Ivanov et al., Atheroscler Open Access 2022, 7:4

Atherosclerosis: Open Access

Review Article Open Access

Immune Cell Diversity in Atherosclerotic Plaque

Ivanov S[1]*, Arvand Haschemi[1] and Alexandre Gallerand[2]

[1]Department of Laboratory Medicine, Medical University of Vienna, 1090, Vienna, Austria
[2]Universit´e Cˆ ote D'Azur, INSERM, C3M, Nice, France

Abstract

Metabolism performs a key position in controlling immune phone functions. In this review, we will talk about the range of plaque resident myeloid cells and will focal point on their metabolic needs that ought to replicate on their particular intraplaque localization. Defining the metabolic configuration of plaque resident myeloid cells in accordance to their topologic distribution should furnish solutions to key questions concerning their features and contribution to disease development.

Keywords: Monocyte; Macrophage; Foamy cells; Immuno metabolism; Glucose; Atherosclerosis

Introduction

Atherosclerosis is a persistent inflammatory sickness characterised by the accumulation of lipids and immune cells in the intima of blood vessels. Atherosclerosis is the underlying reason of cardiovascular events such as myocardial infarctions and strokes, that collectively are responsible for 17.9 million deaths per/yr international (World Health Organization). Atherosclerotic plaque development is preferred in prerequisites of hypercholesterolemia and dyslipidemia. Its improvement initiates when intima-resident macrophages uptake extra lipids and structure foam cells [1]. Subsequent plaque development is based on a steady inflow of monocytes from the blood circulation that fuels plaque macrophage accumulation [1]. In the final two decades, advances in the discipline of atherosclerosis have recognized myelopoiesis, plaque macrophage proliferation and efferocytosis as key factors defining each atherosclerosis development and regression. More recently, it grew to become clear that these parameters are influenced by way of immune cellphone metabolism. The atherosclerotic lesion varieties a complicated micro-environment defined, at least in part, with the aid of its developmental pattern. Newly recruited monocytes are highly motile cells, positioned shut to the lumen. On the different hand, macrophages are sessile and located deeper inside the plaque [2], where particular vitamins ought to hypothetically be scarce, and where necrotic cores develop. Metabolite availability consequently seems as an additional achievable regulator of plaque myeloid mobile metabolism and functions, relying on the cell's intra-plaque localization. Here, we discuss the metabolic legislation of macrophage features and inflammatory houses inside the plaque.

Pioneering research carried out in pre-clinical fashions and human subjects detected the presence of immune cells in atherosclerotic lesions. Multiple immune cells consisting of T cells, each CD4+ and CD8+, B cells, macrophages, monocytes and dendritic cells (DC) had existed in plaques [3-7]. These early reviews used immunostaining and microscopy to determine the mobile composition of the plaque. The fundamental problem of this science is the confined wide variety of markers that ought to be concurrently used to precisely outline the particular nature of plaque-residing cells. More recently, glide cytometry analysis, offering the possibility to significantly prolong the range of membrane markers simultaneously investigated, validated that plaque mobile composition was once more complex than in the beginning described. The presence of tertiary lymphoid organs, buildings enriched in T cells that increase in the vessel adventitia adjoining to plaques [8], may want to additionally make contributions to plaque immune cell contamination in float cytometry analyses. Indeed, this method does not supply insights about the unique intra-plaque localization of the diverse immune cells. Intra-tissue localization is necessary considering the fact that it could have an have an effect on on oxygen and metabolites furnish and consequently on immune telephone metabolism and activation country inside the plaque.

Single-cell RNA sequencing (scRNA seq) analyses similarly enriched our understanding about the phenotypic range of mouse and human plaque-residing immune cells [1, 9-13]. These research published that plaque mobile composition was once impressively complicated and contained many numerous myeloid and lymphoid cells. Macrophages had been the most abundant cells in the plaque. Several wonderful macrophage and monocyte subsets have been recognized in the plaque of atherogenic (LdlR-/- and ApoE-/-) mice and patients. Initially described as a key function of superior lesions, foamy macrophages, a populace of lipid-laden cells, were attributed a pro-inflammatory position mediated by means of the launch of cytokines and chemokines [14,15]. This dogma was once challenged when scRNA seq analysis established that monocytes and inflammatory macrophages, rather than foamy cells, had been enriched in mRNA encoding for pro-inflammatory mediators inclusive of il1β, il12, tnfα, ccl2 and cxcl2 [10].

Two predominant mechanisms account for lesion boom relying on the plaque stage development. Early lesions are frequently sustained through monocyte recruitment from the blood circulation and their nearby retention. In contrast, in superior plaques, in situ macrophage proliferation favors plaque development [12]. Whether these two strategies require a precise metabolic rewiring and count number on different metabolic pathways stays to be established. Macrophage intraplaque proliferation correlates with plasma lipoprotein ranges. Lowering plasma lipid stages and genetic ablation of lipoprotein uptake receptors in macrophages (Msr1 and CD36) lowered plaque macrophage proliferation fee [13]. However, the underlying molecular

***Corresponding author:** Ivanov S, Department of Laboratory Medicine, Medical University of Vienna, 1090, Vienna, Austria, E-mail: Stoyan.i@unice.as

Received: 28-Jun-2022, Manuscript No. asoa-22-76100;**Editor assigned:** 30-Jun-2022, PreQC No. asoa-22-76100 (PQ); **Reviewed:** 14-Jul-2022, QC No. asoa-22-76100; **Revised:** 17-Jul-2022, Manuscript No. asoa-22-76100 (R); **Published:** 25-Jul-2022, DOI: 10.4172/asoa.1000179

Citation: Ivanov S, Haschemi A, Gallerand A (2022) Immune Cell Diversity in Atherosclerotic Plaque. Atheroscler Open Access 7: 179.

and metabolic mechanisms continue to be unknown. A latest find out about the use of multi-isotope imaging mass spectrometry discovered that plaque proliferating cells used preferentially glucose in evaluation to neighboring non-proliferating cells [15]. Surprisingly, foamy cells had been distinctly glucose consuming and this used to be correlated with extended proliferation. This remark is instead shocking due to the fact foamy cells are characterised by massive lipid accumulation, and they rather categorical genes associated with lipid metabolism. Whether glucose or lipids serve as the fundamental strength supply for foamy cells stays to be defined. To higher apprehend the metabolic configuration of plaque resident myeloid cells and foamy cells in particular, this set of records may want to be complemented the use of a new flow cytometry-based method named SCENITH that has currently been described [2]. This strategy gives insights into cell metabolic status with a single-cell resolution, permitting the evaluation of multiple cell kinds contained in a given sample. Although this approach requires relatively low numbers of cells, the evaluation of quiescent or overly-stressed aortic cells after tissue digestion should be challenging.

Heterogeneity and metabolic manage of macrophages and monocytes during atherosclerosis. Metabolism emerged as a central regulator of macrophage and monocyte functions. Indeed, metabolic diversifications modulate key macrophage features along with cytokine production, efferocytosis and phagocytosis (for overview). In vitro studies, the usage of either interleukine-4 (IL-4) or lipopolysaccharide (LPS)/interferon (IFN) γ stimulation led to mimicry of precise macrophage activation states (M1 and M2). These easy fashions had been largely used to define macrophage metabolic adaptation to exterior stimuli.

Anti-inflammatory (M2-like) macrophages show off a mitochondrial oxidative metabolism whilst pro-inflammatory (M1-like) macrophages are characterised by way of a glycolytic metabolism. More than simply another polarization marker, metabolic rewiring is a key participant in these differentiations, and interfering with glucose flux or mitochondrial fitness prohibits M1 and M2 polarization respectively. Nevertheless, whilst such in vitro polarization fashions have fruitfully introduced ahead the significance of metabolism in immune phone selection processes, their translation to telephone selections interior complicated environmental prerequisites is not straightforward.

In athermanous plaque, recently generated scRNA-seq datasets highlighted the co-existence of several distinct populations of pro-inflammatory and anti-inflammatory macrophages and the expression of canonical M1 or M2 macrophages was shared by one or the other population (Figure 1). Canonical M2 markers (mrc1, clec10a, mgl2) prevailed in plaque resident macrophages in comparison to M1 (cd11c, il1β, ccl2) markers. Surprisingly, M2-like macrophages, supposed to have an anti-inflammatory function, displayed a pro-inflammatory transcriptomic signature. These cells highly expressed the mRNAs encoding for pro-inflammatory cytokines (il1β, tnfα) and chemokines (ccl2, cxcl2 and cxcl1). The clinical significance of inflammation, and namely IL-1β, during cardiovascular diseases was perfectly illustrated by the CANTOS trial. The abundance of M2-like macrophages in plaque is surprising because local presence of IL-4 and IL-13 is limited. IL-13 levels in plaques are below the detection limit, while IL-4 concentration is also low Similarly, the impact of IFNγ on plaque macrophage phenotype appears minimal, as myeloid-specific IFNγ receptor deficiency did not alter atherosclerosis development in LdlR-/- mice. Attempts have been made to explore metabolite impact on macrophage activation in vitro. Kratz and colleagues reported that macrophages stimulated with a combination of insulin, glucose and palmitate show an activated phenotype with traits of both M1 and M2 polarization. These cells were named "metabolically activated macrophages" and showed enhanced expression of the inflammatory cytokines TNFα, IL-1β and IL-6. On the other hand, M2 markers were globally unaffected while M2-associated lipid metabolism-related genes were induced in metabolically activated macrophages. Thus, one might consider that locally available metabolites, in combination with metabolic reprogramming induced by M1/M2- polarizing cytokines, could contribute to a specific and spatially defined metabolism and activation state of macrophages during plaque initiation and progression. 1.3. Metabolites and associated pathways mediating macrophage activation 1.3.1. Glucose and cellular carbohydrate metabolism Glucose metabolism plays a central role in macrophage functional adaptation. Pioneering work revealed M1- and M2-like macrophage specific glucose fluxes into the two major pathways of cellular carbohydrate metabolism, namely glycolysis and the pentose phosphate pathway (PPP). Glucose utilization by glycolysis generates energy in form of ATP and crucial intermediates, which can act as substrates for other metabolic pathways. This includes pyruvate, which can be further converted to lactate or Acetyl-CoA, two major metabolites important for macrophage metabolic adaptations. Another example is glycolysis-derived serine generation to sustain cellular one-carbon metabolism,

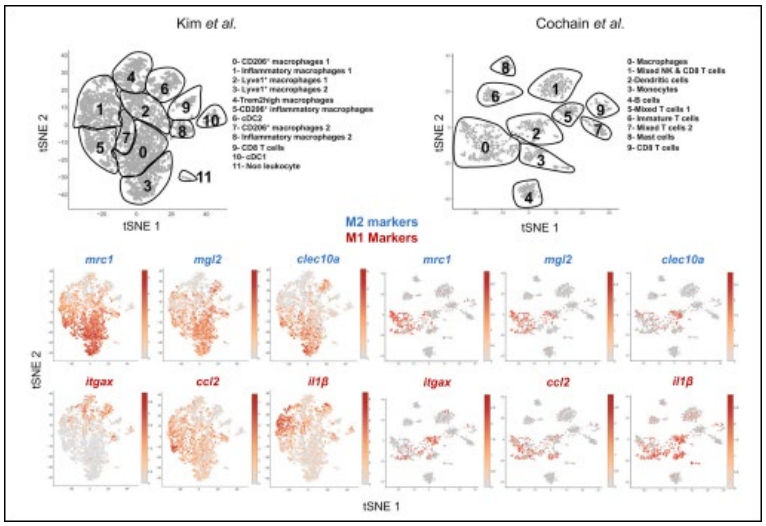

Figure 1: Single-cell analysis of plaque immune cell activation markers.

which is regulating epigenetic reprogramming during macrophage activation. Glucose utilization by the PPP is crucial for generating the required redox power by the formation of NADPH, in order to sustain macrophage functions such as ROS handling and anti-oxidative protection by the generation of reduced glutathione. NADPH is also a critical co-factor for lipid metabolism and other metabolic branches as it acts similar to ATP as a universal energy carrier, which is used by many different enzymes throughout the metabolic networks of cells. Also, redox-sensitive protein signaling during macrophage activation is dependent on PPP activity. Another hallmark of the PPP is to provide pentose molecules, which can serve as precursors for nucleotide metabolism or become reconverted to glycolytic intermediates in the non-oxidative branch of the PPP. We recently comprehensively discussed the function and distribution of key enzymes involved in those two pathways to atherosclerosis development. One critical factor for this metabolic system in macrophages, and in immune cells in general, is glucose uptake mediated by the membrane transporter Glut1 (slc2a1) and subsequent phosphorylation by carbohydrate kinases. Even though macrophages have been suggested to express several Glut-family members, the functional significance of Glut1-mediated glucose uptake was illustrated by the selective Glut1 ablation leading to compromised glucose entry. Under inflammatory conditions, more particularly in a context of atherosclerosis, macrophages display increased glucose metabolism and Glut1 expression. Macrophage-specific Glut1-deficiency greatly affected glycolysis and the PPP, resulting in decreased metabolite content. Interestingly, Glut1-deficiency also led to an increase in the level of some of the metabolites in the aforementioned pathways, including 2- and 3-phosphoglycerate, when compared to control cells. This observation suggests that compensatory pathways were able to restore, at least partially, the absence of glucose entry in macrophages and generate metabolic blocks in glycolysis and the PPP independently of extracellular glucose. However, Glut1-macrophage deletion translated into defective efferocytosis and increased plaque necrotic core area. Whether myeloid-cell specific Glut1 deletion also affects monocyte plaque recruitment and local proliferation, on top of efferocytosis, remains to be documented. It is currently unknown if CCR2 expression, the key chemokine receptor allowing for monocyte recruitment into the growing plaque, is modulated by glucose metabolism. This information will provide a better understating on how Glut1-mediated glucose flux contributes or prevents disease progression. Glucose metabolism was further demonstrated to increase bone marrow hematopoiesis and monocyte generation, thus leading to augmented blood monocyte counts. Monocytosis, high circulating monocyte numbers, is an independent risk factor during atherosclerosis development and managing normal blood monocyte levels is a therapeutic avenue. However, interfering with cellular glucose metabolism of macrophages may also adversely alter efferocytosis efficiency and necrotic core development. Another key aspect of glucose utilization for macrophage functions is the balance of glycolysis and the PPP, which appears to adapt in the course of immune activation to sustain specific metabolic demands of the cells in a timely manner These two pathways are highly interconnected by sharing crucial intermediates and their interfaces appear as highly regulated in macrophages. M1 activated macrophages specifically express isoform 3 of 6-phosphofructo-2-kinase B (PFKFB3) resulting in increased glycolytic flux. Deficiency of PFKFB3 reduces glycolysis and shifts glucose utilization towards the PPP. Regulations of enzyme activities forming the oxidative branch of the PPP are critical for inflammatory activation of macrophages, as independently shown for G6PD or for PDG during hypercholesterolemia [2].

References

1. Ross R (1986) The pathogenesis of atherosclerosis-an update. New Eng J Med 314: 488-500.
2. Duval C, Chinetti G, Trottein F, Fruchart JC, Staels B (2002) The role of PPARs in atherosclerosis. Trends in molecular medicine 8: 422-430.
3. Libby P, Ridker PM, Maseri A (2002) Inflammation and atherosclerosis. Circulation105: 1135-1143.
4. Google Scholar, Cross Ref
5. Falk E (2006) Pathogenesis of atherosclerosis. Exp Clin Cardiol 47: C7-C12.
6. Hansson GK, Hermansson A (2011) The immune system in atherosclerosis. Nat Immunol 12: 204-212.
7. Italis A, Shantsila A, Proietti M, Kay M, Olshansky B, et al. (2021) Peripheral arterial disease in patients with atrial fibrillation: the AFFIRM study. Am J Med 134: 514-518.
8. Rothwell PM (2008) Prediction and prevention of stroke in patients with symptomatic carotid stenosis: the high-risk period and the high-risk patient. Eur J Vasc Endovasc Surg 35: 255-263.
9. Katsi V, Georgiopoulos G, Skafida A, Oikonomou D, Klettas D, et al. (2019) Non cardioembolic stoke in patients with atrial fibrillation. Angiology 70: 299-304.
10. Ugurlucan M, Akay MT, Erdinc I, Ozras DM, Conkbayir CE, et al. (2019) Anticoagulation strategy in patients with atrial fibrillation after carotid endarterectomy. Acta Chir Belg 119: 209-216.
11. Douros A, Renoux C, Yin H, Filion KB, Suissa S, et al. (2017) Concomitant use of direct oral anticoagulants with antiplatelet agents and the risk of major bleeding in patients with nonvalvular atrial fibrillation Am J Med 132: 191-199.
12. Klopper A (2021) Delayed global warming could reduce human exposure to cyclones. Nature 98:35.
13. Skagen FM, Aasheim ET (2020) Health personnel must combat global warming. Tidsskr Nor Laegeforen 14: 1-14.
14. Frolicher TL, Fischer E M, Gruber N (2018) Marine heatwaves under global warming. Nature 560: 360-364.
15. Kay J E (2020) Early climate models successfully predicted global warming. Nature 578: 45-46.
16. Traill LW, Lim LMM, Sodhi NS, Bradshaw CJA (2010) Mechanisms driving change: altered species interactions and ecosystem function through global warming. J Anim Ecol 79: 937-947.