Seminars in Immunology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

A transcriptional perspective on human macrophage biology

Joachim L. Schultze[a,*], Tom Freeman[b], David A. Hume[b], Eicke Latz[c,d,e]

[a] Genomics and Immunoregulation, LIMES-Institute, University of Bonn, 53115 Bonn, Germany
[b] The Roslin Institute and Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush, Edinburgh, Midlothian EH25 9RG, Scotland, UK
[c] Institute of Innate Immunity, University Hospitals, University of Bonn, 53127 Bonn, Germany
[d] Division of Infectious Diseases and Immunology, UMass Medical School, Worcester, MA 01605, USA
[e] German Center of Neurodegenerative Diseases (DZNE), 53175 Bonn, Germany

ARTICLE INFO

Article history:
Received 19 January 2015
Received in revised form 31 January 2015
Accepted 4 February 2015

Keywords:
Macrophage
Transcriptome
Activation
Human

ABSTRACT

Macrophages are a major cell type in tissue homeostasis and contribute to both pathology and resolution in all acute and chronic inflammatory diseases ranging from infections, cancer, obesity, atherosclerosis, autoimmune disorders to neurodegenerative diseases such as Alzheimer's disease. The cellular and functional diversity of macrophages depends upon tightly regulated transcription. The innate immune system is under profound evolutionary selection. There is increasing recognition that human macrophage biology differs very significantly from that of commonly studied animal models, which therefore can have a limited predictive value. Here we report on the newest findings on transcriptional control of macrophage activation, and how we envision integrating studies on transcriptional and epigenetic regulation, and more classical approaches in murine models. Moreover, we provide new insights into how we can learn about transcriptional regulation in the human system from larger efforts such as the FANTOM (Functional Annotation of the Mammalian Genome) consortium.

1. Introduction

Macrophages are an important cell of the innate immune system. They mediate their actions in two ways; through endocytosis and phagocytosis, to remove and destroy components of their extracellular environment such as damaged tissue and pathogens and through exocytosis and secretion of bioactive molecules to regulate the function of other cells. Macrophages are a significant resident cellular component of most tissues, occupying precise anatomical niches especially proximal to the vasculature and epithelia [1–3]. In homeostasis, resident macrophages are actively involved in tissue integrity, through the removal of dead cells and debris and regeneration [4], and in physiological processes such angiogenesis [5,6], lipid homeostasis [7–10], or iron homeostasis [10–13]. Their numbers increase significantly through recruitment and extravasation in response to chemoattractants secreted locally in response to a wide range of pro-inflammatory sterile and non-sterile stressors. The initiation of inflammation involves the recognition of pathogen-associated molecular patterns (PAMPs) [14,15] associated with invading microbes or damage-associated molecular patterns (DAMPs) [16]. Macrophages are equipped with a large number of receptors that can recognize PAMPs or DAMPs. Signaling systems activated by these receptors are integrated in the context of tissue-derived signals, and resident and recruited macrophages quickly generate appropriate effector programs to eliminate the stressor and repair the damage. The nature of the effector mechanism must be appropriate to the challenge, and may change with time as a lesion progresses from initiation to resolution. A simplistic view of macrophage activation states is based upon a binary divide between pro-inflammatory or an anti-inflammatory state. The pro-inflammatory program has also been termed classical or M1 polarization while the anti-inflammatory program is described as alternative or M2 polarization, to parallel the concept of Th1 and Th2 states of T cell activation. M1 macrophages have been linked to stimulation by IFNγ, a cytokine secreted by Th1 cells while M2 macrophages were associated with IL-4, a classical Th2 cytokine [17–22]. Given the fact that macrophages possess regulatory receptors for a bewildering array of growth factors, cytokines, chemokines, prostanoids, etc. [4,23], this binary divide is intrinsically unlikely. A more sustainable view sees macrophage polarization more in the nature of a color wheel [24,25] and recent work clearly suggests a much broader multi-dimensional model [23]. The regulation of macrophage function and the balance between inflammation and resolution is arguably the key event in most disease processes. Dysregulated macrophage function contributes to almost all chronic inflammatory conditions including obesity [10,19,26–29], atherosclerosis [30–33], cancer

* Corresponding author at: Genomics and Immunoregulation, LIMES-Institute, University of Bonn, Carl-Troll-Str. 31, 53115 Bonn, Germany. Tel.: +49 2287362787.
E-mail address: j.schultze@uni-bonn.de (J.L. Schultze).

http://dx.doi.org/10.1016/j.smim.2015.02.001
1044-5323/

[18,34–41], chronic obstructive pulmonary diseases [42–44], chronic infections [17,45,46], and even Alzheimer's [47–50].

Resident tissue macrophages in the mouse respond to the local tissue environment and differ substantially from each other in terms of function and gene expression [51–53]. In the mouse, fate mapping and labeling studies suggested that murine tissue macrophages are derived from yolk sac during embryogenesis [54–58]. Moreover, most tissue macrophage populations can be maintained in the absence of monocytic recruitment through local proliferation [59,60]. This seems to be in contrast to earlier findings, clearly showing that tissue macrophages are replaced ultimately by blood monocytes produced from the bone marrow [1,3]. In fact, several recent reports have already indicated that yolk sac derived murine tissue macrophages are replaced by monocyte-derived macrophages in some organs including the gut [61], the heart [62] and the skin [63] even under homeostatic conditions. Whether these findings of macrophage origin in mice can ever be translated to humans and whether this will be important for human disease, therapy or diagnosis remains to be seen. Clearly, tissue macrophage populations depend upon continued signaling from the key growth factor, macrophage colony-stimulating factor (CSF1) [64,65], and the circulating level of CSF1 is itself controlled by monocytes [58]. So, there is an intrinsic homeostasis regulating tissue macrophage numbers. During an inflammatory response, recruited monocytes differentiate to macrophages and contribute to the pool of macrophages involved in local tissue inflammation [66]. Ongoing studies are addressing the contribution of both types of macrophages during inflammation [67]. Not unexpectedly, there is little known about the origin of macrophages in humans or any other non-rodent species, and there is a need to extend our understanding of human macrophage heterogeneity and origins.

However, genome-wide assessment of transcriptional regulation in murine and human macrophages in their resting and activated states has created doubt about the validity of easily translating findings from murine to human macrophages [68]. For example, mouse macrophages induce the set of genes required to transport and metabolize arginine to produce nitric oxide, whereas human macrophages induce the set of genes required to metabolize tryptophan through indoleamine 2,3-dioxygenase to kynurenine metabolites [68–70]. In fact, some of us have provided evidence that the domestic pig provides a much better approximation of the human macrophage response [71]. We also believe that further work is necessary to build reliable databases for conservation of expression between macrophages derived from humans and other species after a set of different stimuli.

Clearly, there is no perfect substitute for data from humans. With the advent of genome-wide assessment of gene transcription, epigenetic regulation, or translational control completely new approaches for research in human macrophage biology have been introduced over the last decade. Combined with sophisticated biostatistics, biomathematics, bioinformatics and systems approaches, a complementary or even alternative to more conventional or classical animal model system based approaches has evolved. We will give an overview of genome-wide approaches applied to human macrophage biology during the last decade, introduce novel concepts of human macrophage activation, suggest workflows to integrate genome-wide approaches with animal models and other more gene-centered strategies, and give an overview on recent international activities to better understand macrophage biology in the context of other cell types.

2. Existing data on global transcriptional programming of human macrophages

Macrophages respond to exogenous stimuli such as PAMPS with massive changes in gene expression [23,72–74]. The earliest

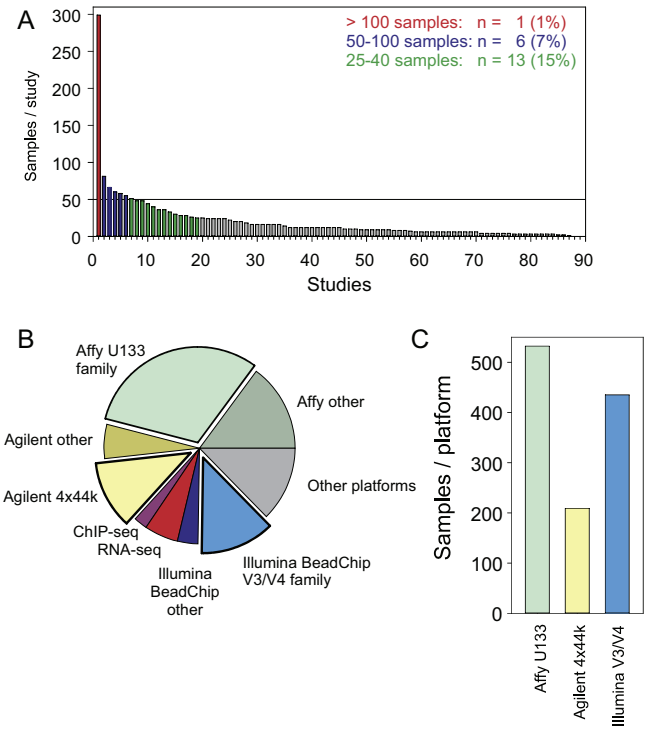

Fig. 1. Existing transcriptomes datasets of human macrophages. (A) Samples per study, (B) use of different array platforms or sequencing to obtain genome-wide data, (C) sample number for the three most used array platforms.

changes can be detected within minutes, and involve the activation of transcriptional elongation from preexisting poised RNAPolII complexes [75]. Thereafter, there is a cascade of transcriptional activation, involving many regulated transcription factors and chromatin reorganization, as macrophage cells transition toward a new steady state over around 24 h. Genome-wide transcriptional profiling studies were performed on these cells soon after the advent of microarray technologies for gene expression profiling. The resulting data is stored in public depositories such as Gene Expression Omnibus [76] or Array Express [77]. A key word search for 'human macrophage' in Array Express (May 2014) revealed 247 datasets (Fig. 1), of which 89 studies contained samples derived from primary human macrophages cultured in vitro and 21 datasets assessed human macrophages in vivo. Of the 89 studies carried out in vitro the majority are rather small (Fig. 1A). Only one was large enough ($n > 200$ samples) allowing performance of more sophisticated bioinformatics analysis such as reverse network engineering of transcriptional regulation [23]. Categorizing the readouts of the analysis and the technological platforms used further indicates that the currently existing data are highly heterogeneous and might not be easily compared (Fig. 1B). However, of the 1809 individual data derived from human macrophage samples in Array Express, about two third have been performed using one of the three major platforms Affymetrix ($n = 532$), Agilent ($n = 209$), or Illumina ($n = 471$) (Fig. 1C) with the largest dataset performed using the Illumina BeachChip technology ($n = 299$) [23].

In 21 studies, 469 human primary macrophage samples have been reported with the largest study on ovarian cancer ($n = 97$). The majority of studies ($n = 13$) including 205 of 469 samples (63%) targeted human alveolar macrophages as these can be obtained by bronchoalveolar lavage without tissue damage. The remainder were derived from carotid atheromatous plaques, from wounds, obese tissue, the decidua, the peritoneum, or germinal centers. This simple assessment of what has been studied during the last decade clearly highlights that we are far from understanding transcriptional responses of human macrophages on a global scale. This is true

Please cite this article in press as: Schultze JL, et al. A transcriptional perspective on human macrophage biology. Semin Immunol (2015), http://dx.doi.org/10.1016/j.smim.2015.02.001