Monocytes, Macrophages, Dendritic Cells and Neutrophils: an update on lifespan kinetics in health and disease

Amit A Patel[1*], Florent Ginhoux[2,3,4*] and Simon Yona[5*]

[1]Inserm U1015, Gustave Roussy, Villejuif, France [2]Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (ASTAR), Singapore, Singapore [3]Shanghai Institute of Immunology, School of Medicine, Shanghai Jiao Tong University, Shanghai, China [4]Translational Immunology Institute, SingHealth Duke-NUS Academic Medical Centre, Singapore, Singapore [5]Institute of Dental Sciences, Faculty of Dental Medicine,Hebrew University, Jerusalem, Israel

* Correspondence: Amitashok.Patel@gustaveroussy.fr, Florent_Ginhoux@immunol.a-star.edu.sg, s.yona@mail.huji.ac.il

Abstract

Phagocytes form a family of immune cells that play a crucial role in tissue maintenance and help orchestrate the immune response. This family of cells can be separated by their nuclear morphology into mononuclear and polymorphonuclear phagocytes. The generation of these cells in the bone marrow, to the blood and finally into tissues is a tightly regulated process. Ensuring the adequate production of these cells and their timely removal, is key for both the initiation and resolution of inflammation. Insight into the kinetic profiles of innate myeloid cells during steady state and pathology will permit the rational development of therapies to boost the production of these cells in times of need or reduce them when detrimental.

Introduction

Under healthy physiological conditions, the human body maintains a steady number of leucocytes by means of cell proliferation, differentiation, survival and cell death. The bone marrow is regarded as the primary hematopoietic factory for the production of the majority of adult immune cells. Following their egression into the circulation and tissues, these cells will fulfil their purpose and then eventually die, only to be replaced by newly produced younger cells thought to keep the immune system alert at all times. The importance of this fine balance can be appreciated in disease such as haematological cancers where a substantial number of abnormal immune cells are present or conversely, where a deficit of specific immune cell subsets consequently results in increased susceptibility to opportunistic infections (1–4).

During inflammation, this finely balanced sequence must quickly adapt to produce sufficient immune cells in order to combat injury or infection and replace those dysregulated by the inflammatory challenge. The cellular kinetics of the inflammatory response encompasses several cell types including white blood cells, endothelial cells and fibroblasts. Here, we focus on the cellular kinetics of professional phagocytes, a group of innate myeloid immune cells (namely monocytes, dendritic cells, macrophages and neutrophils) specialised, but not limited to, their ability to phagocytose foreign bodies. Tissue macrophages are sentinels that reside within every tissue in an organism and act as first responders to an infectious agent. The majority of macrophages are derived from embryonic progenitors (5–8) and play an important role during tissue development and maintenance (6, 9–14). On the other hand, neutrophils are recognised for their mechanisms involved in pathogen clearance (e.g. reactive oxygen species production, degranulation of anti-microbial proteins, neutrophil extracellular traps (NETs)). Patients diagnosed with neutropenia are often more susceptible to infections (15, 16) which highlights the need for an adequate production of these cells. Monocytes also aid in the phagocytosis of pathogens and apoptotic cells, whereas dendritic cells (DC) activate the adaptive immune response by migrating from the periphery to draining lymph nodes. The absence of monocytes and DC has been observed in patients bearing mutations in the transcription factor, interferon regulatory factor 8 (IRF8), as a result, these individuals are more predisposed to infections (1).

Inflammation is necessary to protect an organism from infectious agents, yet an overactive immune response can result in further tissue damage. This can be observed in chronic inflammatory diseases such as rheumatoid arthritis where a constant recruitment of monocytes to the synovial tissue has been observed in humans (17). Therefore, though inflammation has been historically recognised as a salutary reaction (18), ‘more is more’ is not often the case. Striking the fine balance of an essential yet limited inflammatory response may present as a potential therapeutic opportunity. Highlighting the importance of understanding the kinetics of immune cells in health and disease.

Neutrophil Kinetics

Neutrophils are an indispensable component of the innate immune system, if not the most important. Within the circulation, neutrophils constitute the largest proportion of human circulating leucocytes and estimated to be found at ~4.2 x10^9 cells per litre of blood although this can vary with age, ethnicity and sex (19, 20). Neutrophils are often the first white blood cell recruited to sites of injury, which is facilitated by both the upregulation and expression of membrane adhesion molecules on the endothelium and neutrophils (21, 22). Increased levels of neutrophil chemotactic factors such as IL-8 (CXCL8) have been observed early on during models of human inflammation which aids in the guidance of neutrophils to the site of inflammation (23, 24). The initial recognition of pathogens by tissue resident macrophages is also partly responsible for the recruitment of neutrophils (25) although other resident cells

can also modulate their infiltration (26). Recent studies in mice and humans have reported a role for vascular endothelial growth factor α (VEGF-α) released from cDC1 in neutrophil recruitment in cutaneous infections (27).

The generation of neutrophils involves a series of maturation steps starting with granulocyte macrophage progenitors (GMP) in the bone marrow. These cells give rise to pre-neutrophils, which subsequently develop into immature (band) and mature (segmented) neutrophils which egress into the circulation (28–30). CXCR4 is a key chemokine receptor involved in the retention of neutrophils within the bone marrow via interaction with CXCL12, whereas CXCR2 activation promotes the mobilisation of neutrophils from the bone marrow into the blood (31–33). The importance of the CXCR4 axis in the regulation of neutrophil egression can be highlighted in Warts, Hypogammaglobulinemia, Immunodeficiency, and Myelokathexis (WHIM) syndrome patients who primarily suffer from an autosomal, dominant, gain-of-function mutation in CXCR4 (15, 16). Consequently, these patients suffer from defected neutrophil egression and thus circulating neutropenia, making them more vulnerable to infections.

Deuterium labelling has been employed to examine human neutrophil development *in vivo*. Deuterium labelling acts in a non-cytotoxic manner to label dividing cells (34, 35). Using this approach to monitor neutrophil development, following the last proliferation in the bone marrow, the mean transit time before neutrophils enter the circulation has been estimated at 5.8 days (19). Once within the circulation, these cells have an incredibly short half-life of approximately 19 hours. The short half-life of these cells may reflect their function. Whilst homeostatic functions have been assigned to neutrophils (36, 37), these cells are renowned for their defensive mechanisms against invading pathogens such as the production of reactive oxygen species, antimicrobial peptides and NETosis (38, 39). These mechanisms are not pathogen specific and can also result in collateral damage to host tissues, therefore it is thought these cells are likely programmed for a quick cell death in order to prevent excessive damage.

Once in the circulation, neutrophils can either be found within the circulating pool where they are readily accessible for blood sampling or can be located in a marginating pool. Following a number of other stimuli including the administration of adrenaline, an intense burst of exercise, infection or trauma, this marginated pool can be mobilized into the circulating pool in humans (40, 41), it has been calculated that the marginating pool makes up approximately 50% of the total neutrophil pool (19). Neutrophil transit within tissues refers to how quickly cells pass through the capillary beds. Within the spleen and bone marrow, it takes approximately 10 minutes for neutrophils to transit (42, 43). Therefore, the period of time cells spend within tissues may factor in determining the marginated fraction.

Neutrophilia is commonly associated with bacterial infections but can arise from other stimuli. In human models of local and systemic inflammation, neutrophilia accounts for the increase in the total white blood cell count (23, 44–46). Of note, left shift refers to the presence of an increased amount of immature neutrophils within the circulation (47). This observation has been associated with cancer progression (28) and more recently has been observed in severe COVID-19 patients which exhibit an immunosuppressive profile (48).

Elevated levels of systemic G-CSF during inflammation can lead to both the down-regulation of CXCR4 (49) and increased levels of CXCR2 ligands (50), which likely leads to an increase in neutrophil egression. Additionally, an increase in the number of neutrophil progenitors during inflammation can also contribute the elevation of circulating neutrophils (28), in addition to neutrophils from the marginating pool. During the resolution of inflammation, neutrophils are eventually cleared from tissues to restore tissue homeostasis. Neutrophil death can occur in various ways including apoptosis, necrosis, NETosis and autophagy. Efferocytosis refers to the phagocytosis of apoptotic cell bodies. The recognition of 'eat me' signals such as phospholipid phosphatidylserine on apoptotic cells facilitates the recognition by macrophages and monocyte-derived cells to efferocytose apoptotic bodies (14, 51). Under steady physiological conditions, senescent neutrophils can also home back to bone marrow by upregulating CXCR4, where they will also be efferocytosed by resident macrophages (52, 53).

These data demonstrate a significant amount of knowledge regarding neutrophils kinetics in both steady state and inflammation. The next step is to truly understand the kinetic changes within each compartment of the body i.e. bone marrow, blood and tissue, in addition to the cues that skew the lifespan of these cells during pathology which may allow for future targeting to promote an adequate response.

Macrophage Kinetics

Tissue resident macrophages form a network of cells that reside throughout the organism. Tissue specific macrophage nomenclature has evolved and is based on anatomical location or after the scientist who discovered the macrophage population e.g. microglia in the brain, osteoclasts in the bone or Kupffer cells in the liver and Langerhans cells in the epidermis.

The idea that all macrophages arise from monocytes stemmed from studies as early as 1926 demonstrating the ability of monocytes to develop a macrophage phenotype both *in vitro* (54) and *in vivo* (55). In 1969, Ralph van Furth and colleagues proposed the reticulo-endothelial system (RES) was too broad a definition and coined the term the 'Mononuclear Phagocyte System' (MPS) including monocytes and macrophages. Furthermore, Van Furth and colleagues separated macrophages into two clear categories 'free' or 'fixed' macrophages. When distinguishing the macrophages of the spleen, lymph nodes, and bone marrow, 'free' macrophages were described as monocyte in origin, while the origin of the 'fixed' macrophages in these organs remained undetermined (56). This insight into a division of labour of macrophage ontogeny is reflected at this time with the observation that macrophage development was noted within the yolk sac prior to bone marrow haematopoiesis (57, 58). These yolk sac macrophages appeared one day earlier than monocytes in mice and was one of the earliest observations -to the best of our knowledge- to report macrophage development independent of monocytes (58). Furthermore, investigations into the kinetics of monocytes and macrophages by Ralph van Furth and Zan Cohen, using radioactive thymidine, demonstrated low labelling in peritoneal macrophages compared to blood monocytes (59). Unaware at the time, these data supported the maintenance of macrophage populations independently of monocytes. More recently, the use of genetic fate-mapping techniques has confirmed that the majority of tissue-resident

macrophages are embryonically derived and maintained without monocyte input (5–8, 60, 61).

Within the developing embryo, haematopoiesis occurs in a sequential manner, initially occurring within the extra-embryonic yolk sac (primitive haematopoiesis) before transferring to the fetal liver until birth where haematopoiesis is ultimately transferred to the bone marrow (definitive haematopoiesis) (62). Primitive haematopoiesis begins in the yolk sac, where erythromyeloid progenitors (EMP) give rise to erythrocytes, macrophages and mast cells (6, 63). Downstream of the EMP, a pre-macrophage precursor has been identified in mice which arises in the yolk sac before colonising embryonic tissues around embryonic day 9.5 (E9.5) at the same time as organogenesis (6). These pre-macrophages are subjected to tissue-specific signals, which help sculpt a tissue-specific resident macrophage phenotype (64). Recent studies on macrophage development in rodents have been corroborated in humans where similar findings have been made (65).

Following birth, embryonic derived resident macrophages can persist throughout life with little or no monocyte input depending on the tissue compartment under steady state (8, 61, 66) **(Figure 1)**. More recently, a novel fate mapping model utilising the *Ms4a3* gene demonstrated in a more specific quantitative manner, the monocyte contribution to several tissue macrophage compartments (66). In tissues such as the brain, skin and liver, monocytes do not replace the embryonically derived microglia, Langerhans cells and Kupffer cells. Whilst this has been clearly demonstrated in mice, further clarity is required within the human setting. Interestingly, Langerhans cells of the skin have been shown to persist of donor origin - ten years following human hand allograft (67). However, others have found that following bone marrow transplantation, the majority of Langerhans cells were donor derived within 3 months (68–70). It is important to note chemotherapeutic or other pharmacological regimes could impact on these studies. The ontogeny of alveolar macrophages in humans has also been examined in humans where contrasting findings have again been observed (71–73). An interesting study by Réu and colleagues took advantage of atmospheric ^{14}C to estimate the turnover rate of human microglia (74). Increases in atmospheric ^{14}C in the 1950s due to nuclear bomb testing resulted in the increased presence of ^{14}C within the atmosphere and subsequently DNA of newly formed cells, which in turn could provide insight into the age of a cell (75). Réu and colleagues demonstrated that human microglia have a life-span of approximately 4.2 years and renew at a rate of 28% per year (74). Whilst these studies demonstrate that most macrophages are maintained throughout adulthood, this is not a one-size-fits-all phenomenon. **Table 1** lists examples of studies where the longevity of macrophage populations has been examined in both murine models and in the human setting.

In the absence of tissue macrophages, a reduced infiltration of granulocytes has been observed (25), highlighting macrophages as one of the many cell types involved in the initiation of the immune response. Following the initiation of the immune response, an interesting phenomenon known as the ‘macrophage disappearance reaction’ occurs, first described in 1963 (76, 77). This observation has been observed by several groups during experimental peritonitis, where a reduced recovery of resident macrophages was reported (78–80). This has also been extended to other tissues, such as the lung where low numbers

of alveolar macrophages are recovered following influenza challenge in mice (81) and the liver where lower number of Kupffer cells are present during inflammation (82, 83). Zhang and colleagues recently showed that macrophages form clots and adhere to tissues accounting for the reduced recovery of these cells, which could be reversed by the use of anticoagulants (80). Following the resolution of inflammation, the recovery of resident macrophage numbers may occur by proliferation (84), repopulation by monocyte-derived cells (8, 66, 78, 85–87), or a combination of both (88, 89). Expectedly, exceptions to the macrophage disappearance paradigm have been observed in T-helper cell type 2 immune response, where tissue resident macrophages proliferate to combat infection rather than depend on monocyte recruitment (90).

Monocyte Kinetics

In Contrast to macrophages, monocytes and DC are derived from bone marrow progenitors. Initially the monocyte and DC progenitor (MDP) was demonstrated to lack neutrophil potential yet give rise to monocytes via the common monocyte progenitor (cMoP) (91–93). Although more recently, the cMoP has been proposed to descend from the granulocyte and macrophage progenitors (GMP) bypassing the MDP stage in both mice (66) and humans (94). In this study, the GMP and MDP were suggested to generate monocytes through two pathways, a GMP → cMoP → monocyte and a MDP → monocyte pathway that lacks a cMoP intermediate stage (66). Commitment to monocyte development at the cMoP stage is dependent on the transcription factor IRF8 (95). This is consistent with the observation in patients bearing mutations in IRF8 who are also deficient of circulating monocytes (1). Recently, a proliferative CXCR4^{hi} CCR2^{lo} transitional pre-monocyte population was described in mice and humans within the bone marrow which eventually downregulates CXCR4 and upregulates CCR2, resulting in the egression of mature classical monocytes into the circulation (96–98).

The kinetic profiles of circulating monocyte subsets have been examined in mice with the use of BrdU, where a sequential appearance of labelled classical monocytes then non-classical monocytes appear in the circulation (8). This is owed to the fact that Ly6C^{hi} classical monocytes convert into Ly6C^{lo} non-classical monocytes (8, 66, 93, 99, 100). The half-life of classical and non-classical monocytes in mice are estimated at 20 hours and 2.2 days, respectively.

Early insights into the kinetics of human monocytes stemmed from studies nearly fifty years ago with the use of tritiated thymidine where the average monocyte lifespan was estimated at 4.25 days (101). Deuterated glucose labelling studies proposed a half-life of 2.2 days for CD14$^{+\ classical}$ monocytes (102). With regards to monocyte subsets, studies have demonstrated differences in the kinetic profiles of circulating CD14^{+} and CD16^{+} monocytes in patients following hematopoietic stem cell transplantation (103). Using deuterium labelling, a sequential appearance of monocyte subsets has been observed within the circulation (104, 105). Using mathematical modelling, it was estimated classical monocytes are retained within

the bone marrow for approximately 1.6-2 days between the last mitotic division and entry into the circulation (104, 105) **(Figure 2)**. These cells then circulate for approximately 1 day, whereas non-classical monocytes circulate for a longer period of time (~7.5 days) (105). These results are akin to those observed in mice (8), rats (106) and macaques (107, 108) most likely due to a conserved developmental relationship between monocyte subsets.

Non-classical monocytes reside within the circulation for a longer period of time possibly due to their function within the circulation where they are constantly monitoring the endothelium for damage (109, 110). These cells represent a terminally differentiated monocyte and may consequently even represent a 'blood macrophage' (8). Supplemental components encourage non-classical monocyte survival include CX_3CL1 (111) and TNF (112). On the other hand, classical monocytes are continuously recruited to repopulate tissue mononuclear phagocyte compartments (60, 66, 103, 113–116) which may explain their shorter circulating lifespan. Liu *et al.,* demonstrate the rate at which monocytes replaces tissue macrophages in mice is tissue specific, for example, kidney macrophages are gradually replaced overtime but to a lesser extent than lung alveolar macrophages or dermal macrophages (66) (**Figure 1**). The determinants of these rates remain unknown, although, the macrophage niche theory proposes a niche is filled by the competition between an embryonic macrophage and a monocyte derived cell (117). Therefore, the differences between tissue microenvironments most likely dictates the rate of macrophage replacement.

In an inflammatory setting, a reduction in the number of circulating monocytes has been observed in both mice and humans, hours following intravenous endotoxin challenge (44, 96, 105, 118, 119). The lung is a primary location where activated monocytes can marginate to following challenge (96, 120). Given the narrow diameter of lung capillaries (121), changes in the morphology and size of monocytes following activation may result in hinderances and consequently an increased transit time. However, active retention of monocytes within the lung via CXCR4 retention has also been documented in mice (96). Targeting margination in the lung may be of clinical relevance as this accumulation of monocytes can promote further lung injury (120). Following temporary monocytopenia, monocytes can return from various sources. In mice and humans, the spleen has been implicated as a monocyte reservoir which are deployed in response to specific inflammatory cues (122, 123). We and others have shown that bone marrow 'immature' classical monocytes are rapidly released into the circulation in response to bacterial (105) and sterile inflammation (123). More recently, patients with severe COVID-19 present with immature classical monocytes and neutrophils within the circulation (48), suggesting this emergency release of monocytes is also apparent in a viral setting.

Intradermal challenges have allowed for the study of immune cell recruitment to the site of infection in response to various stimuli in humans (23, 124, 125). In response to UV-killed *Escherichia coli* (*E.coli)*, classical monocytes are observed within the skin as early as 8 hours following challenge (23). This observation is akin to mice, where $Ly6C^{hi}$ classical monocytes are typically the subset recruited (126–128) possibly via a CCR2-depedent manner (98, 122, 127, 129). At later time points, a $Ly6C^{lo}$ 'non-classical' phenotype is apparent, but it is thought that this is due to in situ conversion rather than a second wave of monocyte recruitment

(126–128, 130, 131). Similarly, in humans, CD16 expression increases over time (23) and may also represent maturation at the site of infection. While it may seem that classical monocytes are the prime effector subset responsible for inflammation and resolution, the use of Nr4a1-deficient mice (132, 133), has highlighted a role of non-classical monocytes in various pathologies including tumour metastasis (134), Alzheimer's disease (135), Experimental Autoimmune Encephalomyelitis (EAE) (136) and vascular homeostasis (110). The role of non-classical monocytes has recently been extensively covered (137). Of note, following the resolution of inflammation, it is thought that tissues return to baseline homeostasis. Whilst this is true at the symptomatic level, immunological processes have been observed to continue in mice where IFNγ triggers a second wave of monocyte recruitment creating an immune suppressed environment (138). This may be of importance when considering secondary infections, therefore targeting this second wave of monocytes may be of clinical relevance.

The question arises whether these recruited inflammatory monocytes engraft into the long-lived macrophage pool. In models of peritonitis, monocyte derived cells persist up to 8 weeks, where their phenotype gradually changes into that of resident macrophages (8, 78). Similar observations have been extended to the liver (85, 139–141) and lung (86, 87, 142). It is possible that tissue residence could alter the longevity of monocytes although, in mouse models of experimental autoimmune encephalomyelitis, monocyte-derived cells do not contribute to the resident microglia pool (143) yet contribute to pathology (144), which possibly highlights the microglia as a unique population owed to their unique location within the blood-brain barrier. Whether monocyte-derived cells exhibit the same function as their resident macrophage counterparts is of key importance. In a mouse model, the engraftment of monocyte derived cells into the lung was examined following ten months, the graft cells showed a very similar transcriptome to alveolar macrophages and only exhibited a difference of 330 differentially expressed genes (87). In a separate infection study, the replacement of alveolar macrophages with monocyte-derived cells in response to herpesvirus resulted in protection against house dust mite induced asthma compared with mice without initial exposure to herpesvirus (86). Similar findings have recently been documented, where initial exposure to influenza resulted in subsequent protection from *Streptococcus pneumoniae* due to the recruitment and engraftment of monocytes to the alveolar niche (142). These studies demonstrate, in addition to ontogeny, the context in which monocytes are recruited and the type of stimuli may also shape the function of these cells.

Recent monocyte-like populations have been observed only under pathological conditions, $YM1^{+}$ $Ly6C^{hi}$ monocytes are greatly expanded within the bone marrow, blood and spleen of mice following intravenous LPS challenge where these cells exhibit immunoregulatory properties and aid in tissue repair (Ikeda *et al.,* 2018). In the case of fibrosis, a segregated nucleus-containing atypical $Ly6C^{lo}$ monocyte (SatM) has been documented, although they do not arise from the MDP differentiation route and do not arise from $Ly6C^{hi}$ progenitors (Satoh *et al.,* 2017). Inflammation likely skews 'healthy' haematopoiesis, therefore examining the kinetics of these cells under steady conditions will be the initial step and warrants the need to further investigate the development and kinetics of these cells under pathological conditions.

DC Kinetics

A common school of thought was - monocytes are the immature precursor cells to macrophages and DC. However, the identification of the common DC precursor (CDP) that gave rise exclusively to pDC and cDC, but not monocytes (92, 145, 146), challenged this view and established a DC dedicated lineage in both rodents and humans. Prior to the generation of cDC, CDP initially give rise to a cDC precursor (pre-cDC) (145, 147–151) which can be skewed to pre-cDC1 or pre-cDC2 fate depending on the cues present (95, 149, 150, 152–154). In humans, pre-cDC can be found within the circulation where they can further mature into cDC (155–157). On the other hand, mouse pDC are released as mature cells from the bone marrow and are thought to be derived mostly from lymphoid progenitors (158–160), these observations are yet to be confirmed in humans.

DC are renowned for their ability to stimulate naïve T-cells and subsequently bridge the innate and adaptive immune response. Numerous DC subsets have been identified, each interacting with T cells in various ways. DC are found at fewer numbers in comparison to other cell types, nevertheless a single DC can interact with up to 500 T-cells per hour (161), therefore their low abundance should not undermine their functional relevance. Though two major cDC subsets are widely acknowledged (DC1 and DC2), further heterogeneity has recently been identified within the DC lineage (155, 156, 162–166).

BrdU labelling in mice demonstrated a rapid labelling of splenic DC, initially thought to be attributed to the rapid replenishment from circulating DC precursors (167). However, splenic DC are also proliferative therefore the labelling is likely to represent a combination of both *in situ* proliferation and blood derivation (168). Parabiosis studies examined the decay of parabiont-derived DC in the lymphoid and non-lymphoid organs and demonstrated DC are cleared within 10-14 days (148, 168). Taking into consideration, DC replenishment from blood precursors, division and cell death, Liu *et al.,* calculated that lymphoid organ cDC are replenished at a rate of 4,300 cells per hour. This rapid tissue replenishment is supported by the rapid turnover of blood cDC in macaques, where these cells were labelled prior to circulating monocytes (108). In humans, donor dermal DC have been identified as early as 18 days following allogeneic haematopoietic cell transplantation and by 56 days were 94% donor derived (169). Similar studies have also demonstrated that human dermal DC were replaced by donor origin within 40 days (170). On the contrary, pDC have a much slower turnover in comparison to cDC in mice (171) and macaques (108), which is possibly owed to a bias towards cDC production over pDC in the bone marrow (172). Furthermore, the lymphoid origins of pDC (159, 160) may also account for the differences in kinetics between myeloid derived cDC.

Akin to monocytes, a reduced number of circulating cDC and pDC have been reported during inflammation in both mice (173–175) and humans (176–181). The fate of these DC remains unknown although DC death is thought to be a factor (175). An elegant study by Pasquevich and colleagues demonstrated monopoiesis is favoured over DC production following bacterial infection in mice (182). Following TLR4 mediated inflammation, these mice had reduced

numbers of CDP but elevated numbers of cMoP. It is possible the body increases the availability of monocytes to combat infection at the expense of DC, however this leads to an immunosuppressive state. Interestingly, the rescue of DC from cell death (175) or increasing DC production via FLT3 ligand (183) reduced the inflammatory induced immunosuppression and improved DC survival. Similarly, correlations between circulating DC count and survival from secondary infections in sepsis patients have been documented (176, 177). Further exploration into DC kinetics in this setting could present a potential therapeutic target. However, given the diversity of dendritic cell subsets, it is first necessary to understand the foundational biology of these cells and their relationship to one another.

Conclusion

Phagocytes play a crucial role in facilitating the immune response, yet little is known about the tightly regulated processes governing the generation, maturation and disappearance of these cells, which allow them to fulfil their functions. Whilst macrophages are considered as a self-maintaining population it is clear this is not the case for all tissues. The question arises – what determines the longevity of macrophages? Why are the rates of monocyte replacement variable between tissues? And consequently, what does this mean functionally? Similarly, given the recent expansion of DC diversity in humans, our knowledge regarding the relationship of the cells to one another, in addition to their individual functions remains limited. This review summarises both our current understanding and highlights the gaps in our knowledge of one of the foundational aspects of phagocyte biology. By establishing the kinetics and turnover of these cells in addition to the regulatory mechanisms behind, this may allow for therapies to fine tune the immune response.

Figure and Table Legends

Figure 1. **Tissue macrophage kinetics with age**. Illustrative diagram demonstrating the relative and differential rates of blood monocyte contribution to tissue macrophage populations. Adapted from Liu *et al*., 2019

Figure 2. **Overview of monocyte kinetics in health and inflammation.** Under steady physiological conditions, classical monocytes arise from cMoP and reside within the bone marrow for approximately 1.6 days before being released into the circulation. Once within the circulation, these cells mature into intermediate and then non-classical monocytes, which circulate for 4 and 7 days, respectively. During systemic inflammation, classical monocytes are rapidly released into the circulation. Following local injury, classical monocytes are initially recruited later followed an intermediate monocyte phenotype, although the origin of the cells are unknown (dashed lines). HSC, hematopoietic stem cell; cMoP, common monocyte progenitor.

Table 1. **Longevity of phagocytes.** Summary of longevity of phagocyte populations in mouse and humans. Life-spans and half-live have been stated where available. TBC, to be confirmed.

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