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Roles of Growth Differentiation Factor 15 in Atherosclerosis and Coronary Artery Disease

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The majority of acute cardiovascular events (CVE) in patients are caused by occlusive thrombosis because of rupture or erosion of atherosclerotic plaques.[1] Growth differentiation factor 15 (GDF-15), a stress-responsive member of the transforming growth factor-β (TGF-β) cytokine superfamily, has been shown to be a strong and independent predictor of mortality and disease progression in patients with atherosclerosis and coronary artery disease (CAD), such as acute coronary syndromes (ACS) and stable angina pectoris.[2] The development of atherosclerosis is dependent upon a high-inflammatory content, which has been shown to modulate lesion initiation, progression, and potentially devastating thrombotic complications.[3] Angiogenesis plays an important role in the progression of atherosclerotic plaque and complications.[4–6] Atherosclerosis and cancer arise from multiple factors and are consolidated from the very early stages of development up to the advanced forms in inflammatory processes. Uncontrolled cell proliferation and oxidative stress and angiogenesis appear to be unifying causal factors in both diseases.[7] A local inflammatory state occurring in atherosclerotic lesions has been implicated in angiogenesis through activation of endothelial cells, release of chemokines, cytokines, growth factors, lipid mediators, proteases, and increase of endothelial metabolic rate. The angiogenesis allows extravasation of the plasma component, leading to future thromboembolic events.[8–11] GDF-15 might be an acute phase modifier of TGF-βRII-dependent proinflammatory responses to atherosclerotic plaque rupture and thrombus formation[12] (Figure). Although the exact biological functions of GDF-15 are still poorly understood, it has been shown to

regulate inflammatory and angiogenesis pathways (Figure). GDF-15 exhibits differing and even opposing functions under various circumstances. For instance, GDF-15 has proapoptosis, antiapoptosis, proangiogenesis, antiangiogenesis, proinflammatory, and anti-inflammatory properties.[12,13] Therefore, GDF-15 exhibits a complex pattern with beneficial and harmful functions. GDF-15 promoter contains p53-transcription factor binding sites that are required and sufficient for the induction of GDF-15 expression.[14] Activation of p53 is a fundamental cellular response to inflammation, oxidative stress, hypoxia, telomere erosion, and oncogene activation. The circulating levels of GDF-15 reflect these acute and chronic inflammatory conditions linked with atherosclerosis and CAD.

Regulation and Roles of GDF-15

Under normal physiological conditions, placenta is the only tissue expressing large quantities of GDF-15.[15] GDF-15 levels are increased in various pathological conditions and diseases, including inflammation, cardiovascular disease, renal disease, pulmonary disease, and cancer.[12] GDF-15 is produced in activated macrophages,[11] and in pathological conditions including proinflammatory status, vascular injury, pressure overload, and oxidative stress from human endothelial cells,[16] vascular smooth muscle cells,[17] and adipocytes.[18] The expression of GDF-15 in virtually all tissues suggests its importance in general and basic cellular functions. Although the exact biological functions of GDF-15 remain largely unclear, it has been demonstrated to modulate inflammatory, apoptotic, and angiogenesis pathways.

GDF-15 as a Novel Biomarker of CVE

GDF-15 has been recognized as a consistent biomarker of CVE in patients with ACS or stable CAD.[19] GDF-15 levels are independently related to age, high-sensitivity C-reactive protein (hs-CRP), natriuretic peptides, and renal dysfunction in patients with established CAD.[2,20–26] GDF-15 concentrations are enhanced in patients with multivessel disease[21,27] and with a history of myocardial infarction (MI) or heart failure.[27–29] The association of GDF-15 with all-cause mortality, cardiovascular mortality, MI, and stroke was further
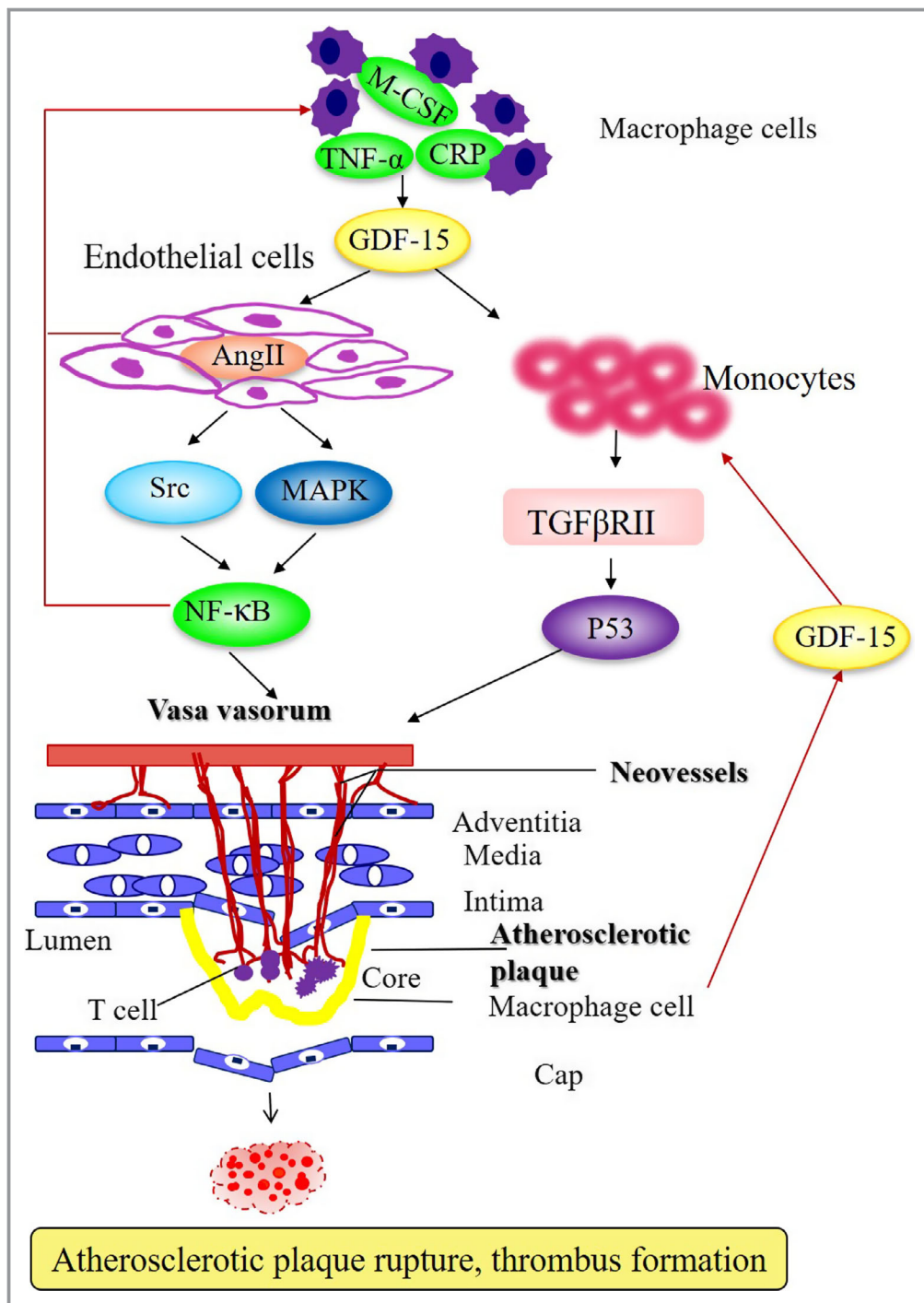
Figure. Schematic overview of a vulnerable plaque in advanced atherosclerosis. Plaque formation is initiated by endothelial cell dysfunction and subsequent angiogenesis and release of proinflammatory factors mediated by GDF-15, contributing to the progression of atherosclerotic lesions and the development of plaque rupture and thrombus formation in atherosclerotic status. CRP indicates C-reactive protein; GDF-15, growth differentiation factor 15; MAPK, mitogen-activated protein kinase; M-CSF, macrophage colony-stimulating factor; TGF-βRII, transforming growth factor-βRII; TNF-α, tumor necrosis factor-α.

explored in our recently published research work, which included 3440 patients with established CAD independent of clinical predictors including age, diabetes mellitus, current smoking, hypertension, hyperlipidemia, and left ventricular ejection fraction.[30] Our study simultaneously evaluated the incremental prognostic value of GDF-15 and provided more

information than other biomarkers (estimated glomerular filtration rate, fibrinogen, D-dimer, sST2, pregnancy-associated plasma protein A, and uric acid). Adding the information on GDF-15 to the baseline clinical model improved the C-index from 0.786 to 0.806. In addition, we examined whether there were heterogeneity in the hazard ratios based on presentation with stable CAD and ACS (unstable angina pectoris, non–ST-segment–elevation myocardial infarction [NSTEMI], and ST-segment–elevation myocardial infarction [STEMI]) beyond traditional risk factors. GDF-15 was significantly associated with stable CAD and ACS. Recently, Gohar et al[31] revealed that high circulating levels GDF-15 are predictive of secondary CVE in women with carotid atherosclerosis, indicating contribution of high GDF-15 levels to increased risk factors of CVE.

Roles of GDF-15 in ACS

GDF-15 is emerging as a prognostic biomarker in patients with ACS, including STEMI, NSTEMI, and unstable angina pectoris (Table 1), which result from the rupture or erosion of vulnerable atherosclerotic plaque leading to death and recurrent MI, which would be occurring at any time after the first attack episode.[32–41] The predictive value of GDF-15 has been confirmed in the 2 large non–ST-segment–elevation ACS (NSTE-ACS) trials: the GUSTO-IV (Global Utilisation of Strategies to Open Occluded Arteries IV) and FRISC II (Fast Revascularization during Instability in Coronary Artery Disease II) cohorts[20,21] (Table 1). As shown in patients from the GUSTO-IV trial, GDF-15 concentrations are closely related to all-cause mortality in NSTE-ACS[20] (Table 1). In FRISC II, cumulative 1-year mortality rates were 1.5, 5.0, and 14.1% in patients with low, moderately increased, and markedly increased concentrations of GDF-15. GDF-15 provided prognostic information beyond clinical predictors and other prognostic biomarkers, including cardiac troponin T, N-terminal pro-brain natriuretic peptide, hs-CRP, and creatinine clearance.[21] The independent association of GDF-15 with mortality is confirmed in other patients with STEMI or NSTE-ACS.[22,23] Lately, the prognostic value of GDF-15 has been reevaluated in 16 876 patients with NSTE-ACS or STEMI randomized to ticagrelor or clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) study[27](Table 1). Based on the large number of patients and outcome events, the PLATO biomarker study was able to explore the relation of GDF-15 to specific outcome events during follow-up. After adjustment for clinical predictors and other biomarkers, higher GDF-15 concentrations were associated with an increased risk of all-cause mortality, cardiovascular mortality, MI, and stroke. The results are confirmed by a secondary analysis of the PLATO study including 17 095 patients with ACS,[42] demonstrating

that GDF-15 was a strong marker associated with all-cause death, death caused by other vascular or nonvascular causes, and death caused by bleeding (Table 1). For GDF-15, the possible signal of association with death caused by bleeding is in line with prior results indicating that GDF-15 reflects nonoverlapping disease pathway contributing to the development of bleeding after ACS. Increased concentrations of GDF-15 also identify patients at increased risk for adverse left ventricular remodeling and hospitalization for heart failure after ACS.[23,28,43] In 3501 patients from the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction-22) trial, GDF-15 was associated with the risks of all-cause mortality, recurrent MI, and hospitalization for new or worsening heart failure.[28] The prognostic information provided by GDF-15 was independent of clinical predictors and other biomarkers (hs-CRP and brain natriuretic peptide). Notably, GDF-15, in contrast to hs-CRP,[44] did not decline over time in response to more intensive statin therapy in PROVE IT–TIMI-22,[28] further indicating that GDF-15 reflects a nonoverlapping atherosclerotic pathway contributing to the development of ACS.

Roles of GDF-15 in Stable CAD

GDF-15 maintains its close association with an adverse prognosis in patients with ACS during the transition to the chronic stage of CAD.[24,25] In a serial analysis from FRISC-II, GDF-15 provided similar independent prognostic information on the composite end point of death or recurrent MI on admission and up to 6 months after an episode of NSTE-ACS.[24] Similarly, GDF-15 was identified as an independent predictor of CAD mortality in patients with stable CAD[2] (Table 2). In the AtheroGene (patients with stable CAD or ACS who had at least 1 stenosis >30% in a major coronary artery were enrolled in the AtheroGene registry) study, which included 1352 patients with stable angina pectoris undergoing coronary angiography, GDF-15 was associated with CAD mortality independent of cardiovascular risk factors, clinical predictors, the number of diseased vessels, left ventricular ejection fraction, and other biomarkers (cTnI, N-terminal pro-brain natriuretic peptide, and hs-CRP).[2] Similarly, in a cohort of 984 patients with stable CAD, higher GDF-15 levels were associated with lower left ventricular ejection fraction, worse diastolic function, and greater inducible ischemia. The association of GDF-15 with MI, heart failure, and cardiovascular death persisted after extensive adjustment for traditional risk factors and the other biomarkers (NT-proBNP, CRP, and hs-cardiac troponin T)[29] (Table 2). Recently, the prognostic value of GDF-15 has been reevaluated in 14 577 patients with stable CAD in specific outcome events from STABILITY (The Stabilization of Atherosclerotic Plaque by Initiation of

Table 1. GDF-15 Related to Outcome Events in ACS

Study	Participants	Outcomes	Follow-Up (y)	Comparisons (ng/L)	RR (95% CI)
CAD patients, Kempf et al[2]	ACS (n =877)	M	6 (maximum)	<1200, 1200 to 1800, >1800	8.5 (3.81–18.99)
GUSTO-IV, Wollert et al[20]	NSTE-ACS (n=2081)	M	1 (maximum)	<1200, 1200 to 1800, >1800	2.08 (1.85–2.34)
FRISC-II, Wollert et al[21]	NSTE-ACS (n=2079)	M, R	2 (maximum)	<1200, 1200 to 1800, >1800	1.75 (1.48–2.07)
ASSENT-2 and ASSENT-plus trials, Kempf et al[22]	STEMI (n =741)	M	1 (maximum)	<1200, 1200 to 1800, >1800	6.6 (2.43–18.23)
AMI patients, Khan et al[23]	AMI (n=1142)	M, HF	1.4 (median)	1470 (240–31 860)	4.24 (3.21–5.62)
FRISC II, Eggers et al[24]	NSTE-ACS (n=950)	M, R	0.5 (maximum)	<1200, 1200 to 1800, >1800	1.9 (1.2–3.0)
PLATO, Hagstrom et al[27]	ACS (n=16 876)	M	1 (maximum)	<1145, 1145 to 1550, 1550 to 2219, >2219	3.96 (2.91–5.39)
PROVE IT-TIMI 22, Bonaca et al[28]	ACS (n=3501)	M	2 (maximum)	<1200, 1200 to 1800, >1800	4.76 (2.67–8.48)
STEMI patients, Eitel I et al[32]	STEMI (n=238)	M,R	0.5 (maximum)	<1319, ≥1319	19 (2.58, 139.66)
NSTE-ACS patients, Widera et al[33]	NSTE-ACS (n=1122)	M, R	0.5 (mean)	1725 (1205–2797)	2.4 (1.9–3.0)
NSTE-ACS patients, Widera et al[34]	NSTE-ACS (n=1146)	M, R	0.5 (mean)	1770 (1262–2981)	2.4 (2.0–3.0)
ICTUS, Damman et al[35]	NSTE-ACS	M	5 (maximum)	<1200, 1200 to 1800, >1800	4.78 (3.71–6.18)
PLATO, Wallentin et al[36]	NSTE-ACS (n=9946)	M,R,S	1 (maximum)	<1200, 1200 to 1800, >1800	NA
NSTE-ACS patients, Dominguez-Rodriguez et al[37]	NSTE-ACS (n=255)	M,R,UA	3 (maximum)	1639 (median)	52.3 (7–388.5)
Shock II, Fuernau et al[38]	AMI (n=190)	M	0.1 (maximum)	7662 (median)	1.88 (1.21–2.94)
FRISC-II, Wallentin et al[39]	NSTE-ACS (n=2457)	M,R	2 (maximum)	<1800, ≥1800	NA
NSTE-ACS patients, Dominguez-Rodriguez et al[40]	NSTE-ACS (n=502)	M,R,UA	2 (maximum)	470 to 1765, 1766 to 2995, 2996 to 11 607	6.6 (4.28–10.2)
Västmanland Myocardial Infarction Study, Skau et al[41]	AMI (n=847)	M	6.9 (median)	NA	2.57 (2.31–2.85)
PLATO, Lindholm et al[42]	ACS (n=17 095)	M	1 (maximum)	NA	2.65 (2.17–3.24)

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; ASSENT, assessment of the Safety and Efficacy of a New Thrombolytic; CAD, coronary artery disease; FRISC II, Fast Revascularization during Instability in Coronary artery disease II; GDF-15, growth differentiation factor 15; GUSTO-IV, Global Utilisation of Strategies to Open Occluded Arteries IV; HF, heart failure; ICTUS, Invasive versus Conservative Treatment in Unstable coronary Syndromes; M, mortality; NA, not applicable; NSTE-ACS, non-ST-segment–elevation acute coronary syndrome; PLATO, Platelet Inhibition and Patient Outcomes; PROVE IT-TIMI-22, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction-22 trial; R, recurrent myocardial infarction; RR, relative risk; S, stroke; STEMI, ST-segment–elevation myocardial infarction; UA, unstable angina.

Darapladib Therapy) study [26] (Table 2). Our recent study further validated that GDF-15 is associated with cardiovascular and noncardiovascular death (eg, cancer morbidity) in stable CAD patients with and without previous cancer diagnosis.[30] Furthermore, our study also indicated the independent associations between the GDF-15 and coronary thrombotic events (eg, MI), even after adjusting for other prognostic biomarkers (estimated glomerular filtration rate and left ventricular ejection fraction).

GDF-15 is a biomarker considered for introduction to the clinic. What questions remain to be answered to establish GDF-15 as a clinically useful biomarker? Moreover, is GDF-15 a risk biomarker or a causative risk factor, or more importantly, what are the circumstances under which GDF-15 is just a marker of risk versus a causative factor? Its function as a protective or disease-inducing factor remains largely unknown. The GDF-15 puzzle is a good example of how epidemiological and mechanistic studies can interact successfully. The predictive value persists even a decade later, and the findings discussed above support the hypothesis that GDF-15 is not a consequence of cardiovascular disease or a passive biomarker of the disease process, but in fact plays an active role in the pathophysiology of atherosclerosis and CAD.[45,46] The clinical significance of newly discovered mechanisms can be evaluated and conversely, the mechanisms behind epidemiologically proven associations can be elucidated.

GDF-15 and Inflammation in Atherosclerosis

Potential mechanisms have been suggested for the association of GDF-15 with adverse outcomes in atherosclerosis,

Table 2. GDF-15 related to outcome events in stable CAD

Study	Participants	Outcomes	Follow-Up (y)	Comparisons (ng/L)	RR (95% CI)
Kempf et al[2]	Stable CAD (n=1352)	M	3.6 (median)	1128 (850–1553)	2.7 (2.2–3.3)
Dallmeier et al[25]	Stable CAD (n=1029)	M	10 (median)	1232 (916–1674)	2.80 (1.98–3.37)
Hagstrom et al[26]	Stable CAD (n=14 577)	M	3.7 (median)	1253 (915–1827)	2.63 (1.91–3.63)
Schopfer et al[29]	Stable CAD (n=948)	M	8.9 (mean)	2166 (1589–3057)	2.97 (2.58–3.43)

CAD indicates coronary artery disease; GDF-15, growth differentiation factor 15; M, mortality; RR, relative risk.

including worse baseline cardiac disease severity, inflammation, ischemia, volume overload, and adipokines.[12] Elevated GDF-15 has been shown to promote inflammation and angiogenesis,[47–49] implying that GDF-15 may play an important role in the pathogenesis of atherosclerosis. While GDF-15 is a cardiovascular risk factor, whether GDF-15 contributes directly to atherosclerosis development has not been established and the precise relationships between GDF-15 and atherosclerosis are incompletely understood. GDF-15 was originally identified as a factor overexpressed in activated macrophages to regulate inflammation, which is involved in all stages of atherosclerosis, from its initiation and progression to its thrombotic complications. de Jager et al[49] demonstrate that leukocyte deficiency of GDF-15 improves atherosclerotic plaque stability by impairing macrophage migration and promoting collagen deposition. GDF-15 deficiency in leukocytes is associated with reduced macrophage accumulation in an atherosclerosis model, suggesting a pro-inflammatory role of GDF-15 in atherosclerosis. Moreover, chromatin immunoprecipitation assays confirmed that p53 was recruited to both p53 binding sites 1 and 2 in the GDF-15 promoter in response to CRP.[50] Accordingly, CRP induces GDF-15 expression through the regulation of p53 binding sites in the GDF-15 promoter. Along this line, GDF-15 is involved in orchestrating atherosclerotic lesion progression by regulating apoptotic cell death and IL-6-dependent inflammatory responses to vascular injury.[51] These data suggest an involvement of GDF-15 in the initiation and progression of atherosclerosis. GDF-15 revealed a central role for this factor as a pro-inflammatory cytokine that accelerates atherosclerosis.

GDF-15 is in fact associated with subclinical atherosclerosis.[52] GDF-15 deficiency resulted in a reduction of early atherosclerotic lesion size after 4 weeks on a high cholesterol Western-type diet. After 12 weeks, no differences in lesion size could be detected.[49] It is known that lesions in mice become quite complex with increased duration of feeding.[53] Moreover, GDF-15 expression is significantly higher in acute stages of human plaque rupture (unstable angina pectoris) than in advanced stable lesions (stable angina pectoris). Paradoxically, overexpression of GDF-15 in macrophages significantly attenuates atherosclerotic lesions in the ApoE$^{-/-}$ mouse model of atherosclerosis.[54] GDF-15 is thought to have

anti-inflammatory effects on cells, including cardiomyocytes.[55] Preusch et al demonstrated a proinflammatory plaque phenotype in mice transplanted with bone marrow from GDF-15$^{-/-}$ donors with enhanced macrophage accumulation, suggesting a protective effect of GDF-15 on the atherosclerosis process.[56] However, this effect may contribute to changes in lesion vulnerability such as thinning of fibrous caps and potential plaque rupture. It should, however, be noted that they did not focus on the onset of atherosclerotic changes within the vascular wall such as lipid accumulation in younger mice. It is known as a model of late-stage disease in atherosclerosis and does not show much progress in early stages. To further elaborate on this, de Jager et al investigated the signal transduction cascades for GDF-15. Blockade of TGFβRII, but not TGFβRI/ALK5, abrogated the GDF-15-elicited MCP-1 response, suggesting the role of GDF-15 in the underlying mechanism of atherosclerosis progress. Thus, GDF-15 has a pleiotropic regulatory effect on the inflammatory process, in line with that of other TGF-β family members such as activin-A[57] and TGF-β1.[58] Previous study pointed out that expression of GDF-15 may be upregulated by a variety of proinflammatory stimuli in macrophages including interleukin (IL)-1β, IL-2, and tumor necrosis factor-α.[11] Recent study found a positive association between the IL-1β and CVE,[59] suggesting there is an interleukin-1β/GDF-15-associated immunity pathway resulting in atherosclerosis. Accordingly, the high levels of GDF-15 may result from high levels of monokines such as IL-1β, tumor necrosis factor-α, and CRP. GDF-15 initiates pro- and anti-inflammatory effects on atherosclerosis development and progression, depending on the pathophysiological context and progression stage. GDF-15 functions as a proinflammatory factor in the process of atherosclerosis via TGFβRII signaling, especially in the early stage and acute inflammatory stage, leading to vulnerable plaque, which provides 1 of the possible mechanisms for the atherosclerosis process.

GDF-15 and Angiogenesis

Plaques that are most at risk are characterized by large necrotic cores with a thin fibrous cap. Plaque angiogenesis and intraplaque hemorrhage are important contributors to

unstable lesions.[6,60] Although commonly regarded as separate disease entities, there is a growing recognition that cardiovascular disease and cancer have various similarities with shared common biology and risk factors, including age, diabetes mellitus, hypertension, smoking, physical inactivity, and unhealthy diet. A novel function for GDF-15 was identified as a potent angiogenic factor to be secreted from melanoma cells together with vascular endothelial growth factor to promote vascular development.[61] During angiogenesis, endothelial cells emerge from the quiescent state and undergo progression in the cell cycle. GDF-15 is causally involved in the pathological process of endothelial proliferation and angiogenesis.[9,62] Jin et al revealed the functional effect of GDF-15 on the cell cycle progression of endothelial cells and demonstrated that GDF-15 upregulates expression of cyclins D1 and E in human umbilical vein endothelial cells, leading to a rapid transition from G1 to S phase.[9] GDF-15 has been shown to promote cell viability, invasion, migration, and angiogenesis in HepG2 cells[48] and hypoxic human umbilical vein endothelial cells possibly through inhibiting p53 signaling.[62] Moreover, GDF-15 induced the pro-angiogenic effects through the phosphorylation of Src and its downstream pathways of AKT, MAPK, and NF-κB signaling, implying regulatory roles of GDF-15 in cell proliferation and angiogenesis in atherosclerosis.[47] Intriguingly, proinflammatory factors such as IL-1β, tumor necrosis factor-α, and CRP induce GDF-15 expression in macrophage cells through the regulation of p53 binding sites in the GDF-15 promoter (Figure). GDF-15 promoted macrophage chemotaxis in a strictly CCR2- and TGF-β type II receptors (TGFβRII)–dependent manner in early and advanced atherosclerosis. Accordingly, the GDF-15/TGFβRII/P53 and the GDF-15/NF-κB pathways are the critical mechanisms involved in the angiogenesis and acute inflammation in the unstable atherosclerotic plaque. The functional proatherogenic roles of GDF-15 in lesion progression indicate that besides other TGF-β superfamily members such as TGF-β1 and BMP, interference with GDF-15 may be a useful novel strategy for therapeutic intervention.[63,64]

GDF-15 and Stress in Atherosclerosis

GDF-15 and brain natriuretic peptide are similarly induced by biomechanical stress in isolated rat cardiomyocytes and in the murine heart. GDF-15 is upregulated in response to stressors including in macrophages exposed to oxidized low-density lipoprotein in atherosclerotic carotid arteries.[65] Specific to atherosclerosis, GDF-15 has shown predictive abilities of CAD mortality and composite outcomes in stable CAD and ACS in patients with prevalent cardiovascular risk factors.[2,21,24,28] Recent findings support that GDF-15 is associated with subclinical atherosclerosis as assessed by maximal internal carotid artery intima-media thickness as well as the presence of carotid plaque. Whether GDF-15 is a mediator of cardiovascular disease or upregulated in response to cardiovascular injury remains unclear. After further adjusting CRP and brain natriuretic peptide, the association of GDF-15 with maximum internal carotid artery intima-media thickness and carotid plaque was more robust. This suggests that GDF-15 may reflect an orthogonal pathway associated with cardiovascular disease, the mechanism of which remains unclear.

Roles of GDF-15 in Cancer and Other Diseases

GDF-15 is characterized by a wide tissue distribution pattern with high expression in the prostate and placenta, heart, intestine, liver, kidney, pancreas, colon, lung, brain, and skeletal muscle.[66] It acts as a multifunctional cytokine by controlling numerous physiological and pathological processes. Acting on the hypothalamus and hindbrain, GDF-15 is a key inducer of cancer-related anorexia and weight loss.[67] Moreover, GDF-15 plays an important role in the physiological regulation of energy intake and expenditure, with a more pronounced effect in women than in men.[68] Although several studies suggest antitumoral activity, the protumoral effects of GDF-15 appear to prevail.[12,47,69]

Like the other members of the TGFβ-superfamily, GDF-15 has opposite effects depending on cellular context, disease stage, or microenvironment. GDF-15 has both antitumorigenic and protumoral properties. In fact, these apparently paradoxical data could be explained by a dual role of GDF-15 in cancer progression: inhibition of carcinogenesis in normal tissue at early stages of tumor development and promotion of tumor at late stages of the disease.[70] GDF-15 induces pleiotropic effects in cancer by modulating cancer cell proliferation and chemoprotection but also the tumoral microenvironment (angiogenesis, invasion and metastasis processes, and immunomodulation), as well as more unexpected processes (cancer-induced anorexia). GDF-15 has been implicated in chronic disease, such as rheumatoid arthritis, end-stage renal failure, or diabetes mellitus.[71–73] As for cancer or cardiovascular diseases, GDF-15 plasma concentration was an independent predictor of disease worsening and/or death. The biological processes that could explain such a link are obscure and often not known. A recent study emphasizes the positive effects of GDF-15 on peripheral nerve regeneration.[74] In this case, GDF-15 seems to reduce the number of regenerated axons but it increases the maturation of newly formed ones. This leads to better recovery of sensorimotor function.

Potential Implications of GDF-15 in Atherosclerosis

GDF-15 functions as a direct participant in the atherosclerotic process. Plaque angiogenesis is a physiological response to the increased oxygen demand in the plaque but has adverse effects by facilitating intraplaque hemorrhage and influx of inflammatory mediators. The angiogenesis inhibitor angiostatin reduces plaque angiogenesis, and the secondary reduction of macrophages may have beneficial effects on plaque stability.[75] GDF-15 deficiency contributes to angiogenesis and improves atherosclerotic plaque stability by impairing macrophage migration and promoting collagen deposition. A high level of serum GDF-15 is detected in human atherosclerotic lesions,[49,65] which are broadly proportional to the disease burden. Thus, we speculate that GDF-15 is located in arteriosclerotic lesions or in circulation and promotes atherosclerotic plaque vulnerability by increasing angiogenesis and inflammation. Intriguingly, GDF-15 promotes indirect proinflammatory effects in atherosclerosis[49,51] but mediates anti-inflammatory effects in acute MI by directly inhibiting myeloid cell recruitment.[76] Although it is possible that GDF-15 itself could be causative in the development of ACS,[54] GDF-15 has anti-apoptotic and antihypertrophic properties of in cardiomyocytes subjected to simulated ischemia/reperfusion injury.[77] Notably, the biological effects of GDF-15 are context dependent and may vary with the stage of the disease.[34,36,55,56,76,78–80] In line with these investigations, GDF-15 has been shown to be associated with subclinical atherosclerosis involved in macrophage accumulation in atherosclerosis.[52] Correspondingly, GDF-15 is responsible for early-stage atherosclerotic lesions. Inflammatory factors (IL-1β or CRP) secreted from macrophages induce GDF-15 expression through the regulation of p53 binding sites in the GDF-15 promoter further activates its downstream NF-κB signaling, accelerating the progression of atherosclerosis in the early stage, and promoting the formation of vulnerable plaque. GDF-15 is also linked with endothelial dysfunction and more advanced coronary atherosclerosis, suggesting the regulatory roles of GDF-15 in chronic myocardial and vascular damage in the late stage of the atherosclerosis process.[19] More basic research into the pathobiological features of GDF-15 is needed to explore the mechanism related to the risk of new atherosclerosis and recurrent ischemic events after ACS.

Potential Implications for GDF-15 in ACS and CAD

GDF-15 appears to be a very consistent marker of adverse long-term outcome in ACS. However, may GDF-15 be used to identify groups of patients who will or will not benefit from various interventions or treatments? Are there any treatments for which monitoring of GDF-15 concentrations might be useful to guide the treatment (dose and/or duration)? Several studies illustrate the potential of the marker to risk stratify unselected contemporary patient populations treated outside clinical trials. In a recent investigation that compared the incremental prognostic value of 9 biomarkers on top of the GRACE (Global Registry of Acute Coronary Events) score in unselected patients with NSTE-ACS, GDF-15 emerged as the most promising biomarker.[34] Underscoring its potential to add information to what is clinically available, GDF-15 also added discriminatory information to GRACE when hs-cardiac troponin T was considered as an additional continuous variable. In accordance with previous observations, we noted in our population-based cohort that addition of GDF-15 to standard cardiovascular risk factors resulted in modest but significant improvements in the C-statistic (discrimination) as well as reclassification, as measured by the integrated discrimination improvement and net reclassification improvement for all-cause death and cardiovascular death.[30] In addition, GDF-15 predicted all-cause mortality more accurately independently of hs-cardiac troponin T and N-terminal pro-brain natriuretic peptide in patients with acute pain.[81] The PLATO trial showed that GDF-15 contributes information on the magnitude of benefit by a successful intervention such as ticagrelor regardless of invasive or noninvasive management.[36] The FRISC-II trial supported that a high concentration of the biomarker GDF-15 implies heightened risk and functions as a useful identification of patients who might expect the longest postponement of death or MI with an early invasive strategy.[39] Thresholds offer a convenient way to classify patients into risk categories that may be linked to treatment decisions. However, the use of thresholds may reduce statistical power given the continuous association of GDF-15 with cardiovascular risk. Alternatively, GDF-15 might be incorporated as a continuous variable into established or novel risk scores that can be presented as nomograms or applications on (handheld) electronic devices. Therefore, in a setting with a need for prioritization among different patients with NSTE-ACS for early invasive procedures, direct access to treatment for patients with elevated troponin, in addition to a fast track for those with high GDF-15, might be a useful strategy. New algorithms for decision support in ACS are currently under evaluation, including variables such as troponin and GDF-15 showing significant interactions with the effects of an early invasive treatment strategy. More importantly, there are medical therapies that reduce the risk of cardiovascular disease and cancer. For example, use of daily aspirin for the primary prevention of major CVE reduces the incidence of cancer and cancer mortality, although more research is required to identify which individuals are likely to benefit most.[82] In previous studies of patients with NSTE-ACS, GDF-15 has been found to predict future events and

contribute to the identification of high-risk patients with a benefit of an early invasive strategy. Thus, GDF-15 might be of clinical value in refining risk stratification and tailoring treatment of patients with ACS. GDF-15 provides unique information on underlying disease processes leading to a raised risk of severe events, eg, fatal CVE and death.[27] Moreover, the previous studies published on the functional proatherogenic role of GDF-15 in lesion progression indicate that besides other TGF-β superfamily members such as TGF-β1 and BMP,[83] interference with GDF-15 may be a useful novel strategy for therapeutic intervention.[48,51] Therefore, circulating levels of GDF-15 are suggested as a prognostic marker to improve risk stratification of patients with ACS, along with benefit from treatment with a high-dose, highly efficient statin. Increased GDF-15 plasma concentrations at the time of PCI and stent implantation might classify high-risk patients with ACS who benefit from high-dose, highly efficient statins, implicating that high-dose statins are more effective in high-risk patients and obtaining GDF-15 may help identify these patients.[45,46]

Conclusions and Future Directions

GDF-15 functions as a cardiovascular risk and outcome marker and appears to be a direct participant in the atherosclerotic process. GDF-15 is responsible for vulnerable atherosclerotic lesions by proinflammation and angiogenesis, accelerating the progression of atherosclerosis especially in the early stage, subsequently contributing to promotion of the vulnerable plaque formation. Moreover, GDF-15 has been found to predict CVE and identify high-risk patients with a benefit of an early invasive strategy. The importance of the GDF-15/TGFβRII/P53 and the GDF-15/NF-κB signaling pathways in the cardiovascular system sparked hopes that manipulating its pathophysiological activity could provide novel therapeutic agents for atherosclerosis and CAD. In fact, the clinical and experimental studies clearly support a physiological and pathophysiological role for the GDF-15 system in atherosclerosis and CAD. Targeting the GDF-15 pathway represents a novel therapeutic approach against atherosclerosis and CAD that will increase our understanding of the pathophysiology of these diseases.

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