CHEMERIN: A POTENTIAL TARGET IN CORONARY ARTERY DISEASE – A REVIEW

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Abstract
Currently, Coronary Artery Disease (CAD) is considered as a major ailment in humans with widespread prevalence. CAD also accounts for high mortality rates around the world that involves several known risk factors. Recently, it was discovered that epicardial adipose tissue (EAT) and its secretory adipokines play an imperative role in the development of CAD. Among the secretory adipokines, chemerin, a serpentine chemotactic agonist has been identified as one of the factor which contributes for the progression of CAD. Since serum chemerin levels are elevated during CAD condition, it is being considered to be a valiant marker but then the chimeric property of chemerin is yet to be explored. Though chemerin has been identified as one of the factors responsible for the development of CAD, it is still being studied at the marker level. This review aims to study whether chemerin can only be used as a marker or can it also be used as a novel target for treating or suppressing or delaying the progression of coronary artery disease.

Keywords: Chemerin; coronary artery disease; adipokines; marker; target

1. Introduction
1.1 Coronary artery disease (CAD) known to be the disease of rich in past, has been classified by World Health Organization as the disease of 21st century with high prevalence that can occur to almost all population without rationality. CAD can be characterized as a disease with high morbidity, mortality, reduced quality of life and substantial economic burden. Even though age, gender, race and genes are responsible for the occurrence of CAD, risk factors such as dietary habits, diabetes, high blood pressure, cholesterol; smoking, chronic kidney disorders, obesity and sedentary lifestyle can also lead to the development of premature CAD. Presently, CAD has developed as an epidemic and is no longer restricted to geographical area or sex or age or socio economic boundaries. In comparison with western countries and other parts across the world, Asia, has raised itself as a hub of CAD with increased premature mortality rates. It has been studied that in low and middle income countries nearly 80% of deaths happens due to cardiovascular diseases.
non-calcified plaques was seen elevated\textsuperscript{32} and also a study shows that differential expression pattern of the adipokines such as adiponectin, leptin, vaspin, visfatin and chemerin that are locally produced adipokines affect the atherosclerotic process in different locations\textsuperscript{33}. This review will focus on the chemokine chemerin and study whether it can be used only as a marker or can it also be used as target for the treatment of Coronary Artery Disease (CAD).

2. CHEMERIN:

Chemerin, also known as retinoic acid receptor responder protein 2 (RARRES2) or tazarotene induced gene 2 protein (TIG2) is a 14KDa, 137 amino acid residues containing active form derived from an inactive precursor pro-chemerin containing 143 amino acid residues. The inactive pro-chemerin is activated by cleavage of 6 amino acid peptide in the C-terminal end by serine proteases of the coagulation, fibrinolytic, and inflammatory cascades\textsuperscript{8}. The active form binds to a G-PROTEIN COUPLED RECEPTOR (GPCR) namely ChemR23, also known as chemokine receptor like-1 (CMKLR-1) that is expressed in macrophages and DC\textsuperscript{8}. Chemerin and its receptor chemR23 play an important role in recruitment of blood NK cells and strongly connect chemerin to be a key factor for co-localization of NC cells and DC’s in peripheral pathologic tissues and thus provides an evidence of the incidence also occurring in vivo\textsuperscript{34}. Chemerin also plays a significant role in adipocyte differentiation, in stimulating lipolysis, in pathogenesis of obesity and metabolic syndrome\textsuperscript{10}.

2.1 Scientific Approaches:

Chemerin, the chemokine expresses its chimeric nature through an orphan GPCR, CCR2L which provides a distinctive mechanism through which chemerin enhances inflammation. Also chemerin derived peptides have anti-inflammatory properties that may be involved in both initiation and resolution of inflammation\textsuperscript{11}. Cash et al. for the first time demonstrated that chemerin exhibits both anti-inflammatory and pro inflammatory effects. The results established that classically activated macrophages have the capability to convert chemerin into potent anti-inflammatory peptides by cysteine protease mediated cleavage of the parent molecule involving calpains and cathepsin S\textsuperscript{12}.

Zabel et al. disclosed the presence of a silent chemokine receptor – like GPCRs, which binds with its ligands and present it to the signaling receptors expressed on the neighboring cells. This proves that chemerin is a multifunctional protein having both stimulatory and inhibitory signaling capabilities, whereas cell-bound chemerin sends the stimulatory signals by bridging cells that express the silent receptor with those expressing the ChemR23 receptor\textsuperscript{13}.

Chemerin, being a secretory product of adipose tissue, many researchers have correlated its circulating levels with many disease conditions. Pfau and his co-workers showed that chronic hemodialysis (CD) is an independent predictor of chemerin. Serum levels of chemerin had been positively correlated with Body Mass Index (BMI), fasting insulin (FI), leptin and C-reactive protein (CRP)\textsuperscript{14}. Clement et al revealed that after bariatric surgery elevated plasma chemerin levels came down while the weight, fat mass loss, improvement of insulin sensitivity and inflammatory markers increased. They concluded that plasma chemerin levels are correlated with BMI, insulin resistance, adipose tissue inflammation, hepatosteatosis and liver inflammation\textsuperscript{15}.

Serum chemerin levels were elevated in patients with inflammatory bowel disease (IBD) especially in Crohn’s disease\textsuperscript{16}. A pilot study conducted by Stejskal and his team on Caucasian population concluded that serum chemerin levels could serve as an independent marker for metabolic syndrome where chemerin is said to play a vital role in the pathogenesis of the metabolic syndrome\textsuperscript{17}. Experiments in Psammomys obesus, an animal model of obesity and Type 2 Diabetes clearly demonstrate a strong relationship between chemerin and several key aspects of the metabolic syndrome\textsuperscript{18}. Apart from this, chemerin also acts as a mediator between obesity and vascular inflammation\textsuperscript{19} and is also used for prognosis in patients with non-small cell lung cancer\textsuperscript{20}. Albanesi and his group correlated chemerin expression with psoriatic skin lesions and also with plamocytoid dendritic cell recruitment\textsuperscript{21}.

2.2 Chemerin: Heart, EAT and CAD:

Clinical studies conducted by Lehrke et al, 2009 on 303 consecutive Caucasian subjects suggested that serum chemerin levels are strongly associated with the inflammatory markers and the components of metabolic syndrome but is not associated with coronary atherosclerotic plaque morphology\textsuperscript{22}. Most recently, Becker and his co-workers reported that long-term over expression of chemerin, did not significantly affect the extent of atherosclerotic lesion area in vivo\textsuperscript{24}. A study conducted in Korean patients by Yu-Jin...
Hah and his co-workers explains that the serum chemerin levels had significant correlations with cardiometabolic parameters and severity of coronary artery stenosis in Korean patients with CAD23.

However, studies conducted by Xiuying Gao and his team suggested that expression of chemerin mRNA and protein are higher in Epicardial Adipose Tissue (EAT) from Han Chinese CAD patients. They also concluded that the severity of CAD is associated with the level of chemerin mRNA in EAT rather than its circulating level23. Yet another study discusses that chemerin secreted locally by epicardial adipose tissue increases the risk and progression of CAD23. Likewise, several studies correlates that chemerin is closely associated with heart and in the progression of coronary artery disease.

2.3 For treatment: Though chemerin is considered as a marker for coronary artery disease, it can still be used as a target for treating CAD and also as a drug for various other inflammatory disorders. David R Greaves and his team had invented C-terminal end of chemerin protein which can be used in the treatment of inflammation and/or endotoxic shock and or treatment of wounds and/or reduction of levels of inflammatory chemokines in a subject26 Trevor et al, had invented pyrrolidinone carboxamide derivatives that can be used as a therapeutic agent for treating various inflammatory diseases and metabolic syndromes including but not limited to obesity and cardiovascular diseases by modulating ChemR23, a GPCR to chemerin 27. Recently conducted studies on adipocytes reveal that expression of chemerin is regulated by pro-inflammatory stimuli in adipocytes but not in hepatocytes. Upon treatment of the stimulated adipocytes with aspirin, chemerin expression did not reduce which suggest that aspirin reduces inflammation in adipose tissue and in turn it reduces adipocyte expression of chemerin 35. This demonstrates that chemerin secreted by adipose tissue, especially Epicardial adipose tissue establishes itself as a factor which is actively involved in the progression or development of CAD.

Conclusion
It is apparent from the present review that properties of the chimeric protein chemerin had been explored at the marker level alone. Nevertheless researchers have also suggested that chemerin can be used as potential therapeutic agent or inflammatory agent or can also used as a target in certain diseases or disorders. At present only few evidences are available for contemplating chemerin as a target or treatment in inflammatory disorders such as CAD. Nonetheless, a comprehensive and/or a detailed experimental study are yet to be accounted to explain the pro-inflammatory and anti-inflammatory roles of chemerin. This will provide new insights in therapeutic developments for many disorders and also for considering chemerin as a target for treating coronary artery disease (CAD).

References
1. Heart Failure Society of America. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. J Card Fail 2006; 12(1):10-38.
2. Sathish Kenchaiah, Jane C. Evans, Daniel Levy, Peter. W. F. Wilson, Emelia J. Benjamin, Martin G. Larson, et al. Obesity and the risk of heart failure. N Engl J Med 2002; 347(5): 305-13.
3. Jason H. Cole and Laurence S. Sperling. Premature coronary artery disease: Clinical risk factors and prognosis. Curr. Ahero rep 2004; 6(2): 121-125.
4. Karen Okrainec, Devi K Banerjee, Mark J Eisenberg. Coronary artery disease in the developing world. American Heart Journal 2004; 148(1): 7-15.
5. Meenakshi Sharma, Nirmal Kumar Ganguly. Premature coronary artery disease in Indians and its associated risk factors. Vascular Health and Risk Management 2005; 1(3): 217–225.
6. Jin-Won Jeong, Myung Ho Jeong, Kyeeong Ho Yun, Seok Kyu Oh, Eun Mi Park, Yun Kyung Kim et al. Echocardiographic Epicardial Fat Thickness and Coronary Artery Disease. Circ J 2007; 71: 536-539.
7. Tomasz Mazurek, LiFeng Zhang, Andrew Zalewski, John D. Mannion, James T. Diehl, Hwyda Arafat et al. Human Epicardial Adipose Tissue Is a Source of Inflammatory Mediators. Circulation 2003; 108: 2460-2466.
8. Brian A. Zabel, Samantha J. Allen, Paulina Kulig, Jessica A. Allen, Joanna Cichy, Tracy M. Handel et al. Chemerin Activation by Serine Proteases of the Coagulation, Fibrinolytic, and Inflammatory Cascades. The journal of biological chemistry 2005; 280(41): 34661–34666.
9. Iannone and Lapadula. Chemerin/ChemR23 pathway: a system beyond chemokines. Arthritis Research & Therapy 2011; 13:104.
10. Bozaoglu K, Bolton K, McMillian J, Zimmet P, Jowett J, Collier G, Walder K, Segal D. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 2007; 148(10):4687-94.
11. Teizo Yoshimura and Joost J. Oppenheim. Chemerin reveals its chimeric nature. J. Exp. Med 2008; 205(10): 2187-2190.
12. Jenna L. Cash, Rosie Hart, Andreas Russ, John P.C. Dixon, William H. Colledge, Joanne Doran et al.
Synthetic chemerin-derived peptides suppress inflammation through ChemR23. J. Exp. Med. 2008; 205(4): 767-775.

13. Zabel, B.A., A.M. Silverio, and E.C. Butcher. Chemokine-like receptor 1 expression and chemerin-directed chemotaxis distinguish plasmacytoid from myeloid dendritic cells in human blood. J. Immunol. 2005; 174: 244 – 251.

14. Dörte Pfau, Anette Bachmann, Ulrike Lüssner, Jürgen Kratzsch, Matthias Blüher, Michael Stumvoll et al. Serum Levels of the Adipokine Chemerin in Relation to Renal Function. Diabetes Care 2010; 33:171–173.

15. Henriek Sell, Adeline Divoux, Christine Poitou, Arnaud Basdevant, Jean-Luc Bouillon, Pierre Bedossa et al. Chemerin Correlates with Markers for Fatty Liver in Morbidly Obese Patients and Strongly Decreases after Weight Loss Induced by Bariatric Surgery. J Clin Endocrinol Metab 2010; 95(6): 2892–2896.

16. Johanna Weigert, Florian Obermeier, Markus Neumeier, Josef Wanninger, Michael Filarsky, Sabrina Bauer et al. Circulating Levels of Chemerin and Adiponectin Are Higher in Ulcerative Colitis and Chemerin Is Elevated in Crohn’s Disease. Inflamm Bowel Dis 2010; 16: 630–637.

17. Stejskal D, Karpisek M, Hanulova Z, Svestak M. Chemerin is an independent marker of the metabolic syndrome in a Caucasian population—a pilot study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2008; 152(2): 217-21.

18. Kiymet Bozaoglu, Kristy Bolton, Janine McMillan, Paul Zimmet, Jeremy Jowett, Greg Collier et al. Chemerin Is a Novel Adipokine Associated with Obesity and Metabolic Syndrome. Endocrinology 2007; 148(10): 4687–4694.

19. Kathrin Landgraf, Daniela Friebe, Tina Ullrich, Jürgen Kratzsch, Kathrin Dittrich, Gunda Herbert et al. Chemerin as a Mediator between Obesity and Vascular Inflammation in Children. JCEM 2012; 97: E556-E564.

20. Shen Zhao, Chao Li, Yun-bin Ye, Feng Peng and Qiang Chen. Expression of Chemerin Correlates With a Favorable Prognosis in Patients with Non-Small Cell Lung Cancer. Lab Medicine 2011; 42: 553-557.

21. Cristina Albanesi, Claudia Scarponi, Sabatino Pallotta, Roberta Daniele, Daniela Bosio, Stefania Madonna et al. Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. J. Exp. Med. 2008; 206(1):249-258.

22. Michael Lehrke, Alexander Becker, Martin Greif, Renee Stark, Rüdiger P Laubender, Franz von Ziegler et al. Chemerin is associated with markers of inflammation and components of the metabolic syndrome but does not predict coronary atherosclerosis. Eur J Endo 2009; 161: 339–344.

23. Xiuying Gao, Shuhua Mi, Fuzhuang Zhang, Fengying Gong, Yongqiang Lai, Feng Gao et al. Association of chemerin mRNA expression in human epicardial adipose tissue with Coronary atherosclerosis. Cardio Diabet 2011; 10: 87.

24. Becker M, Rabe K, Leberherz C, Zugwurst J, Göke B, Parhofer KG et al. Expression of human chemerin induces insulin resistance in the skeletal muscle but does not affect weight, lipid levels, and atherosclerosis in LDL receptor knockout mice on high-fat diet. Diabetes 2010; 59: 2898-2903.

25. Yu-Jin Hah, Nam-Keong Kim, Mi-Kyung Kim, Hye-Soon Kim, Seung-Ho Hur, Hyuck-Jun Yoon et al. Relationship between Chemerin Levels and Cardiometabolic Parameters and Degree of Coronary Stenosis in Korean Patients with Coronary Artery Disease. Diabetes Metab J 2011; 35:248-254.

26. David R.Greaves, Andreas Russ and Jenna L. Cash. Treatment of inflammation and/or endotoxic shock. US publication 20100150990. 2010 Jun.

27. Charvat TT, Chu H, Krasinski A. Pyrrolidine carboxylate derivatives as Chemerin-R (ChemR23) modulators. WIPO publication 2011035332. 2011 May.

28. World Health Organization, Fact Sheet 2010.

29. Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends Endocrinol Metab 2011; 22(11):450-7.

30. Zabel BA, Allen SJ, Kulig P, Allen JA, Cichy J, Handel TM et al. Chemerin activation by serine proteases of the coagulation, fibrinolytic, and inflammatory cascades. J Biol Chem 2005; 280(41): 34661-6.

31. Yoshimura T, Oppenheim JJ. Chemerin reveals its chimeric nature. J Exp Med 2008; 205(10): 2187-90.

32. Alexopoulos N, McLean DS, Janik M, Arepalli CD, Stillman AE, Raggi P. Epicardial adipose tissue and coronary artery plaque characteristics. Atherosclerosis 2009; 210(1):150-4.

33. Sofia G.Spiroglou, Christos G. Kostopoulos, John N. Varkis and Helen H. Papadaki. Adipokines in periaortic and Epicardial adipose tissue: Differential expression and relation to atherosclerosis. J. Atheroscler Thromb 2010; 17: 115-130.

34. Silvia Parolini, Amerigo Santoro, Emanuela Marcenaro, Walter Luini, Luisa Massardi, Fabio Facchetti et al. The role of chemerin in the colocalization of NK and dendritic cell subsets into inflamed tissues. Blood 2007; 109(9): 3625-3632.

35. M. Herova, M. Schmid, M. Hersberger. Low Dose Aspirin Reduces Plasma Chemerin Levels in Coronary Artery Disease Patients Through Reduction of Adipose Tissue Inflammation. Clinical Chemistry and Laboratory Medicine, Swiss MedLab Abstracts; 2012 May 5; Zurich