung mesenchymaler Zellen zu Adipozyten in AAA Proben, verglichen mit atherosklerotischen Aorten, detektieren. Mesenchymale Zellen der Adventitia zeigten in *in-vitro* Experimenten eine erhöhte Fettakkumualtion in Zellen die aus AAA gewonnen wurden, verglichen mit Kontrollaorten. Unsere Transkriptomanalysen zeigten, dass fünf der elf am stärksten hochregulierten Gene in rupturierten AAA verglichen zu elektiven AAA mit der Adipogenese assoziiert sind, sowie dass der Adipogenese-Signalweg als auch der PPAR-Signalweg in rupturierten AAA pertubiert werden.
Unser Studie hat damit gezeigt, dass die Akkumulation von Adipozyten und die adipogene Degradation der Adventitia mit der Ausbildung und Ruptur der AAA assoziiert sind.

4.2 Eigener Anteil

In der vorliegenden Arbeit habe ich Transkriptomanalysen von humanen und murinen Aortenwänden durchgeführt, um ein besseres Verständnis der Pathophysiologie von Aneurysmen zu erhalten. Die Expressionshöhe der RNA Moleküle habe ich sowohl mittels qRT-PCRs als auch mit Hochdurchsatzmethoden wie Microarrays und RNA-Seq analysiert. Die Anwendung von bioinformatischen und statistischen Analysen ermöglichte es mir, sowohl in öffentlich zugänglichen Datensätzen als auch in neu generierten Hochdurchsatzdaten, differentiell exprimierte Gene sowie modulierte Signalwege in den unterschiedlichen Zuständen zu identifizieren.
Meine durchgeführten Transkriptomanalysen gaben neue Einblicke in die Pathogenese der Aneurysmen, ermöglichten die Identifikation von neuen Targets zur Behandlung von Aneurysmen, und helfen perspektivisch die Translation von prä-klinischen Mausstudien zu verbessern.

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Acknowledgment

First of all, I would like to thank Prof. Dr. Dr. Lesca M. Holdt and Prof. Dr. Daniel Teupser for the opportunity to work on this thesis at the Institute of Laboratory Medicine of the University Hospital Munich. I am grateful for the critical discussions, your valuable inspirations and your excellent support through all the years.

I would also like to express my gratitude towards PD Dr. Gabor Gäbel and Prof. Dr. Jan H. Lindeman for the great collaboration and the new insights into the field of AAAs, which made this thesis possible.

I would like to thank Wolfgang Wilfert, Dr. Alexandros Nicolaou, Anika Stahringer and Dr. Alisa Kleinhempel not only for your support and the stimulating discussions, but also for the great team spirit and the amazing time inside and outside the lab.

I am also grateful to Frau Dr. Kristina Sass for the inspiring discussions.

I would like to thank PD Dr. Andreas Herbst and Dr. Alexander Zigman Kohlmaier for their valuable input as well as Nadine Bock, Magdalena Mock, Maria Eberle, Yasemin Alkier and Franziska Jossen for their technical assistance.

Finally, I am deeply grateful to my family - Silvia, Emily and Jonathan - for your enduring support and understanding over the whole time.