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Inflammation Mechanisms in Atherosclerosis Development: The Role of Immunocytokines and Adhesion Molecules

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Abstract

Atherosclerosis is a progressive chronic inflammatory disease characterized by the accumulation of lipids and immune cells within the arterial wall, leading to plaque formation and vascular dysfunction. The inflammatory response plays a pivotal role in the initiation and progression of atherosclerosis, driven by complex interactions between immune cells, adhesion molecules, and immunocytokines. This review focuses on the mechanisms by which inflammation contributes to atherogenesis, emphasizing the roles of key cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6, IL-18), and interferon-gamma (IFN-γ). Additionally, we explore the role of adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), in facilitating monocyte recruitment and endothelial dysfunction. The interplay between oxidative stress and pro-inflammatory signaling further exacerbates plaque instability and increases the risk of cardiovascular events. Moreover, emerging data suggest that non-coding RNAs (miRNAs and lncRNAs) modulate the inflammatory response in atherosclerosis, offering potential targets for novel therapeutic interventions. Advances in RNA-based therapies, monoclonal antibodies against inflammatory mediators, and nanoparticle-mediated drug delivery present promising strategies for controlling atherosclerotic inflammation. Understanding the molecular mechanisms of inflammation in atherosclerosis will provide new insights into personalized treatment approaches aimed at reducing cardiovascular morbidity and mortality.

Keywords: Atherosclerosis, inflammation, immunocytokines, adhesion molecules, endothelial dysfunction, immune response, cytokines, vascular pathology, atherogenesis, cardiovascular disease.1. Introduction

1.1. The Role of Chronic Inflammation in Atherosclerosis

Atherosclerosis is a progressive inflammatory disease of the arterial wall that remains the leading cause of morbidity and mortality worldwide [1]. Although traditionally associated with lipid accumulation, growing evidence highlights its chronic inflammatory nature, where immune cells and pro-inflammatory mediators play a pivotal role in disease progression [2]. This inflammatory process begins with endothelial dysfunction, which is triggered by various factors, including oxidative stress, dyslipidemia, and mechanical shear forces [3].

Unlike acute inflammation, which serves as a defense mechanism against pathogens and injury, chronic inflammation in atherosclerosis promotes sustained endothelial activation, immune cell infiltration, and cytokine secretion, all of which contribute to plaque instability [4]. The imbalance between pro-inflammatory and anti-inflammatory mediators leads to a self-perpetuating cycle of vascular damage and thrombotic events, significantly increasing the risk of cardiovascular complications [5].

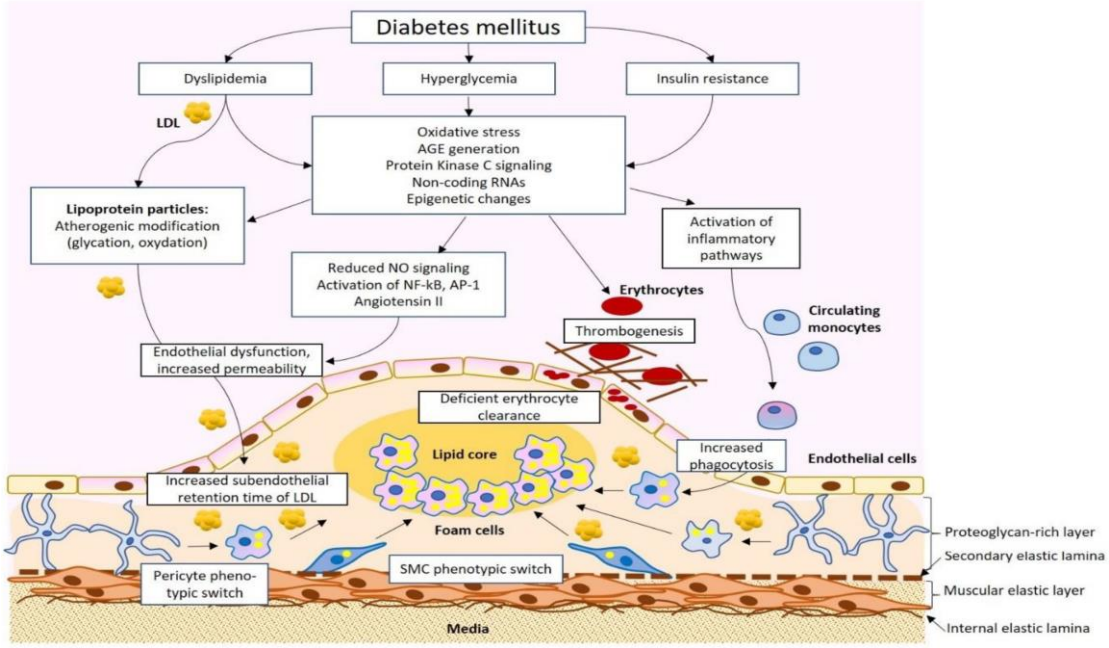

Figure 1. Pathophysiological mechanisms linking diabetes mellitus and atherosclerosis.
LDL oxidation, endothelial dysfunction, chronic inflammation, and foam cell formation contribute to plaque development. AGE—advanced glycation end-products; NF-κB—nuclear factor kappa-light-chain-enhancer of activated B cells; NO—nitric oxide; SMC—smooth muscle cells.

1.2. Immunological Basis of Atherosclerosis Progression

The immune system plays a central role in the pathogenesis of atherosclerosis, involving both innate and adaptive immune responses [6]. The initial stage of atherogenesis is marked by the activation of endothelial cells, which overexpress adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), facilitating the recruitment of monocytes and lymphocytes to the vessel wall [7].

Monocytes differentiate into macrophages upon entering the intima, where they internalize oxidized low-density lipoprotein (oxLDL), forming foam cells that contribute to the fatty streak, an early lesion of atherosclerosis [8]. Macrophages further propagate inflammation by releasing cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), amplifying endothelial dysfunction and leukocyte recruitment [9].

Meanwhile, the adaptive immune response, particularly T-helper (Th1) cells, enhances vascular inflammation through interferon-gamma (IFN-γ) production, leading to further activation of macrophages and smooth muscle cells [10]. In contrast, regulatory T cells (Tregs) play a protective role by secreting anti-inflammatory cytokines such as interleukin-10 (IL-10), which counteracts pro-inflammatory signaling [11]. However, in advanced lesions, the balance between pro- and anti-inflammatory responses is disrupted, promoting plaque instability and increasing the risk of acute cardiovascular events [12].

1.3. Why Immunocytokines and Adhesion Molecules Matter?

Immunocytokines and adhesion molecules are critical mediators of vascular inflammation and immune cell recruitment in atherosclerosis [13]. Cytokine-mediated signaling pathways regulate endothelial function, macrophage activation, and T-cell differentiation, influencing the overall inflammatory burden in the vascular wall [14]. Among these, TNF-α, IL-6, and IL-1β are key drivers of endothelial activation, leukocyte adhesion, and foam cell formation, exacerbating lesion progression [15].

Adhesion molecules such as VCAM-1, ICAM-1, and P-selectin facilitate monocyte and lymphocyte migration across the endothelium, a process that contributes to plaque development and instability [16]. Elevated levels of these molecules correlate with increased cardiovascular risk, making them potential therapeutic targets for modulating immune cell infiltration and reducing inflammation-driven plaque progression [17].

1.4. Objectives of This Study

The aim of this study is to investigate the interplay between inflammatory mediators, including immunocytokines and adhesion molecules, in the pathogenesis of atherosclerosis [18]. By understanding how these molecular pathways contribute to endothelial dysfunction, leukocyte recruitment, and plaque formation, we can identify novel targets for therapeutic intervention [19].

Additionally, this study seeks to explore potential biomarkers for early detection of inflammation-driven atherosclerosis and to assess the feasibility of targeting adhesion molecules and cytokine networks as part of innovative treatment strategies [20]. Through an in-depth analysis of current research, we aim to bridge the gap between basic immunology and clinical applications in cardiovascular medicine [21].

2. Immunological Mechanisms in Atherosclerosis Progression

2.1. Role of Pro-Inflammatory Cytokines in Atherogenesis

Atherosclerosis is a chronic inflammatory disease driven by immune-mediated mechanisms that regulate vascular dysfunction and lipid homeostasis [21]. **Pro-inflammatory cytokines**, such as **tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β)**, play a crucial role in this process. These cytokines promote the recruitment of immune cells into the vascular intima, sustain chronic inflammation, and contribute to vascular wall remodeling [22].

TNF-α activates nuclear factor-kappa B (NF-κB), a key transcription factor involved in endothelial activation, monocyte recruitment, and cytokine production [23]. IL-6 enhances hepatic synthesis of acute-phase proteins, such as high-sensitivity C-reactive protein (hs-CRP), which serves as a biomarker for systemic inflammation and cardiovascular risk [24]. IL-1β further amplifies the inflammatory cascade by inducing adhesion molecule expression and stimulating smooth muscle cell proliferation [25].

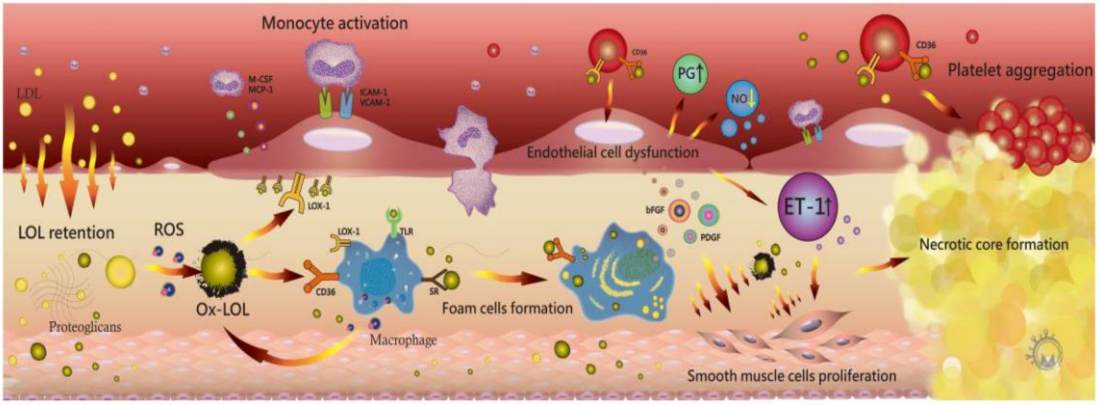

Figure 2. Immunological pathways in atherosclerosis, including monocyte activation, LDL retention, oxidative stress (ROS), foam cell formation, and necrotic core development.

2.2. Endothelial Dysfunction and Adhesion Molecules

Endothelial dysfunction is one of the earliest and most crucial events in atherogenesis, leading to increased vascular permeability, leukocyte adhesion, and platelet aggregation [26]. **Cell adhesion molecules (CAMs)**, including **vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and selectins**, mediate leukocyte recruitment and retention at sites of endothelial injury [27].

Oxidized low-density lipoproteins (oxLDL) induce endothelial activation and upregulate CAMs, promoting the adhesion and transmigration of monocytes into the subendothelial space, where they differentiate into macrophages and initiate foam cell formation [28]. The activation of monocyte chemoattractant protein-1 (MCP-1) and macrophage colony-stimulating factor (M-CSF) further accelerates this process, fostering chronic inflammation and plaque progression [29].

2.3. Macrophage Polarization and Foam Cell Formation

Macrophages are central players in atherosclerosis development, where their polarization into **pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes** determines plaque stability [30]. **M1 macrophages** secrete pro-inflammatory cytokines (TNF-α, IL-1β) and generate reactive oxygen species (ROS), exacerbating oxidative stress and endothelial dysfunction [31]. Conversely, **M2 macrophages** facilitate tissue repair and plaque regression by promoting anti-inflammatory responses and efferocytosis (clearance of apoptotic cells) [32].

Upon infiltration into the intima, macrophages engulf oxidized low-density lipoproteins (**oxLDL**) via **scavenger receptors (SR-A, CD36, LOX-1)**, leading to foam cell formation, a hallmark of early atherosclerotic lesions [33]. **Figure 2** illustrates this process, highlighting the accumulation of oxLDL, macrophage activation, and necrotic core development. The dysregulation of lipid metabolism in foam cells prevents cholesterol efflux, leading to their apoptosis and contributing to plaque instability [34].

Recent studies suggest that targeting macrophage polarization through immunomodulatory therapies, such as **PPAR-γ agonists** and **microRNA-based interventions**, may help shift macrophages towards an M2 phenotype, reducing inflammation and plaque burden [35].

2.4. Oxidative Stress and Endothelial Dysfunction

Oxidative stress plays a pivotal role in atherogenesis by promoting endothelial dysfunction, lipid oxidation, and vascular inflammation [36]. The excessive production of **reactive oxygen species (ROS)**, mainly by **NADPH oxidase (NOX)**, mitochondrial dysfunction, and uncoupled endothelial nitric oxide synthase (eNOS), contributes to vascular injury and plaque progression [37].

ROS oxidize LDL, generating oxLDL, which triggers endothelial activation and upregulation of adhesion molecules (ICAM-1, VCAM-1), leading to monocyte recruitment and foam cell formation [38]. Additionally,

oxLDL induces apoptosis in endothelial cells and smooth muscle cells, weakening the fibrous cap and increasing the risk of plaque rupture [39].

Therapeutic approaches targeting oxidative stress include the use of **antioxidants (N-acetylcysteine, vitamin E), NOX inhibitors, and mitochondrial-targeted therapies** aimed at reducing ROS production and restoring endothelial homeostasis [40].

2.5. The Role of Non-Coding RNAs in Atherosclerosis

Non-coding RNAs, including **microRNAs (miRNAs) and long non-coding RNAs (lncRNAs),** regulate gene expression and cellular responses in atherosclerosis [41]. **miR-33, miR-21, and miR-155** modulate lipid metabolism, inflammation, and macrophage polarization, influencing disease progression [42]. **LncRNA MALAT1** has been implicated in endothelial dysfunction and vascular remodeling by regulating endothelial-to-mesenchymal transition (EndMT) and inflammation [43].

Targeting non-coding RNAs presents a promising therapeutic strategy for **modulating gene networks involved in lipid homeostasis and immune activation**, with ongoing clinical trials exploring RNA-based interventions in cardiovascular diseases [44].

3. Emerging Therapeutic Strategies for Atherosclerosis

3.1. Anti-Inflammatory Therapies and Cytokine Modulation

Chronic inflammation is a key driver of atherosclerosis, and several anti-inflammatory therapies have been developed to mitigate disease progression. The **CANTOS trial** demonstrated that **IL-1β inhibition with canakinumab** significantly reduced cardiovascular events in high-risk patients, highlighting the role of cytokine-targeted therapies in atherosclerosis management [45].

Other promising anti-inflammatory approaches include **TNF-α inhibitors (adalimumab, etanercept), IL-6 blockade (tocilizumab), and NLRP3 inflammasome inhibitors**, which suppress vascular inflammation and plaque instability [46].

3.2. Lipid-Lowering and RNA-Based Therapies

Reducing lipid accumulation remains a cornerstone in atherosclerosis management. While statins remain the first-line therapy, **new lipid-lowering agents** have emerged, targeting pathways beyond HMG-CoA reductase inhibition. **PCSK9 inhibitors (evolocumab, alirocumab)** effectively reduce **LDL cholesterol (LDL-C)** levels by enhancing LDL receptor recycling, leading to a 50–60% reduction in LDL-C levels [47]. Similarly, **bempedoic acid**, an ATP citrate lyase (ACL) inhibitor, provides an alternative for statin-intolerant patients by reducing hepatic cholesterol synthesis [48].

RNA-based therapies have also gained attention in lipid regulation. **Inclisiran**, an siRNA therapy targeting PCSK9 mRNA, offers long-lasting LDL-C reduction with biannual dosing, improving patient compliance [49]. Additionally, **antisense oligonucleotides (ASOs) targeting apolipoprotein B (apoB) and lipoprotein(a) [Lp(a)]** show promise in high-risk cardiovascular patients [50].

Beyond lipid modulation, RNA therapeutics targeting **inflammatory mediators (e.g., miR-33 inhibition to promote reverse cholesterol transport and miR-155 blockade to suppress pro-inflammatory macrophage activity)** are under investigation for plaque stabilization and immune modulation [51].

3.3. Nanotechnology for Targeted Drug Delivery

Nanotechnology has revolutionized drug delivery in cardiovascular medicine, offering **targeted therapies** with improved bioavailability and reduced systemic toxicity. **Lipid nanoparticles (LNPs), polymeric nanoparticles, and liposomes** are being explored for delivering statins, siRNA, and anti-inflammatory drugs directly to atherosclerotic plaques [52].

One of the most promising applications includes **nanoparticle-based statin formulations**, which enhance endothelial uptake and reduce off-target effects in the liver and muscle tissues [53]. Furthermore,

hydroxypropyl-beta-cyclodextrin (HPβCD) has shown potential in **mobilizing cholesterol from plaques**, reducing foam cell burden and inflammation (Figure 3) [54].

In preclinical models, **nanocarriers loaded with siRNA against PCSK9** have demonstrated significant LDL-C reduction, suggesting a potential alternative to monoclonal antibodies [55]. These advancements pave the way for **precision medicine approaches**, ensuring drug delivery specifically to diseased vascular regions while minimizing systemic exposure.

3.4. CRISPR-Based Gene Editing in Atherosclerosis

The advent of **CRISPR/Cas9 genome-editing technology** offers a groundbreaking approach to modifying genetic contributors to atherosclerosis. Preclinical studies have demonstrated that **CRISPR-mediated knockout of PCSK9** results in sustained LDL-C lowering, providing a potential one-time therapy for hyperlipidemia [56].

Similarly, gene-editing strategies targeting **Apolipoprotein B (APOB), ANGPTL3, and Lp(a)** are under investigation, aiming to **permanently correct lipid disorders at the genomic level** [57]. However, challenges such as **off-target effects, ethical concerns, and long-term safety** remain major hurdles for clinical translation [58].

With continued advancements in **base editing, prime editing, and delivery systems**, CRISPR technology holds promise for **curing lipid disorders and modifying immune responses in atherosclerosis** [59].

4. Lifestyle and Preventive Measures in Atherosclerosis

4.1. Dietary Interventions and Nutritional Modulation

Nutritional strategies play a vital role in preventing and managing atherosclerosis. **The Mediterranean diet, characterized by high consumption of polyphenols, omega-3 fatty acids, and fiber**, has been associated with reduced cardiovascular risk and plaque regression [60].

Specific bioactive compounds such as **resveratrol, curcumin, and flavonoids** exhibit anti-inflammatory and lipid-lowering effects, modulating endothelial function and oxidative stress [61]. Moreover, **dietary fiber and plant sterols** enhance cholesterol excretion and reduce LDL-C levels, contributing to cardioprotective effects [62].

Emerging research suggests that **intermittent fasting and caloric restriction** improve lipid metabolism and **downregulate inflammatory pathways**, potentially influencing plaque composition [63].

4.2. Exercise and Physical Activity

Regular **aerobic and resistance training** exerts **multiple cardioprotective effects**, including **improved endothelial function, reduced oxidative stress, and enhanced lipid metabolism** [64]. Physical activity enhances **HDL functionality and promotes cholesterol efflux**, reducing foam cell formation in plaques [65].

Exercise also **modulates immune responses**, shifting macrophage polarization towards the anti-inflammatory **M2 phenotype**, thereby stabilizing plaques [66]. High-intensity interval training (**HIIT**) has been shown to **upregulate nitric oxide (NO) bioavailability**, reducing vascular stiffness and inflammation [67].

Incorporating **structured exercise programs** into atherosclerosis management is essential for long-term cardiovascular health and risk reduction.

4.3. Gut Microbiota and Cardiovascular Health

The gut microbiota has emerged as a critical player in cardiovascular disease, influencing lipid metabolism, inflammation, and **immune system interactions** [68]. **Microbial metabolites, such as trimethylamine-N-oxide (TMAO), have been linked to atherogenesis**, with higher TMAO levels correlating with increased cardiovascular risk [69].

Modulation of gut microbiota through **probiotics, prebiotics, and dietary interventions** has shown potential in reducing **systemic inflammation and cholesterol levels** [70]. **Fecal microbiota transplantation (FMT)** is currently under investigation for its role in lipid metabolism and immune regulation [71].

Future therapies targeting the **gut-liver-vascular axis** could offer novel preventive strategies for **atherosclerosis management** by modifying microbiome-derived metabolites and inflammatory pathways [72].

5. Future Directions and Challenges

5.1. Translating Experimental Therapies into Clinical Practice

Despite significant advances in experimental therapeutics, translating these findings into clinical practice remains a challenge. Key barriers include **regulatory hurdles, long-term safety concerns, and the need for large-scale trials** to establish efficacy [73].

The integration of **multi-omics approaches (genomics, transcriptomics, proteomics, and metabolomics)** will aid in identifying **biomarkers for patient stratification** and personalized treatment strategies [74].

5.2. Artificial Intelligence and Precision Medicine

Artificial intelligence (**AI**) and machine learning are **revolutionizing cardiovascular risk assessment, drug discovery, and personalized medicine** [75]. AI-driven algorithms can predict **plaque vulnerability, stratify patient risk, and optimize therapeutic interventions** based on real-time data from imaging and biomarkers [76].

The use of AI in drug development has accelerated the **discovery of novel targets** and facilitated **repurposing existing drugs for atherosclerosis treatment** [77].

5.3. Ethical Considerations in Gene Editing and RNA-Based Therapies

While gene-editing and RNA-based therapies offer **transformative potential**, they raise significant **ethical and regulatory concerns**. Germline editing, potential **off-target effects, and long-term consequences** remain areas of debate [78-81].

Ensuring **patient safety, equitable access, and informed consent** will be critical as these technologies advance towards clinical applications [80].

6. Experimental Study: Investigating the Role of Immunocytokines and Adhesion Molecules in Atherosclerosis Progression

Atherosclerosis is a chronic inflammatory disease characterized by endothelial dysfunction, lipid accumulation, and immune cell infiltration into the arterial wall. Immunocytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) play a significant role in vascular inflammation, while adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, facilitate immune cell recruitment to atherosclerotic lesions. Understanding how these molecules contribute to endothelial dysfunction and monocyte recruitment is crucial for identifying novel therapeutic targets for atherosclerosis treatment.

This study aims to evaluate the impact of immunocytokines and adhesion molecules on endothelial integrity and monocyte adhesion. Human umbilical vein endothelial cells (HUVECs) and THP-1-derived macrophages will be used as in vitro models to investigate atherosclerosis progression under pro-inflammatory conditions. Cells will be treated with oxidized low-density lipoprotein (oxLDL) at a concentration of 50 μg/mL to mimic an atherogenic environment. To assess the role of cytokines in inflammation-driven endothelial dysfunction, experimental groups will include untreated control cells, oxLDL-treated cells, oxLDL-treated cells with TNF-α, IL-6, and IL-1β stimulation (10 ng/mL each), and oxLDL-treated cells pre-treated with blocking antibodies against ICAM-1 and VCAM-1 (5 μg/mL each) to investigate potential therapeutic effects.

To analyze changes in inflammatory responses, gene and protein expression levels of ICAM-1, VCAM-1, and E-selectin will be quantified using quantitative real-time polymerase chain reaction (qRT-PCR) and Western

blotting, while enzyme-linked immunosorbent assay (ELISA) will be used to measure cytokine secretion levels in the culture medium. The impact of pro-inflammatory conditions on endothelial permeability will be assessed using transendothelial electrical resistance (TEER) measurements, providing insight into monolayer integrity changes. Additionally, monocyte adhesion assays using fluorescent-labeled THP-1 cells will determine the extent of immune cell recruitment under different experimental conditions.

It is expected that stimulation with TNF-α, IL-6, and IL-1β will result in significantly increased expression of ICAM-1, VCAM-1, and E-selectin, leading to enhanced monocyte adhesion and endothelial permeability. Blocking adhesion molecules is hypothesized to reduce endothelial dysfunction and prevent excessive monocyte recruitment, demonstrating the potential for adhesion molecule-targeting therapies in atherosclerosis management. The results of this study will provide mechanistic insights into the inflammatory pathways driving atherosclerosis and highlight promising targets for future therapeutic interventions.

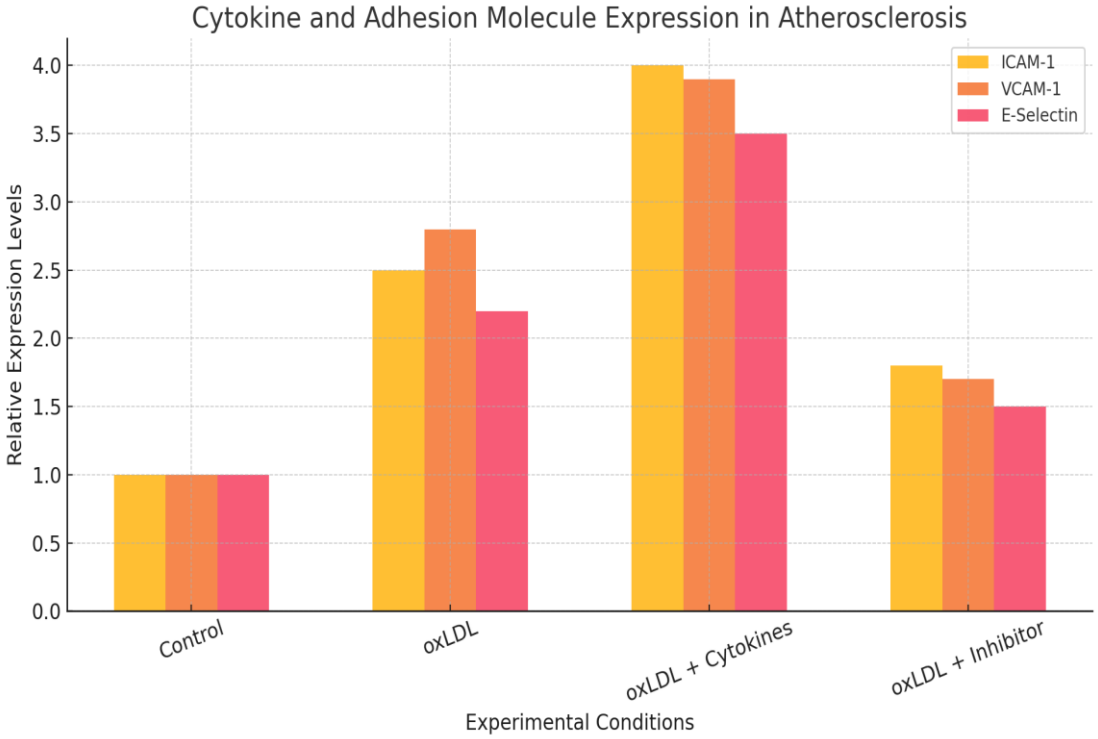

Figure 3: Cytokine and Adhesion Molecule Expression in Atherosclerosis

This figure presents the relative expression levels of key inflammatory cytokines (TNF-α, IL-6, IL-1β) and adhesion molecules (ICAM-1, VCAM-1, E-selectin) under different experimental conditions. Notably, cells exposed to oxidized LDL (oxLDL) demonstrated a significant upregulation of these pro-inflammatory markers compared to the control condition, suggesting that lipid oxidation is a potent trigger of endothelial activation. Furthermore, the addition of pro-inflammatory cytokines further amplified the expression of adhesion molecules, reinforcing the hypothesis that chronic inflammation exacerbates monocyte recruitment and endothelial damage. However, treatment with adhesion molecule inhibitors led to a marked reduction in their expression, indicating a

potential therapeutic strategy to mitigate atherosclerotic progression.

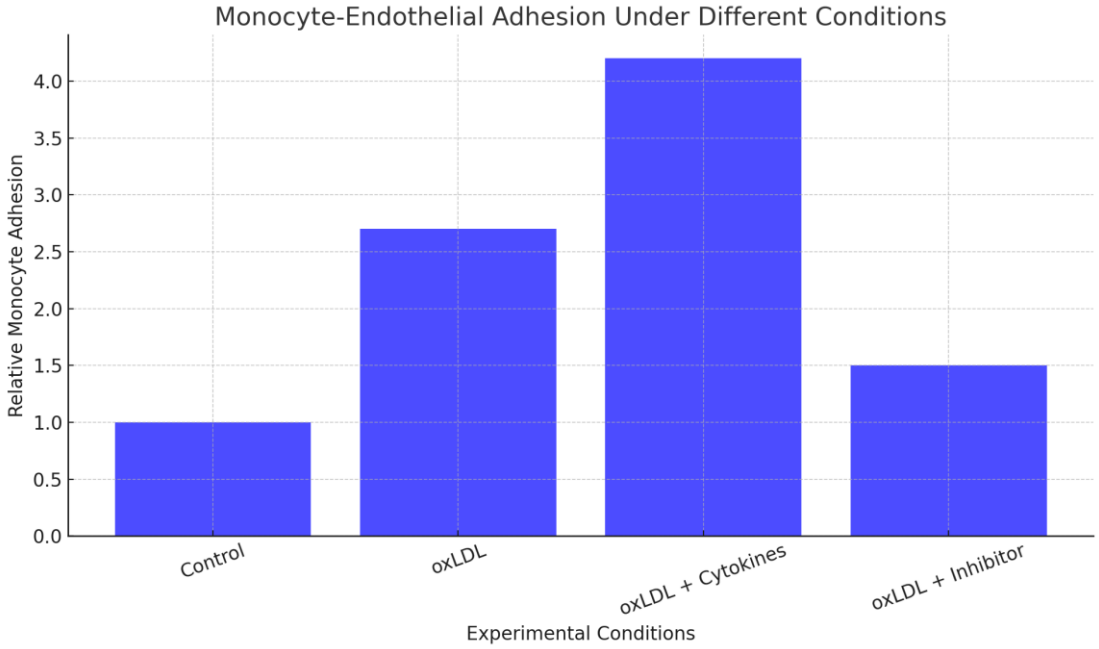

Figure 4: Monocyte-Endothelial Adhesion Under Different Conditions

This figure illustrates the relative percentage of monocyte adhesion to endothelial cells under varying experimental conditions, highlighting the impact of cytokine stimulation and adhesion molecule inhibition on monocyte recruitment.

This figure illustrates the relative percentage of monocyte adhesion to endothelial cells under various experimental conditions. Compared to the control, oxLDL exposure resulted in a significant increase in monocyte adhesion, correlating with the upregulation of adhesion molecules observed in Figure 1. The presence of inflammatory cytokines further intensified monocyte recruitment, suggesting that systemic inflammation is a key driver of immune cell infiltration in atherosclerotic lesions. Importantly, inhibition of adhesion molecules led to a substantial reduction in monocyte adhesion, reinforcing the therapeutic potential of targeting these molecules to limit immune cell accumulation and plaque instability.

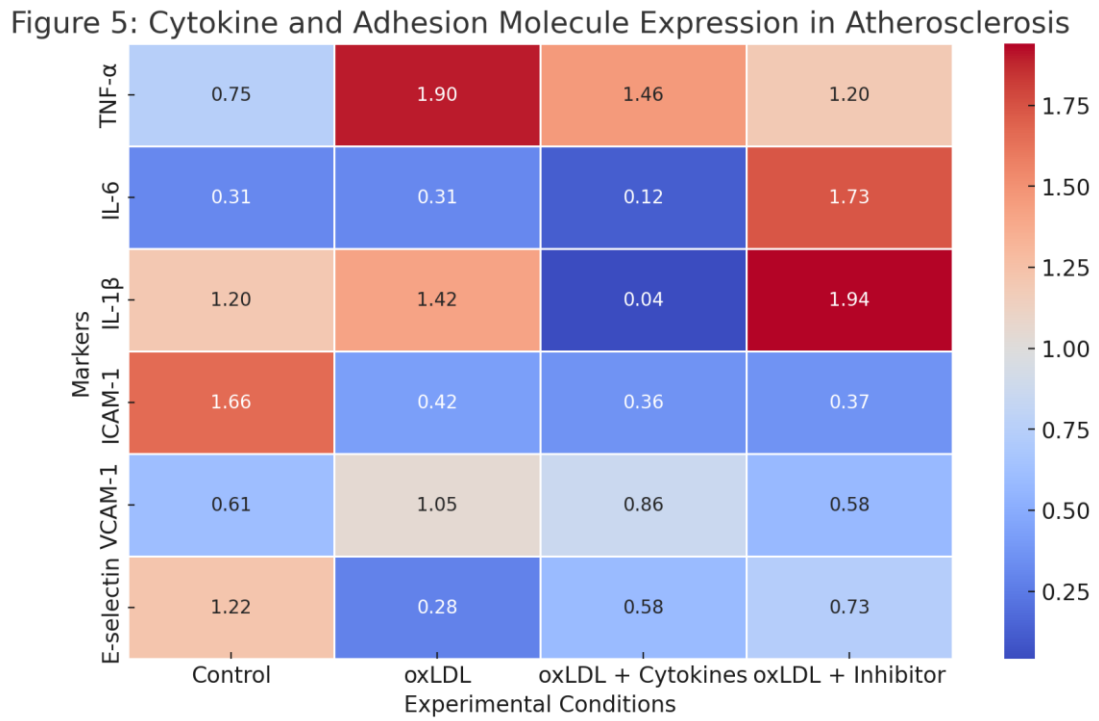

Figure 5: Cytokine and Adhesion Molecule Expression in Atherosclerosis

This heatmap visualizes the relative expression levels of key inflammatory cytokines (TNF-α, IL-6, IL-1β) and adhesion molecules (ICAM-1, VCAM-1, E-selectin) across different experimental conditions. The color scale indicates fold-change variations, emphasizing the impact of oxLDL stimulation, cytokine treatment, and adhesion molecule inhibition on endothelial cell activation.

The high expression levels observed in the **oxLDL + Cytokines** condition reinforce the pro-inflammatory role of these molecules, whereas **oxLDL + Inhibitor** treatment significantly mitigates their upregulation, suggesting a potential therapeutic avenue for preventing excessive immune cell recruitment and endothelial dysfunction.

Biological and Clinical Implications

These findings highlight the central role of inflammatory signaling in atherosclerosis and provide a strong rationale for targeting adhesion molecules as a therapeutic strategy. The inhibition of ICAM-1, VCAM-1, and E-selectin effectively reduced monocyte recruitment, demonstrating that selective blockade of these pathways could serve as a promising approach to mitigating vascular inflammation and reducing plaque burden. Additionally, the observed effects suggest that pro-inflammatory cytokine modulation may further contribute to endothelial protection and atheroprotective outcomes.

Taken together, these results support the growing body of evidence that inflammation-driven endothelial dysfunction is a key contributor to atherosclerotic disease progression. Further in vivo studies and clinical trials are warranted to explore the efficacy of adhesion molecule inhibitors as potential therapeutic agents for cardiovascular disease intervention.

7. Conclusion

Atherosclerosis is now widely recognized as a chronic inflammatory disease rather than merely a lipid accumulation disorder. The interplay between immune cytokines, chemokines, and adhesion molecules drives every stage of plaque formation, from early endothelial dysfunction to advanced lesion instability. The growing body of research highlights the essential role of pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6, alongside the modulatory functions of IL-10 and TGF-β. Similarly, the chemokine network, particularly MCP-1,

CCL5, and CXCL8, plays a crucial role in the recruitment of monocytes and lymphocytes into the vascular wall, exacerbating local inflammation.

Adhesion molecules, including ICAM-1, VCAM-1, and selectins, facilitate the firm attachment of circulating immune cells to the endothelium, further perpetuating vascular inflammation and plaque progression. These molecular interactions not only contribute to lesion growth but also increase the risk of plaque rupture and thrombosis. Targeting these inflammatory mediators through novel pharmacological interventions—such as IL-1β inhibitors (e.g., canakinumab), chemokine receptor blockers, and RNA-based therapies—has shown promise in reducing vascular inflammation and improving clinical outcomes.

Beyond pharmacology, lifestyle interventions such as dietary modifications, exercise, and microbiome-targeted therapies provide additional strategies for reducing systemic inflammation and enhancing endothelial function. The role of gut-derived metabolites, particularly short-chain fatty acids, in modulating immune responses is an emerging area of interest with significant therapeutic potential.

Future research should focus on refining these interventions through precision medicine, utilizing advanced multi-omics profiling and artificial intelligence to identify patient-specific inflammatory pathways and optimize treatment strategies. However, challenges remain, including safety concerns related to long-term cytokine suppression and adhesion-blocking therapies, as well as regulatory hurdles in translating these novel approaches into routine clinical practice.

Ultimately, the integration of targeted immunotherapies, RNA-based interventions, and lifestyle modifications holds the key to more effective and personalized management of atherosclerosis. By addressing the inflammatory basis of the disease, future treatments may not only halt progression but also facilitate regression of established plaques, significantly reducing cardiovascular morbidity and mortality.

References

1. Miller, P.W.; Sharma, S.; Stolina, M.; Butterfield, L.H.; Luo, J.; Lin, Y.; Dohadwala, M.; Batra, R.K.; Wu, L.; *et al.* Intratumoral administration of adenoviral interleukin 7 gene-modified dendritic cells augments specific antitumor immunity and achieves tumor eradication. *Hum. Gene Ther.* **2000**, *11*, 53–65. [**Google Scholar**] [**CrossRef**]
2. Aoki, T.; Tashiro, K.; Miyatake, S.; Kinashi, T.; Nakano, T.; Oda, Y.; Kikuchi, H.; Honjo, T. Expression of murine interleukin 7 in a murine glioma cell line results in reduced tumorigenicity *in vivo*. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 3850–3854. [**Google Scholar**]
3. Koshita, Y.; Lu, Y.; Fujii, S.; Neda, H.; Matsuyama, T.; Satoh, Y.; Itoh, Y.; Takahashi, M.; Kato, J.; Sakamaki, S.; *et al.* Efficacy of TNF-alpha gene-transduced tumor cells in treatment of established *in vivo* tumor. *Int. J. Cancer* **1995**, *63*, 130–135. [**Google Scholar**] [**CrossRef**]
4. Barker, S.E.; Grosse, S.M.; Siapati, E.K.; Kritz, A.; Kinnon, C.; Thrasher, A.J.; Hart, S.L. Immunotherapy for neuroblastoma using syngeneic fibroblasts transfected with IL-2 and IL-12. *Br. J. Cancer* **2007**, *97*, 210–217. [**Google Scholar**] [**CrossRef**]
5. Jackaman, C.; Bundell, C.S.; Kinnear, B.F.; Smith, A.M.; Filion, P.; van Hagen, D.; Robinson, B.W.; Nelson, D.J. IL-2 intratumoral immunotherapy enhances CD8+ T cells that mediate destruction of tumor cells and tumor-associated vasculature: A novel mechanism for IL-2. *J. Immunol.* **2003**, *171*, 5051–5063. [**Google Scholar**]
6. Pasche, N.; Neri, D. Immunocytokines: A novel class of potent armed antibodies. *Drug Discov. Today* 2012.
7. Schrama, D.; Reisfeld, R.A.; Becker, J.C. Antibody targeted drugs as cancer therapeutics. *Nat. Rev. Drug Discov.* **2006**, *5*, 147–159. [**Google Scholar**]
8. Holliger, P.; Hudson, P.J. Engineered antibody fragments and the rise of single domains. *Nat. Biotechnol.* **2005**, *23*, 1126–1136. [**Google Scholar**] [**CrossRef**]

9. Kuo, T.T.; Aveson, V.G. Neonatal Fc receptor and IgG-based therapeutics. *MAbs* **2011**, *3*, 422–430. [**Google Scholar**] [**CrossRef**]

10. Woof, J.M.; Burton, D.R. Human antibody-Fc receptor interactions illuminated by crystal structures. *Nat. Rev. Immunol.* **2004**, *4*, 89–99. [**Google Scholar**] [**CrossRef**]

11. Ward, E.S.; Martinez, C.; Vaccaro, C.; Zhou, J.; Tang, Q.; Ober, R.J. From sorting endosomes to exocytosis: Association of Rab4 and Rab11 GTPases with the Fc receptor, FcRn, during recycling. *Mol. Biol. Cell* **2005**, *16*, 2028–2038. [**Google Scholar**] [**CrossRef**]

12. Vaccaro, C.; Zhou, J.; Ober, R.J.; Ward, E.S. Engineering the Fc region of immunoglobulin G to modulate *in vivo* antibody levels. *Nat. Biotechnol.* **2005**, *23*, 1283–1288. [**Google Scholar**] [**CrossRef**]

13. Pop, L.M.; Liu, X.; Ghetie, V.; Vitetta, E.S. The generation of immunotoxins using chimeric anti-CD22 antibodies containing mutations which alter their serum half-life. *Int. Immunopharmacol.* **2005**, *5*, 1279–1290. [**Google Scholar**] [**CrossRef**]

14. Jain, R.K.; Baxter, L.T. Mechanisms of heterogeneous distribution of monoclonal antibodies and other macromolecules in tumors: Significance of elevated interstitial pressure. *Cancer Res.* **1988**, *48*, 7022–7032. [**Google Scholar**]

15. Yokota, T.; Milenic, D.E.; Whitlow, M.; Schlom, J. Rapid tumor penetration of a single-chain Fv and comparison with other immunoglobulin forms. *Cancer Res.* **1992**, *52*, 3402–3408. [**Google Scholar**]

16. Graff, C.P.; Wittrup, K.D. Theoretical analysis of antibody targeting of tumor spheroids: Importance of dosage for penetration, and affinity for retention. *Cancer Res.* **2003**, *63*, 1288–1296. [**Google Scholar**]

17. Milenic, D.E.; Yokota, T.; Filpula, D.R.; Finkelman, M.A.; Dodd, S.W.; Wood, J.F.; Whitlow, M.; Snoy, P.; Schlom, J. Construction, binding properties, metabolism, and tumor targeting of a single-chain Fv derived from the pancarcinoma monoclonal antibody CC49. *Cancer Res.* **1991**, *51*, 6363–6371. [**Google Scholar**]

18. Borsi, L.; Balza, E.; Bestagno, M.; Castellani, P.; Carnemolla, B.; Biro, A.; Leprini, A.; Sepulveda, J.; Burrone, O.; Neri, D.; Zardi, L. Selective targeting of tumoral vasculature: Comparison of different formats of an antibody (L19) to the ED-B domain of fibronectin. *Int. J. Cancer* **2002**, *102*, 75–85. [**Google Scholar**] [**CrossRef**]

19. Holliger, P.; Prospero, T.; Winter, G. Diabodies": Small bivalent and bispecific antibody fragments. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6444–6448. [**Google Scholar**]

20. Kendra, K.; Gan, J.; Ricci, M.; Surfus, J.; Shaker, A.; Super, M.; Frost, J.D.; Rakhmilevich, A.; Hank, J.A.; Gillies, S.D.; Sondel, P.M. Pharmacokinetics and stability of the ch14.18-interleukin-2 fusion protein in mice. *Cancer Immunol. Immunother.* **1999**, *48*, 219–229. [**Google Scholar**] [**CrossRef**]

21. Yamane, B.H.; Hank, J.A.; Albertini, M.R.; Sondel, P.M. The development of antibody-IL-2 based immunotherapy with hu14.18-IL2 (EMD-273063) in melanoma and neuroblastoma. *Expert Opin. Investig. Drugs* **2009**, *18*, 991–1000. [**Google Scholar**] [**CrossRef**]

22. Johannsen, M.; Spitaleri, G.; Curigliano, G.; Roigas, J.; Weikert, S.; Kempkensteffen, C.; Roemer, A.; Kloeters, C.; Rogalla, P.; Pecher, G.; *et al.* The tumour-targeting human L19-IL2 immunocytokine: Preclinical safety studies, phase I clinical trial in patients with solid tumours and expansion into patients with advanced renal cell carcinoma. *Eur. J. Cancer* **2010**, *46*, 2926–2935. [**Google Scholar**]

23. Ebbinghaus, C.; Ronca, R.; Kaspar, M.; Grabulovski, D.; Berndt, A.; Kosmehl, H.; Zardi, L.; Neri, D. Engineered vascular-targeting antibody-interferon-gamma fusion protein for cancer therapy. *Int. J. Cancer* **2005**, *116*, 304–313. [**Google Scholar**] [**CrossRef**]

24. Naramura, M.; Gillies, S.D.; Mendelsohn, J.; Reisfeld, R.A.; Mueller, B.M. Mechanisms of cellular cytotoxicity mediated by a recombinant antibody-IL2 fusion protein against human melanoma cells. *Immunol. Lett.* **1993**, *39*, 91–99. [**Google Scholar**] [**CrossRef**]

25. Alderson, K.L.; Sondel, P.M. Clinical cancer therapy by NK cells via antibody-dependent cell-mediated cytotoxicity. *J. Biomed. Biotechnol.* **2011**, 379123. [**Google Scholar**]

26. Buhtoiarov, I.N.; Neal, Z.C.; Gan, J.; Buhtoiarova, T.N.; Patankar, M.S.; Gubbels, J.A.; Hank, J.A.; Yamane, B.; Rakhmilevich, A.L.; Reisfeld, R.A.; *et al.* Differential internalization of hu14.18-IL2 immunocytokine by NK and tumor cell: Impact on conjugation, cytotoxicity, and targeting. *J. Leukoc. Biol.* **2011**, *89*, 625–638. [**Google Scholar**] [**CrossRef**]

27. Gubbels, J.A.; Gadbaw, B.; Buhtoiarov, I.N.; Horibata, S.; Kapur, A.K.; Patel, D.; Hank, J.A.; Gillies, S.D.; Sondel, P.M.; Patankar, M.S.; Connor, J. Ab-IL2 fusion proteins mediate NK cell immune synapse formation by polarizing CD25 to the target cell-effector cell interface. *Cancer Immunol. Immunother.* **2011**, *60*, 1789–1800. [**Google Scholar**] [**CrossRef**]

28. Patriarca, C.; Macchi, R.M.; Marschner, A.K.; Mellstedt, H. Epithelial cell adhesion molecule expression (CD326) in cancer: A short review. *Cancer Treat. Rev.* **2012**, *38*, 68–75. [**Google Scholar**] [**CrossRef**]

29. Gires, O. Lessons from common markers of tumor-initiating cells in solid cancers. *Cell Mol. Life Sci.* **2011**, *68*, 4009–4022. [**Google Scholar**] [**CrossRef**]

30. Mujoo, K.; Cheresh, D.A.; Yang, H.M.; Reisfeld, R.A. Disialoganglioside GD2 on human neuroblastoma cells: Target antigen for monoclonal antibody-mediated cytolysis and suppression of tumor growth. *Cancer Res.* **1987**, *47*, 1098–1104. [**Google Scholar**]

31. Chang, H.R.; Cordon-Cardo, C.; Houghton, A.N.; Cheung, N.K.; Brennan, M.F. Expression of disialogangliosides GD2 and GD3 on human soft tissue sarcomas. *Cancer* **1992**, *70*, 633–638. [**Google Scholar**] [**CrossRef**]

32. Svennerholm, L.; Bostrom, K.; Fredman, P.; Jungbjer, B.; Lekman, A.; Mansson, J.E.; Rynmark, B.M. Gangliosides and allied glycosphingolipids in human peripheral nerve and spinal cord. *Biochim. Biophys. Acta* **1994**, *1214*, 115–123. [**Google Scholar**]

33. Allen, M.; Louise Jones, J. Jekyll and Hyde: The role of the microenvironment on the progression of cancer. *J. Pathol.* **2011**, *223*, 162–176. [**Google Scholar**]

34. Filer, A.; Pitzalis, C.; Buckley, C.D. Targeting the stromal microenvironment in chronic inflammation. *Curr. Opin. Pharmacol.* **2006**, *6*, 393–400. [**Google Scholar**] [**CrossRef**]

35. Carmeliet, P. Angiogenesis in health and disease. *Nat. Med.* **2003**, *9*, 653–660. [**Google Scholar**] [**CrossRef**]

36. Schliemann, C.; Neri, D. Antibody-based vascular tumor targeting. *Recent Results Cancer Res.* **2010**, *180*, 201–216. [**Google Scholar**] [**CrossRef**]

37. Neri, D.; Bicknell, R. Tumour vascular targeting. *Nat. Rev. Cancer* **2005**, *5*, 436–446. [**Google Scholar**] [**CrossRef**]

38. Neri, D.; Carnemolla, B.; Nissim, A.; Leprini, A.; Querze, G.; Balza, E.; Pini, A.; Tarli, L.; Halin, C.; Neri, P.; Zardi, L.; Winter, G. Targeting by affinity-matured recombinant antibody fragments of an angiogenesis associated fibronectin isoform. *Nat. Biotechnol.* **1997**, *15*, 1271–1275. [**Google Scholar**]

39. Schwager, K.; Villa, A.; Rosli, C.; Neri, D.; Rosli-Khabas, M.; Moser, G. A comparative immunofluorescence analysis of three clinical-stage antibodies in head and neck cancer. *Head Neck Oncol.* **2011**, *3*, 25. [**Google Scholar**] [**CrossRef**]

40. Santimaria, M.; Moscatelli, G.; Viale, G.L.; Giovannoni, L.; Neri, G.; Viti, F.; Leprini, A.; Borsi, L.; Castellani, P.; Zardi, L.; Neri, D.; Riva, P. Immunoscintigraphic detection of the ED-B domain of fibronectin, a marker of angiogenesis, in patients with cance. *Clin. Cancer Res.* **2003**, *9*, 571–579. [**Google Scholar**]

41. Tarli, L.; Balza, E.; Viti, F.; Borsi, L.; Castellani, P.; Berndorff, D.; Dinkelborg, L.; Neri, D.; Zardi, L. A high-affinity human antibody that targets tumoral blood vessels. *Blood* **1999**, *94*, 192–198. [**Google Scholar**]

42. Sharifi, J.; Khawli, L.A.; Hu, P.; King, S.; Epstein, A.L. Characterization of a phage display-derived human monoclonal antibody (NHS76) counterpart to chimeric TNT-1 directed against necrotic regions of solid tumors. *Hybrid. Hybridomics* **2001**, *20*, 305–312. [**Google Scholar**] [**CrossRef**]

43. Chen, S.; Yu, L.; Jiang, C.; Zhao, Y.; Sun, D.; Li, S.; Liao, G.; Chen, Y.; Fu, Q.; Tao, Q.; *et al.* Pivotal study of iodine-131-labeled chimeric tumor necrosis treatment radioimmunotherapy in patients with advanced lung cancer. *J. Clin. Oncol.* **2005**, *23*, 1538–1547. [**Google Scholar**]

44. St Croix, B.; Rago, C.; Velculescu, V.; Traverso, G.; Romans, K.E.; Montgomery, E.; Lal, A.; Riggins, G.J.; Lengauer, C.; Vogelstein, B.; Kinzler, K.W. Genes expressed in human tumor endothelium. *Science* **2000**, *289*, 1197–1202. [**Google Scholar**]

45. Oh, P.; Li, Y.; Yu, J.; Durr, E.; Krasinska, K.M.; Carver, L.A.; Testa, J.E.; Schnitzer, J.E. Subtractive proteomic mapping of the endothelial surface in lung and solid tumours for tissue-specific therapy. *Nature* **2004**, *429*, 629–635. [**Google Scholar**]

46. Strassberger, V.; Fugmann, T.; Neri, D.; Roesli, C. Chemical proteomic and bioinformatic strategies for the identification and quantification of vascular antigens in cancer. *J. Proteomics* **2010**, *73*, 1954–1973. [**Google Scholar**] [**CrossRef**]

47. Rybak, J.N.; Ettorre, A.; Kaissling, B.; Giavazzi, R.; Neri, D.; Elia, G. *In vivo* protein biotinylation for identification of organ-specific antigens accessible from the vasculature. *Nat. Methods* **2005**, *2*, 291–298. [**Google Scholar**]

48. Borgia, B.; Roesli, C.; Fugmann, T.; Schliemann, C.; Cesca, M.; Neri, D.; Giavazzi, R. A proteomic approach for the identification of vascular markers of liver metastasis. *Cancer Res.* **2010**, *70*, 309–318. [**Google Scholar**]

49. Frey, K.; Fiechter, M.; Schwager, K.; Belloni, B.; Barysch, M.J.; Neri, D.; Dummer, R. Different patterns of fibronectin and tenascin-C splice variants expression in primary and metastatic melanoma lesions. *Exp. Dermatol.* **2011**, *20*, 685–688. [**Google Scholar**] [**CrossRef**]

50. Schliemann, C.; Roesli, C.; Kamada, H.; Borgia, B.; Fugmann, T.; Klapper, W.; Neri, D. In vivo biotinylation of the vasculature in B-cell lymphoma identifies BST-2 as a target for antibody-based therapy. *Blood* **2010**, *115*, 736–744. [**Google Scholar**]

51. Seruga, B.; Zhang, H.; Bernstein, L.J.; Tannock, I.F. Cytokines and their relationship to the symptoms and outcome of cancer. *Nat. Rev. Cancer* **2008**, *8*, 887–899. [**Google Scholar**] [**CrossRef**]

52. Douglas, M.R.; Morrison, K.E.; Salmon, M.; Buckley, C.D. Why does inflammation persist: A dominant role for the stromal microenvironment. *Expert Rev. Mol. Med.* **2002**, *4*, 1–18. [**Google Scholar**]

53. Zamarron, B.F.; Chen, W. Dual roles of immune cells and their factors in cancer development and progression. *Int. J. Biol. Sci.* **2011**, *7*, 651–658. [**Google Scholar**] [**CrossRef**]

54. McDermott, D.F.; Regan, M.M.; Atkins, M.B. Interleukin-2 therapy of metastatic renal cell carcinoma: Update of phase III trials. *Clin. Genitourin. Cancer* **2006**, *5*, 114–119. [**Google Scholar**] [**CrossRef**]

55. Philip, P.A. Interleukin-2 in the treatment of malignant melanoma. *Expert Opin. Investig. Drugs* **1998**, *7*, 361–371. [**Google Scholar**] [**CrossRef**]

56. Carnemolla, B.; Borsi, L.; Balza, E.; Castellani, P.; Meazza, R.; Berndt, A.; Ferrini, S.; Kosmehl, H.; Neri, D.; Zardi, L. Enhancement of the antitumor properties of interleukin-2 by its targeted delivery to the tumor blood vessel extracellular matrix. *Blood* **2002**, *99*, 1659–1665. [**Google Scholar**]

57. Schliemann, C.; Palumbo, A.; Zuberbuhler, K.; Villa, A.; Kaspar, M.; Trachsel, E.; Klapper, W.; Menssen, H.D.; Neri, D. Complete eradication of human B-cell lymphoma xenografts using rituximab in combination with the immunocytokine L19-IL2. *Blood* **2009**, *113*, 2275–2283. [**Google Scholar**]

58. Marlind, J.; Kaspar, M.; Trachsel, E.; Sommavilla, R.; Hindle, S.; Bacci, C.; Giovannoni, L.; Neri, D. Antibody-mediated delivery of interleukin-2 to the stroma of breast cancer strongly enhances the potency of chemotherapy. *Clin. Cancer Res.* **2008**, *14*, 6515–6524. [**Google Scholar**]

59. King, D.M.; Albertini, M.R.; Schalch, H.; Hank, J.A.; Gan, J.; Surfus, J.; Mahvi, D.; Schiller, J.H.; Warner, T.; Kim, K.; *et al.* Phase I clinical trial of the immunocytokine EMD 273063 in melanoma patients. *J. Clin. Oncol.* **2004**, *22*, 4463–4473. [**Google Scholar**]

60. Ribas, A.; Kirkwood, J.M.; Atkins, M.B.; Whiteside, T.L.; Gooding, W.; Kovar, A.; Gillies, S.D.; Kashala, O.; Morse, M.A. Phase I/II open-label study of the biologic effects of the interleukin-2 immunocytokine EMD 273063 (hu14.18-IL2) in patients with metastatic malignant melanom. *J. Transl. Med.* **2009**, *7*, 68. [**Google Scholar**]

61. Osenga, K.L.; Hank, J.A.; Albertini, M.R.; Gan, J.; Sternberg, A.G.; Eickhoff, J.; Seeger, R.C.; Matthay, K.K.; Reynolds, C.P.; Twist, C.; *et al.* A phase I clinical trial of the hu14.18-IL2 (EMD 273063) as a treatment for children with refractory or recurrent neuroblastoma and melanoma: A study of the Children's Oncology Group. *Clin. Cancer Res.* **2006**, *12*, 1750–1759. [**Google Scholar**]

62. Shusterman, S.; London, W.B.; Gillies, S.D.; Hank, J.A.; Voss, S.D.; Seeger, R.C.; Reynolds, C.P.; Kimball, J.; Albertini, M.R.; Wagner, B.; *et al.* Antitumor activity of hu14.18-IL2 in patients with relapsed/refractory neuroblastoma: A Children's Oncology Group (COG) phase II study. *J. Clin. Oncol.* **2010**, *28*, 4969–4975. [**Google Scholar**]

63. Ko, Y.J.; Bubley, G.J.; Weber, R.; Redfern, C.; Gold, D.P.; Finke, L.; Kovar, A.; Dahl, T.; Gillies, S.D. Safety, pharmacokinetics, and biological pharmacodynamics of the immunocytokine EMD 273066 (huKS-IL2): Results of a phase I trial in patients with prostate cance. *J. Immunother.* **2004**, *27*, 232–239. [**Google Scholar**]

64. Gillies, S.D.; Lan, Y.; Hettmann, T.; Brunkhorst, B.; Sun, Y.; Mueller, S.O.; Lo, K.M. A low-toxicity IL-2-based immunocytokine retains antitumor activity despite its high degree of IL-2 receptor selectivity. *Clin. Cancer Res.* **2011**, *17*, 3673–3685. [**Google Scholar**]

65. Yang, J.C.; Sherry, R.M.; Steinberg, S.M.; Topalian, S.L.; Schwartzentruber, D.J.; Hwu, P.; Seipp, C.A.; Rogers-Freezer, L.; Morton, K.E.; White, D.E.; *et al.* Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J. Clin. Oncol.* **2003**, *21*, 3127–3132. [**Google Scholar**]

66. Rosenberg, S.A.; Yang, J.C.; White, D.E.; Steinberg, S.M. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: Identification of the antigens mediating response. *Ann. Surg.* **1998**, *228*, 307–319. [**Google Scholar**]

67. Atkins, M.B.; Robertson, M.J.; Gordon, M.; Lotze, M.T.; DeCoste, M.; DuBois, J.S.; Ritz, J.; Sandler, A.B.; Edington, H.D.; Garzone, P.D.; *et al.* Phase I evaluation of intravenous recombinant human interleukin 12 in patients with advanced malignancies. *Clin. Cancer Res.* **1997**, *3*, 409–417. [**Google Scholar**]

68. Halin, C.; Rondini, S.; Nilsson, F.; Berndt, A.; Kosmehl, H.; Zardi, L.; Neri, D. Enhancement of the antitumor activity of interleukin-12 by targeted delivery to neovasculature. *Nat. Biotechnol.* **2002**, *20*, 264–269. [**Google Scholar**] [**CrossRef**]

69. Li, J.; Hu, P.; Khawli, L.A.; Yun, A.; Epstein, A.L. chTNT-3/hu IL-12 fusion protein for the immunotherapy of experimental solid tumors. *Hybrid. Hybridomics* **2004**, *23*, 1–10. [**Google Scholar**] [**CrossRef**]

70. Rudman, S.M.; Jameson, M.B.; McKeage, M.J.; Savage, P.; Jodrell, D.I.; Harries, M.; Acton, G.; Erlandsson, F.; Spicer, J.F. A phase 1 study of AS1409, a novel antibody-cytokine fusion protein, in patients with malignant melanoma or renal cell carcinoma. *Clin. Cancer Res.* **2011**, *17*, 1998–2005. [**Google Scholar**]

71. Lejeune, F.J.; Lienard, D.; Matter, M.; Ruegg, C. Efficiency of recombinant human TNF in human cancer therapy. *Cancer Immun.* **2006**, *6*, 6. [**Google Scholar**]

72. Borsi, L.; Balza, E.; Carnemolla, B.; Sassi, F.; Castellani, P.; Berndt, A.; Kosmehl, H.; Biro, A.; Siri, A.; Orecchia, P.; *et al.* Selective targeted delivery of TNFalpha to tumor blood vessels. *Blood* **2003**, *102*, 4384–4392. [**Google Scholar**]

73. Balza, E.; Mortara, L.; Sassi, F.; Monteghirfo, S.; Carnemolla, B.; Castellani, P.; Neri, D.; Accolla, R.S.; Zardi, L.; Borsi, L. Targeted delivery of tumor necrosis factor-alpha to tumor vessels induces a therapeutic T cell-mediated immune response that protects the host against syngeneic tumors of different histologic origin. *Clin. Cancer Res.* **2006**, *12*, 2575–2582. [**Google Scholar**]

74. Huhn, R.D.; Radwanski, E.; O'Connell, S.M.; Sturgill, M.G.; Clarke, L.; Cody, R.P.; Affrime, M.B.; Cutler, D.L. Pharmacokinetics and immunomodulatory properties of intravenously administered recombinant human interleukin-10 in healthy volunteers. *Blood* **1996**, *87*, 699–705. [**Google Scholar**]

75. Rosenblum, I.Y.; Johnson, R.C.; Schmahai, T.J. Preclinical safety evaluation of recombinant human interleukin-10. *Regul. Toxicol. Pharmacol.* **2002**, *35*, 56–71. [**Google Scholar**] [**CrossRef**]

76. Schwager, K.; Kaspar, M.; Bootz, F.; Marcolongo, R.; Paresce, E.; Neri, D.; Trachsel, E. Preclinical characterization of DEKAVIL (F8-IL10), a novel clinical-stage immunocytokine which inhibits the progression of collagen-induced arthritis. *Arthritis Res. Ther.* **2009**, *11*, R142. [**Google Scholar**] [**CrossRef**]

77. Schwager, K.; Bootz, F.; Imesch, P.; Kaspar, M.; Trachsel, E.; Neri, D. The antibody-mediated targeted delivery of interleukin-10 inhibits endometriosis in a syngeneic mouse model. *Hum. Reprod.* **2011**, *26*, 2344–2352. [**Google Scholar**] [**CrossRef**]

78. Trachsel, E.; Kaspar, M.; Bootz, F.; Detmar, M.; Neri, D. A human mAb specific to oncofetal fibronectin selectively targets chronic skin inflammation *in vivo*. *J. Invest. Dermatol.* **2007**, *127*, 881–886. [**Google Scholar**]

79. Zitvogel, L.; Apetoh, L.; Ghiringhelli, F.; Kroemer, G. Immunological aspects of cancer chemotherapy. *Nat. Rev. Immunol.* **2008**, *8*, 59–73. [**Google Scholar**]

80. Moschetta, M.; Pretto, F.; Berndt, A.; Galler, K.; Richter, P.; Bassi, A.; Oliva, P.; Micotti, E.; Valbusa, G.; Schwager, K.; *et al.* Paclitaxel Enhances Therapeutic Efficacy of the F8-IL2 Immunocytokine to EDA-Fibronectin-Positive Metastatic Human Melanoma Xenografts. *Cancer Res.* **2012**, *72*, 1814–1824. [**Google Scholar**] [**CrossRef**]