Chapter 8

Polarisation of Macrophage and Immunotherapy in the Wound Healing

Yu-Sheng Wu, Fan-Hua Nan, Sherwin Chen and Shiu-Nan Chen

Additional information is available at the end of the chapter

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Abstract

Immune cells are involved in virtually every aspect of the wound repair process, from the initial stages where they participate in haemostasis and work to prevent infection to later stages where they drive scar formation. Immunotherapy is being developed offers some advantageous immunomodulation factors that are known in the field of alternative medicine, such as mushroom beta-glucan, anti-microbial peptides and triterpenoid; these factors represent a novel therapeutic approach for anti-inflammation to promote the wound healing.

Keywords: healing, immunotherapy, inflammation, macrophage, polarisation, wound

1. Inflammation

When an organism is injured by a wound injury or infected by a pathogen, inflammation is a crucial response. Inflammation is a complex interaction with molecular mediators; it includes the function of immune cells in a microenvironment through a response that occurs at all levels of biological organisation [1]. Following previous studies, this paper illustrates that the inflammation response involves cooperation between cells and a wide range of mediators, such as cytokines, chemokines and non-enzyme factors involved in the classical immune response. The macrophage is one of the critical inflammatory immune cells involved in the uptake and degradation of infectious agents and senescent cells and also plays critical roles in tissue growth, tissue remodelling and inflammation by producing oxidants, proteinases and anti-microbial peptides [2–4]. Activated inflammatory cells are sources of reactive oxygen

species (ROS) and reactive nitrogen species (RNS) that can initiate changes in cell functions, including cell signalling pathways, transcription factor activation, mediator release and apoptosis. However, whether the ROS and RNS that are produced and released by neutrophils or macrophages are sufficient to diffuse through the extra-cellular matrix, enter epithelial cells and cross the cytoplasm is not clear [5–7]. Even the physiological roles of ROS and RNS in the cellular response are not clear [8–11]. The results obtained from experiments performed on the livers of tilapia showed that extra-cellular hydrogen peroxide (H_2O_2) attracted cell migration. These results suggested that ROS is a crucial factor in initiating the migration of macrophages that trigger cascades of phagocytic activity.

In the microenvironment of inflammation, the platelet-derived growth factor (PDGF), the tumour necrosis factors (TNF)-α and TNF-β, the hepatocyte growth factor, transforming growth factor (TGF)-β2, the epidermal growth factor (EGF) and the fibroblast growth factor all play an important role in physiological immune response. The interleukins (IL)-1, IL-6, IL-8, IL-10, and the interferon gamma (INF-γ) also detain key functions in the natural inflammatory response [12–16]. These factors hold a primordial function in fibroblast activation and regulation, also concerning reactive fibrosis that follows their continuing activation. Although these growth factors are also related to fibroblast migration and activation, particular research was recently focused on the PDGF family of growth factors and their relative receptors [17, 18]. Research has documented that PDGF exerts autocrine, mitogenic effects on keratinocytes to support epidermal proliferation and stabilisation of the epidermal junction during wound closure. In addition, it stimulates vessel maturation by recruiting and differentiating pericytes to the immature-endothelial channel [19–22]. According to these references, we investigate whether the produced ROS/RNS is related to the released factors and (if so) what type of relationship exists among ROS/RNS and these factors.

2. Reactive oxygen species production and physical response

The production and scavenging of ROS may be initiated by adverse environmental factors. Research has shown that intra-cellular levels of ROS may rapidly rise and ROS may be generated by the activation of various oxidases and peroxidases in response to certain environmental changes [23]. ROS forms through energy transfer or through electron transfer reactions. ROS formation causes the formation of singlet oxygen, which results in sequential reduction to superoxide, H_2O_2 and hydroxyl radicals [24]. Mitochondria are a crucial source of ROS production in most cells. This ROS production contributes to mitochondrial stress and plays a critical role in redox signalling from the organelles [25]. Mitochondria have a 4-layer structure composed of the outer mitochondrial membrane, intermembrane space, inner mitochondrial membrane and matrix [26]. NADPH oxidase is an enzymatic source in the mitochondrial structure that generates ROS and plays a fundamental role in maintaining normal cell functions. Recent research has focussed on the influence of this enzyme to cellular oxidative stress that may contribute to various pathophysiological conditions and diseases [27, 28]. A crucial function of NADPH oxidase is modulating multiple redox-sensitive intra-cellular signalling pathways; NADPH modulates these pathways by generating ROS molecules,

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inhibiting protein tyrosine phosphatases and activating certain redox-sensitive transcription factors. Moreover, the ROS consist of numerous molecular species, including H_2O_2, oxide ions (O_2) and hydroxide (OH^-) [29]. Molecular oxygen is a biradical, containing two unpaired electrons in the outer structure; because these two electrons have the same spin, oxygen can only react with one electron; therefore it is not very reactive when these two electrons have the same spin. Oxygen's unpaired electrons can become excited and can change the spin of one electron. This transforms oxygen into a powerful oxidant because the two electrons with opposing spins can rapidly react with other pairs of electrons [30]. Electrons can be contributed from NADH and FADH2 enzymes and can pass through the electron transport chain, generating superoxide (O_2^-) at complexes I and III. This generated superoxide can be reduced to H_2O_2 by superoxide dismutase and can be completely reduced into water by glutathione peroxidase, as presented in **Figure 1**.

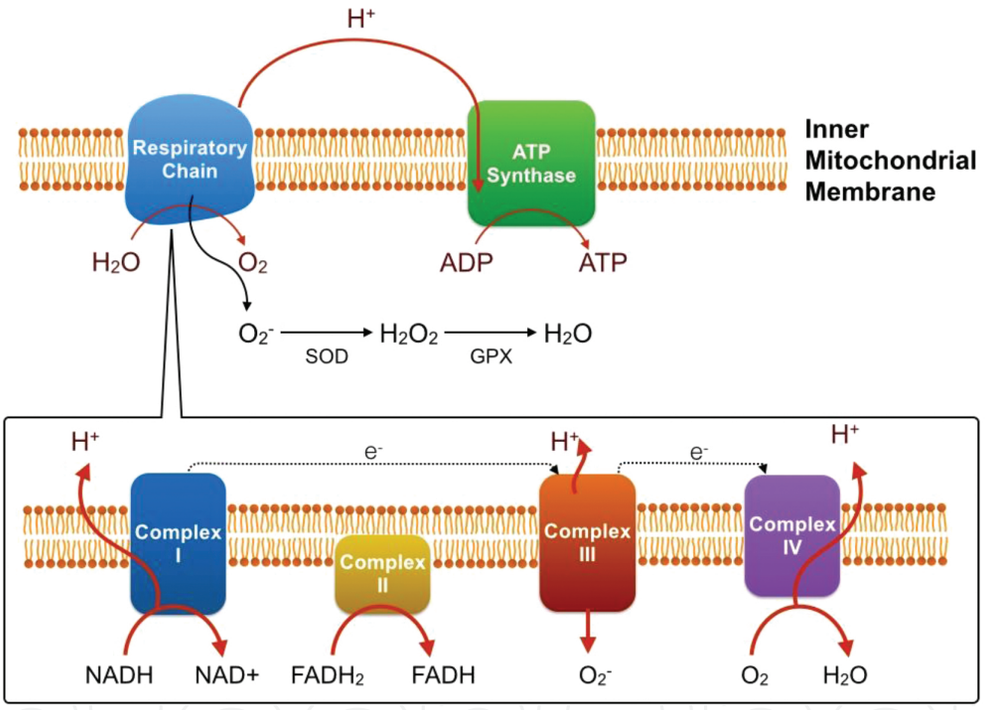

Figure 1. ROS are produced from the electron transport pathway to form superoxide (O_2^-) at complex I and complex III released into the matrix and reduced O_2 to form H_2O at complex IV. Following, the generated O_2^- is transferred to the form of H_2O_2 by superoxide dismutase (SOD) and completely reduced to water (H_2O) by glutathione peroxidase (GPX).

Research has shown that ROS consist of numerous molecular species, including H_2O_2, oxide ions (O_2^-) and OH^{-29}. These molecular species act as signalling molecules in the migration of profibrogenic cells [31] and peripheral blood monocytes [23, 32]. One of the crucial physiological functions of ROS is the modulation of ion channels. Research has illustrated that ROS may act through Ca^{2+} as an intra-cellular second messenger involved in regulating diverse functions, such as fertilisation, electrical signalling, contraction, secretion, memory, gene transcription and cell death [33, 34]. Furthermore, studies have reported that H_2O_2 may affect

cell energy stores [35], induce DNA strand breaks [36], enhance cell adhesion [37], increase endothelial tissue permeability [38] and stimulate the release of cytokines.

In the research presented in **Figure 2**, the concentration of ROS seems to be considered the concentration of a crucial signalling molecule. Low concentrations of generated ROS are believed to be critical for metabolic adaptation in the organelle. Moderate concentrations of ROS can be produced and released by stress; pathogen-infected and bacterial endotoxin lipopolysaccharide (LPS) are involved in the inflammatory response. The high concentration of ROS in the induced apoptosis/autophagy process can cause cell death [39] and initiate self-healing [40].

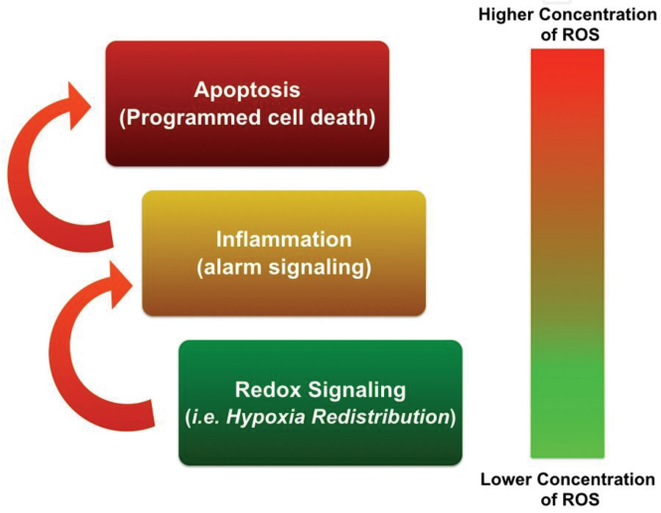

Figure 2. Concentration of generated ROS may involve in the different physiological response. At the low concentration, the ROS regulate in the redox signalling, and at the moderate concentration of induced ROS which participated in the inflammation process. At the high level of ROS concentration increased and was to be involved in the cellular apoptosis.

3. Tissue resident macrophages

Macrophages, which are present in almost all body tissue and display distinct location-specific phenotypes and gene expression profiles, display remarkable functional diversity in innate immune responses, tissue development and tissue homeostasis [41]. In different organs, the resident macrophages are given various appellations: microglia cells have fundamental importance in assessing the pathogenetic significance of perivascular inflammatory phenomena within the brain [42]; Kupffer cells are resident and recruited macrophages that play major roles in the homeostatic function of the liver and in its response to tissue damage [43]; alveolar macrophages are key determinants pulmonary immune responses and in the lung inflammation caused by asthma [44]. Previously, it was hypothesised that tissue macrophages were recruited from circulating blood monocytes. Recent studies have demonstrated that tissue macrophages such as microglia, Kupffer cells and Langerhans cells are established prenatally

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and arise independently of the hematopoietic transcription factor Myb [45]. Myb is required for developing hematopoietic stem cells (HSCs) and all CD11b^{high} monocytes and macrophages but is not required for yolk sac (YS) macrophages and for developing YS-derived F4/80^{bright} macrophages. Such macrophages can persist independently of HSCs in several types of tissue in adult mice [46]. Kupffer cells as well as other resident macrophages (e.g., microglia) originate from the YS in a colony-stimulating factor-1/receptor (CSF-1R)-dependent and Myb-independent manner. Researchers have suggested that these macrophages are maintained by local proliferation, which results in extensive mitosis after stress or an exchanged tissue microenvironment [43, 47].

Macrophages are the most crucial and abundant immune cells. They can be categorised into two primary types according to function and differentiation: classically activated macrophages (M1 macrophages) and alternatively activated macrophages (M2 macrophages) [48]. Macrophages are relevant to innate resistance and to the relationship between inflammation and autoimmune disease. In mouse models, macrophages present CD11b, F4/80 and CSF-1R, with F4/80 being the surface proteins for M1 and M2 macrophages [49, 50]. When pathogens enter the organism from the intestinal portal vein, circulating monocytes (surrounding the pathogens and present in the peripheral blood) respond to chemokines (e.g., CCL2) and are exposed to antigens. While interacting with pattern recognition receptors (PRRs), antigens may exert either M1 or M2 polarising activities, depending on the Th1 (IFN-γ) and Th2 (IL-4 and IL-13) cytokines and immune factors [51, 52].

4. Inflammation and macrophages

Inflammation is an important adaptive physiological response of the organism. Inflammation response embodies a complicated interaction among molecular mediators and cells. It globally affects the leukocytes, also the lymphocytes in their micro-environmental function and organisation [48]. Throughout their response, numerous factors are involved in the classical immune response. Macrophages detain a critical role in the uptake and degradation of infectious agents and senescent cells; they also play crucial roles in tissue growth, tissue remodelling and inflammation by producing oxidants, proteinases and anti-microbial peptide [40].

Resident macrophages sense exogenous or endogenous danger signals (e.g., bacterial products or necrotic cell debris) through PRRs. In response to Toll-like receptor (TLR) ligands and interferon-gamma (IFN-γ) or IL-4/IL-13, macrophages undergo M1 (classical) or M2 (alternative) activation. The activation of M1 and M2 macrophages mirrors TH1-TH2 polarisation; M1 and M2 activation span the extremes of a continuum. M1 macrophages, which display a morphology that depends on their tissue location, develop in response to stimulation with IFN-γ and microbial products such as LPS. M1 macrophages can secrete substantial amounts of pro-inflammatory cytokines, such as IL-1β, IL-15, IL-18, TNF-α and IL-12 [53]. M2 macrophages adapt to similarities and differences between IL-4, TLR ligands with IL-10 and glucocorticoids [54].

The phenotypes of M1 and M2 macrophages exhibit observable differences. The M1 phenotype is characterised by the expression of high levels of pro-inflammatory cytokines, high production of reactive nitrogen and oxygen intermediates, promotion of Th1 response and antimicrobial and tumour-inhibiting activity [43]. The M2 macrophage uses immune inhibitory effects to secrete large amounts of IL-10, TGF-β, and C-C motif chemokine ligands 17 (CCL17) and CCL22. Moreover, the M2 macrophage attracts non-cytotoxic T_{reg} and Type 2 T-helper cells (TH2 cells) to aggregate in tumour tissue, inhibit T-cell differentiation and function, lower cytotoxic T-cell function, induce T-cell apoptosis, secrete CCL18 and attract naive T cells [55].

Macrophage	**M1**	**M2**
Transcription factor		
Interferon regulatory factor	IRF-3 [61, 62]	IRF-4 [63]
(IRF)		
	IRF-5 [64]	
	IRF-8 [65]	
Nuclear factor	NF-κB [43]	
Signal transducer and activator of transcription	STAT-1 [66]	STAT-3 [43]
(STAT)		
		STAT-5 [67]
		SATA-6 [68]
Suppressor	SOCS-1	
of cytokine signalling	SOCS-2	
(SOCS)	SOCS-3	
	(controversial) [58]	
Phenotype	iNOS [69, 70]	YM-1 [71]
	IL-6 [72]	Arg-1 [73, 74]
	TNF-α [75]	Fizz-1 [76]
		IL-10 [77]

Table 1. Regulators in the M1 and M2 macrophage.

Macrophage polarisation is highly related to expressions of various TLRs on macrophages [56, 57]. The evidence indicates that TLR signalling (e.g., TLR4), which is activated by LPS and other microbial ligands, drives macrophages to prefer the M1 phenotype. In this reaction, MyD88 and TRIF activate a cascade of kinases, including IRAK4, TRAF6 and IKKβ; this results in the activation of nuclear factor kappa B (NF-κB), which drives the macrophage forward to the M1 phenotype. By contrast, IL-4 and IL-13 drive the macrophage's phenotype forward to M2. Activation of STAT6 through the IL-4 receptor alpha (IL-4Rα) and IL-10 induce activation of STAT3 through receptor IL-10R, which activates JAK1 and JAK3 (38), causing STAT6 activation [58, 59]. IL-10, TGF-β, IL-4 and IL-13 enhance inflammation and cellular immune response with NO, which is generated through IFN-γ-induced iNOS and is reduced in macrophages by Arg1 interactions with mast cells, basophils, eosinophils, NKT cells, IgE and selected subclasses of IgG. This promotes allergies and hypersensitivity [60] (**Table 1**).

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5. Inflammation and disease

Accumulating evidence indicates that chronic low-grade inflammation contributes to the systemic metabolic dysfunction that is associated with inflammation disorders [78]. Cytokines and pathogen-associated molecular patterns have been shown to co-stimulate cell surface receptors, including TLRs, to initiate intra-cellular signalling that activates NF-κB. NF-κB activation was thought to induce the target gene's expression to promote cellular proliferation and to activate the immune response. However, research has revealed that NF-κB activation can occur in most cell types; recent reports have demonstrated that high level activation of NF-κB signalling pathways in the liver, adipose tissue and central nervous system (CNS) is involved in the development of inflammation-associated metabolic diseases [79]. The mutants of the brain-specific serpin, neuroserpin, also form ordered polymers that accumulate within the ER of neurons; these mutations cause an autosomal-dominant type of dementia known as familial encephalopathy with neuroserpin inclusion bodies, which is believed to be an inflammation disorder [80, 81].

Research has shown that, in specific tissue lesions, extra-cellular lipid droplets are forming a core region surrounded by smooth muscle cells and collagen-rich matrix. Lymphocytes as the T cells, monocyte, macrophages and mast cells are infiltrating in the lesion particularly in regions where the atheroma grows. These immune cells also generate important signals in the defence cascade by producing the inflammatory cytokines, largely involved in the athero-sclerotic process [82]. A case report indicated that Alzheimer's disease (AD) inflammation appears to arise from within the CNS. Little or no involvement of lymphocytes or monocytes in AD was observed beyond their normal brain surveillance. This observation has placed AD outside the realm of conventional neuroimmunologic studies that largely focus on humoral aspects of such CNS inflammatory disorders as multiple sclerosis [83]. Judging from published reports, we believe that metabolic disorders and even neuronal diseases are highly related to abnormal inflammation.

6. Macrophage and T-cell differentiation

In pathogen infection, dendritic cells (DCs) and macrophages primarily act as phagocytotic antigen-presenting cells (APCs) that degrade infected pathogens into fragments, and then move those fragments to the nearby lymphoid organs. The pathogen fragments combine with cell surface histocompatibility complex (major histocompatibility complex) to activate and differentiate T cells. **Figure 3** displays the cooperation of the antigen-presenting cells, co-stimulatory molecules and cytokines.

The metabolic organs, such as the liver, pancreas and adipose tissue, are composed of paren-chymal and stromal cells, which include macrophages to maintain metabolic homeostasis. Bacterial infection innately activates macrophages, causing the secretion of proinflammatory cytokines, such as TNF-α, IL-6 and IL-1β. This promotes peripheral insulin resistance and reduces nutrient storage during the metabolic reaction. Furthermore, some additional

physiological mechanism can lead to the activation of macrophages. For these latest, the regulatory T cells (T_{reg}), the Fcγ receptors, the apoptotic cells and the prostaglandins are increasing the number of macrophages involved in the regulation of inflammation and anti-tumour defences [84]. These inflammatory mediators are involved in activating anti-microbial defence mechanisms, including oxidative processes that contribute to killing pathogens and the secreted IL-12 and IL-23. These direct the differentiation and expansion of anti-microbial T_H1 and T_H17 cells that help to drive inflammatory responses [85]. Recent research shows that intestinal antigen-presenting cells can be divided into $CD11c^+CD11b^-$, $CD11c^+CD11b^+$ and $CD11c^{dull}CD11b^+$ categories. Particularly, the $CD11c^{dull}CD11b^+$ cells are $CD103^-F4/80^+$macrophages, with efficient role in inducing the $Foxp3^+$ regulatory T (T_{reg}) cells [86]. Tumour cells affect the surrounding cellular environment by promoting tumour growth and metastasis by establishing a tumour microenvironment that is conducive to tumour development [87–90]. In the tumour microenvironment, tumour cells secrete inflammatory cytokines, such as TGF-β and IL-10. These cytokines stimulate differentiation of regulatory T and T_{reg} cells [91, 92] as well as differentiation of tumour-associated macrophages (TAMs) into M2 macrophages. This causes the host immune system to locate and attack cancer cells, which generates subsequent tumour cell evasion of this immune surveillance and attack, which enhances tumour growth and metastasis [87, 93–98]. Various cytokines, chemokines and growth factors in the tumour microenvironment are the primary elements that affect the host's anti-tumour ability and evasion of tumour cells [89, 99]. Tumour microenvironments are complicated cellular microcosms [89, 97], and numerous immune cells are located throughout tumour microenvironments. Macrophages are the most crucial and abundant immune cells in the tumour microenvironment. The two most critical types of macrophages, based on function and differentiation, are M1 and M2 macrophages. M1 macrophages are characterised by tumour

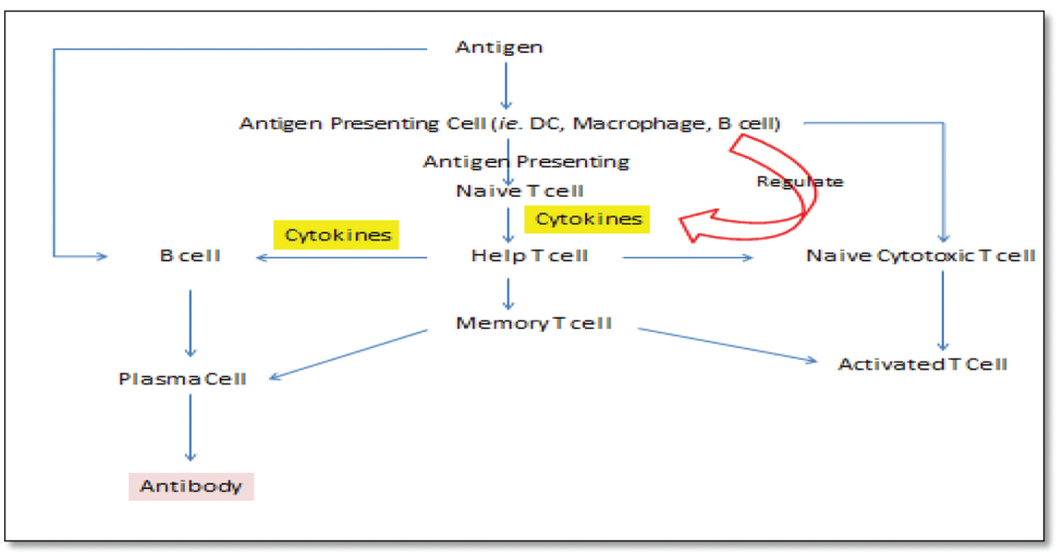

Figure 3. The cooperation of the antigen-presenting cells, costimulatory molecules, and cytokines. Bacterial infection innately activates macrophages, causing the secretion of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β. This promotes peripheral insulin resistance and reduces nutrient storage during the metabolic reaction. Furthermore, several additional mechanisms can also contribute to the activation of macrophages for immune-regulatory activity.

resistance, whereas M2 macrophages are characterised by tumour promotion [98, 100]. In mouse models, macrophages present CD11b, F4/80, CSF-1R and F4/80 as the surface proteins for M1 and M2 macrophages [93, 101]. Recent studies have noted large quantities of TAMs in tumour tissue. TAMs are the most abundant and critical immune cells in the tumour microenvironment [102–104] and are the main factors that enable the tumour microenvironment to exert immune inhibitory effects [101, 102]. In the tumour microenvironment, tumour cells and the surrounding stoma cells secrete cytokines and growth factors that stimulate TAMs and activate the various expression, function, receptor regulation and secretion types of chemokines [103, 105], including anti-tumour M1 macrophages and pro-tumour M2 macrophages [98, 106–108]. In the tumour microenvironment, the proportions of M1 and M2 macrophages are unequal. Tumour microenvironments contain large amounts of transmitters, such as M-CSF, IL-6, IL-10, TGF-β and COX-2, that induce transformation of TAMs into M2 macrophages that secrete immune inhibitory chemokines and have poor antigen-presenting and cytotoxic abilities, which generates tumour growth and metastasis [49, 98, 102–104, 109–114]. M2 macrophages and TAMs have protumour and immune inhibitory effects, secrete large amounts of IL-10, TGF-β, CCL17 and CCL22, attract non-cytotoxic T_{reg} and TH2 cells to aggregate in tumour tissue, inhibit T-cell differentiation and function, lower cytotoxic T-cell function, induce T-cell apoptosis, secrete CCL18 and attract naïve T cells [49, 98, 115]. NADPH oxidase is a major enzymatic source of cellular ROS. NADPH plays a fundamental role in maintaining normal cell functions. Recent research has focussed on this enzyme's role in cellular oxidative stress, which may eventually contribute to various pathophysiological conditions and diseases [27, 28]. Studies have found that NADPH oxidase modulates multiple redox-sensitive intra-cellular signalling pathways by generating ROS molecules. This modulation includes inhibition of protein tyrosine phosphatases and activation of certain redox-sensitive transcription factors [116, 117]. ROS consist of numerous molecular species, including H_2O_2, oxide ions (O_2^-) and OH^{-29}, that act as signalling molecules involved in the migration of hepatic profibrogenic cells [118] and the functioning of peripheral blood monocytes [119]. ROS and RNS, generated endogenously or in response to environmental stress, have long been implicated in tissue injury for a variety of disease states [120, 121]. Stimulation of the mitochondrial apoptotic pathway through ROS and mitochondrial DNA damage promotes outer membrane permeabilisation, which triggers caspase-dependent or caspase-independent cytosolic signalling events [122]. Activated inflammatory cells serve as sources of ROS and RNS that can initiate the alteration of the cell function, gathering specific cellular signalling, transcription factor activation, physiological factors release, the apoptosis process and compensatory cell proliferation. However, it remains unclear whether the ROS or the RNS production and release through neutrophils or macrophages enhance sufficient diffusion into the intra-cellular cytoplasm as to affect the cellular response [123, 124].

7. Wound healing

Immune cells are involved in virtually every aspect of the wound repair process, from the initial stages, where they participate in haemostasis and work to prevent infection, to later

stages where they drive scar formation [125, 126]. T lymphocytes exercise crucial in vivo effects on various parameters of healing [127–129]. Neutrophils help control infection during wound healing, but they also release harmful enzymes that damage healthy tissue surrounding the wound site [130–132]. Recent researchers have noted that several specific proteins produced by wound macrophages at the site of injury are involved: (1) in the recruitment and activation of additional macrophages infiltrating in the wound; (2) in the production of growth factors that promote cellular proliferation and tissue recovery synthesis; (3) in stimulating proteases and extra-cellular matrix growth and (4) in the process of tissue remodelling [133]. β-catenin-dependent Wnt pathways, which are classified according to their ability to promote stabilisation of β-catenin in the cytoplasm, act as cellular signals through cytoplasmic stabilisation and accumulation of β-catenin in the nucleus to activate gene transcription [134]. This could enhance wound healing by lymphocytes [135, 136]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase modulates multiple redox-sensitive intra-cellular signalling pathways by generating ROS molecules. This includes inhibiting protein tyrosine phosphatases and activating certain redox-sensitive transcription factors [116, 137, 138]. This shows that ROS regulate the expression of key chemical mediators that further modulate the inflammatory response in animal models; it has also been reported that these redox-sensitive processes may include cytokine action, angiogenesis, cell motility and extra-cellular matrix formation [139–141]; this can enable reliable estimates of wound-healing capacity, which is altered by various conditions, such as inflammation. Furthermore, research on one of the ROS has indicated that H_2O_2 plays a critical role in wound repair, inflammation and anti-inflammation mechanisms [142, 143]. Our published research also showed that the production of ROS (i.e., H_2O_2 after an injury has occurred) may cause healing to generate inflammation through the apoptosis of the cell. Over-inhibition of NADPH oxidase activity may reduce the normal progress of apoptosis under the wound and might delay healing [29].

Inflammation enhances vascular permeability, active migration of blood cells and the passage of plasma constituents into the injured tissue [144]. Blood leukocytes actively participate in the defence and inflammation responses, being activated since the earliest phases of atherosclerosis process. Inflammation and atherosclerosis shelter intricate mechanisms relied to leukocytes recruitment [145]. Neuro-inflammation mediators are described to be closely related to brain cells functioning (such as microglia and astrocytes), to the complement system activation and to cytokines, and chemokines production [146]. Regarding cancer development [147], pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, IL-8, IL-18, chemokines, matrix metallopeptidase-9 and vascular endothelial growth factor, are primarily regulated by the transcription NF-κB, which is active in most tumours and is induced by carcinogens [148]. Cutaneous wound repair is a tightly regulated and dynamic process involving blood clotting, inflammation, formation of new tissue and tissue remodelling [149]. Thrombin is the protease involved in blood coagulation. Its deregulation can cause haemostatic abnormalities, which range from subtle subclinical problems to serious life-threatening coagulopathies (i.e., during septicaemia) [150]. Inflammation and coagulation are both parts of the natural mechanism that protects the organism against infection. The endothelial cells and the platelets are capable to react in the acute, also in the chronic inflammatory environment. They release pro-inflammatory mediators that produce adhesion of molecules, proteases and clotting factors associated

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to leukocytes recruitment [151]. The elements of the PAR family serve as sensors that detect blood-clotting serine proteinases in the inflamed target cells. Activation of PAR-1 by thrombin and of PAR-2 by other factors on the membrane of endothelial cells generates rapid expression and exposure of adhesive proteins that mediate an acute inflammatory reaction and of the tissue factor that initiates the blood coagulation cascade [152] as presented as **Figure 4**.

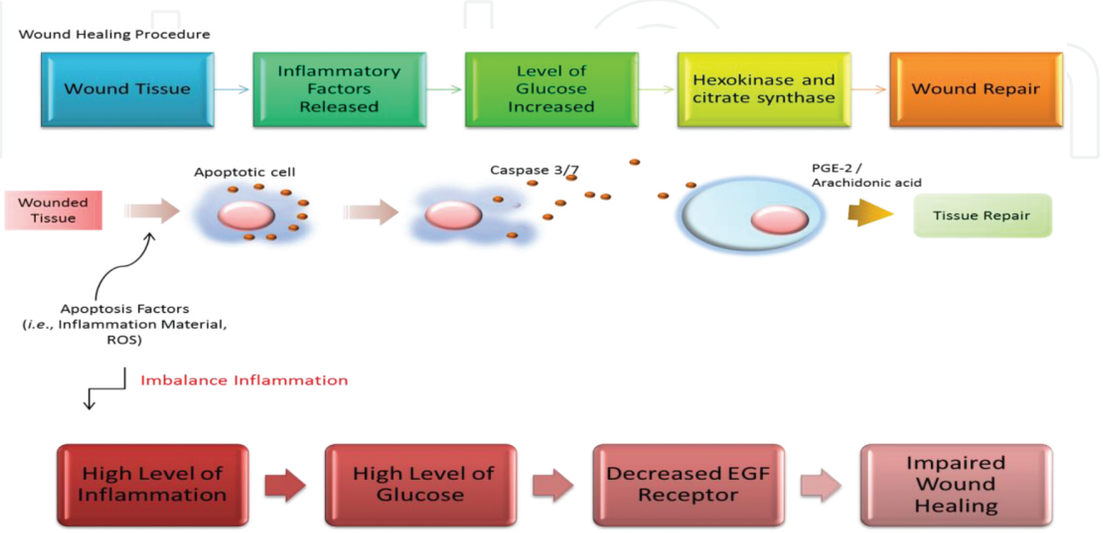

Figure 4. Wound healing was initiated after the injury of the cell, tissue even the organ. In the early stage of the healing, the damaged tissue producing a lot of ROS leading to neighbour cells into the apoptosis, following the apoptotic cells collapsed and released caspases were able to induce the tissue repair. However, the imbalance inflammatory may induce over-production of blood glucose that is leading to decrease the EGF receptor expression further to impair the wound healing.

8. Immunomodulation in anti-inflammation therapy

Nakanishi et al. found that celecoxib can alter the immune inhibitory effects of the tumour microenvironment by promoting transformation of TAMs into M1 macrophages, inhibiting tumour growth [153]. In 1968, Ikekawa et al. found that the fruiting body extracts from *Lentinus edodes*, *Trametes versicolor*, *Ganoderma tsugae*, *Flammulina velutiper* and *Tricholoma matsutake* demonstrated substantial anti-tumour activities towards transplanted tumour cells of Sarcoma 180 [154, 155]. *Autrodia comphorata*-derived beta-glucan inhibited tumour growth for Sarcoma 37, Sarcoma 180, Erlich ascites sarcoma and Yoshida sarcoma as well as inhibited LLC1 transplanted tumour growth [156]. Daily intake of *A. comphorata*-derived beta-glucan for 18 consecutive days was demonstrated to slow tumour growth and reduce the rate of metastasis [157]. Cytotoxic T-cell activity and tumour occurrence rates were observed, and the results illustrated that daily oral intake of *Grifola frondosua*-derived beta-glucan or Lentinan can enhance cytotoxic T-cell activity and reduce tumour occurrence rates [158]. The addition of a conditioned medium along with tumour cells into the progenitor cells of DCs was found to further inhibit maturation of DCs and lower the antigen-presenting capability of the DCs [159]. Tumour cells were found to secrete M-CSF, inhibiting dendritic and T-cell differentiation and

anti-tumour ability [87, 159–161]. In the inflammation environment, the amounts of M1 and M2 macrophages are not equal [162]. The tumour environment contains vast quantities of transmitters such as M-CSF, IL-6, IL-10, TGF-β and COX-2 that induce tumour megakaryocytes to differentiate into M2 macrophages, which, in addition to having inferior antigen-presenting and cytotoxic abilities, also secrete factors that inhibit immune cells, resulting in enhanced immune inhibitory effects in the tumour environment [49, 98, 102–104, 109–114]. M2 macrophages in tumour bearing mice enhance tumour growth and immune inhibitory effects. They also secrete cytokines, such as IL-10 and TGF-β, in high quantities, which attract non-cytotoxic T_{reg} cells and TH2 cells to congregate in tumour tissue; those cells inhibit the differentiation and normal function of T cells, including their cytotoxic ability, and further promote T-cell apoptosis [49, 98, 115, 163, 164]. The polarisation of TH1 and TH2 is built on cytokine patterns; polarisation begins when the antigen-presenting cells interact with naive T cells; they polarise into Type 1 (TH1) and TH2 cells in response to the type of antigen encountered [165]. TH1 and TH2 cells secrete different cytokines; TH1 cells rely on IL-2, IFN-γ and TNF, which are involved in cell-mediated immunity against pathogens, but TH2 cells depend mostly on IL-4 and IL-5, which stimulate the production of IgE antibodies and eosinophil responses, resulting in allergic diseases [166, 167]. Although an imbalanced TH1/TH2 immune response is linked to certain hypersensitivity disorders such as allergies, asthma and hay fever [168], studies have suggested that using a biological response modifier to restore the balance between TH1 and TH2 immune response can be a potential treatment option for IgE-dependent hypersensitivity [169]. *Ganoderma lucidum* is a medicinal mushroom that has been widely used as a folk medicine in Asian countries such as China and Japan for hundreds of years for its immunomodulating and anti-tumour effects. Numerous biologically available substances with immunity enhancement effects, particularly polysaccharides, have been isolated from the extract of *G. lucidum* [170].

Anti-microbial peptides are effective components of innate immunity that exist widely in biological systems. One of the specific anti-microbial peptides, hepcidin, is a 25-amino acid antibiotic peptide synthesised in the liver. Hepcidin is responsible for regulating iron balance and recycling iron in humans and mice. Studies have reported 0–100 μg/ml concentrations of hepcidin incubated with HT1080, Hep-G2 and HeLa for 24 h. The results have indicated higher growth inhibition ratios after 70 μg/ml treatment with hepcidin in HT1080 cells; the treatment has been very effective in inhibiting the growth of fibrosarcoma cells [171, 172]. Tachyplesin is an anti-microbial peptide present in the leukocytes of the horseshoe crab (*Tachypleus tridentatus*); it inhibited the growth of TSU tumour cells on the CAM of chicken embryos as well as the growth of B16 tumour cells in syngenic mice; moreover, it blocked the proliferation of both tumour and endothelial cells in culture in a dose-dependent manner, whereas proliferation was relatively unaffected in non-tumourigenic cell lines Cos-7 and NIH-3T3 [173]. D-K4R2L9 is a peptide comprised of Leu, Lys and Arg residues, totalling 15 amino acid residues that bind to and lyse B16-F10 mouse melanoma cells in culture at concentrations that do not harm normal 3T3 fibroblasts or erythrocytes; this can be conducted to prevent intravenous-injected D122 lung carcinoma cells from forming lung tumours in mice [174, 175]. Bovine lactoferricin (LfcinB), an anti-microbial peptide, is a 25-amino acid long highly basic peptide with a disulfide bridge between two cysteines, thus giving it a cyclic twisted anti-parallel β-sheet solution

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structure. LfcinB has been tested on neuroblastoma growth *in vivo*; nude rats carrying SH-SY-5Y xenografts were given injections of 1.0 or 2.0 mg LfcinB; these rats' cancer was significantly inhibited after LfcinB treatment, compared with untreated controls [176]. Anti-microbial peptides can activate specific innate immune responses and immunomodulatory effects in the host, even if the host is at risk or has been damaged. Furthermore, researchers have proposed that anti-microbial peptides can modulate the host's immune system through inflammatory responses and can stimulate beneficial inflammation; anti-microbial peptides might be able to inhibit tumour growth.

9. Conclusion

From the injury to the wound recovery, there are a series of physiological responses that occur in relation to immune cells. Polarisation of the macrophage is an important response in wound healing. A series of inflammatory factors are cited having notable function in the differentiation from novel macrophage into the classical macrophage (M1). The cellular mechanism involved in the regulation of classical macrophage (M1) and alternative macrophage (M2) was documented in the wound healing process. At the present time, the M1/M2 differentiation was studied for selected immune responses. However, future studies may allow possible therapeutic targets considering this process in wound healing.

The immunotherapy that is being developed offers some advantageous immunomodulation factors that are known in the field of alternative medicine, such as mushroom beta-glucan, anti-microbial peptides and triterpenoid; these factors represent a novel therapeutic approach for anti-inflammation. These factors may be a viable alternative approach to the problem of drug resistance. Recent insights into wound healing and anti-inflammation are promising; however, exploiting these insights is complex because it involves chemistry, biology, instrumentation science and formulation science. Discovering new methods that are more effective in targets is difficult. Immunotherapy might be an alternative therapy that can be applied in the early phases of clinical therapy. Similarly, immunomodulation might be applicable in the early phases of immune disease.

Author details

Yu-Sheng Wu[1], Fan-Hua Nan[2], Sherwin Chen[1] and Shiu-Nan Chen[1*]

*Address all correspondence to: d97b45004@ntu.edu.tw; snchen@ntu.edu.tw

1 College of Life Science, National Taiwan University, Taipei, Taiwan

2 Department of Aquaculture, National Taiwan Ocean University, Keelung, Taiwan

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