



The Role of Adiponectin in the Skin

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Abstract

Adiponectin (Ad), a 30 kDa molecule, is an anti-diabetic adipokine; although derived from adipose tissue, it performs numerous activities in various other tissues. It binds to its own receptors, namely adiponectin receptor 1 (AdipoR1), adiponectin receptor 2 (AdipoR2), and T-cadherin (CDH13). Ad plays several roles, especially as a regulator. It modulates lipid and glucose metabolism and promotes insulin sensitivity. This demonstrates that Ad has a robust correlation with fat metabolism. Furthermore, although Ad is not in direct contact with other tissues, including the skin, it can be delivered to them by diffusion or secretion via the endocrine system. Recently it has been reported that Ad can impact skin cell biology, underscoring its potential as a therapeutic biomarker of skin diseases. In the present review, we have discussed the association between skin cell biology and Ad. To elaborate further, we described the involvement of Ad in the biology of various types of cells in the skin, such as keratinocytes, fibroblasts, melanocytes, and immune cells. Additionally, we postulated that Ad could be employed as a therapeutic target to maintain skin homeostasis.

Key Words: Adiponectin, Keratinocyte, Melanocyte, Fibroblast, Innate immunity, Adaptive immunity

INTRODUCTION

Twenty years ago, Ad was discovered and characterized as a fat-derived hormone. As a crosstalk molecule between adipose tissue and other metabolism-related organs, it has been widely studied (Scherer, 2006; Deng and Scherer, 2010). Ad has been the subject of considerable interest in the field of metabolism, and significant steps have been taken to analyze and unravel its mechanism of action. A crucial study on Ad was published. At that time, because of the striking similarity between the C-terminal globular domain of Ad (gAd) and the subunit of complement factor C1q, it was named Acrp30 (Scherer *et al.*, 1995).

Spiegelman and colleagues identified mouse Ad using mRNA differential display analysis, which confirmed that Ad expression was initiated by adipogenic differentiation process (Hu *et al.*, 1996). Several key pieces of evidence in the early literature concerning this field indicated that Ad may be involved in the regulation of whole-body energy homeostasis (Hu *et al.*, 1996). Using a cDNA library from human adipose

tissue, other researchers determined that Ad is the most prevalent transcript, and they termed it the most abundant gene transcript 1 (APM1) (Maeda *et al.*, 1996).

Major technological advancements enabled researchers to separate natural Ad into three types of complexes using more refined size separation methods. They include low molecular form of Ad (LMW) with trimeric structure, medium molecular form (MMW) with hexameric structure, and high molecular form of Ad (HMW, 12mer to 18mer) (Pajvani *et al.*, 2004). Existing literature purports that Ad itself acts on pancreatic β cells, as well as on cells of the pancreas, heart, liver, potential muscle, kidney, and several other types of cells in various tissues. Ad is instrumental in mediating other crucial effects: it can also inhibit hepatic gluconeogenesis by downregulating genes related to glucose production. Moreover, Ad can promote insulin sensitization and improve whole-body energy homeostasis through its localized function in key metabolic tissues. Ad exerts a strong protective effect on several pathological processes in various cells by inhibiting cell death and inflammatory process, thereby concomitantly promoting cell

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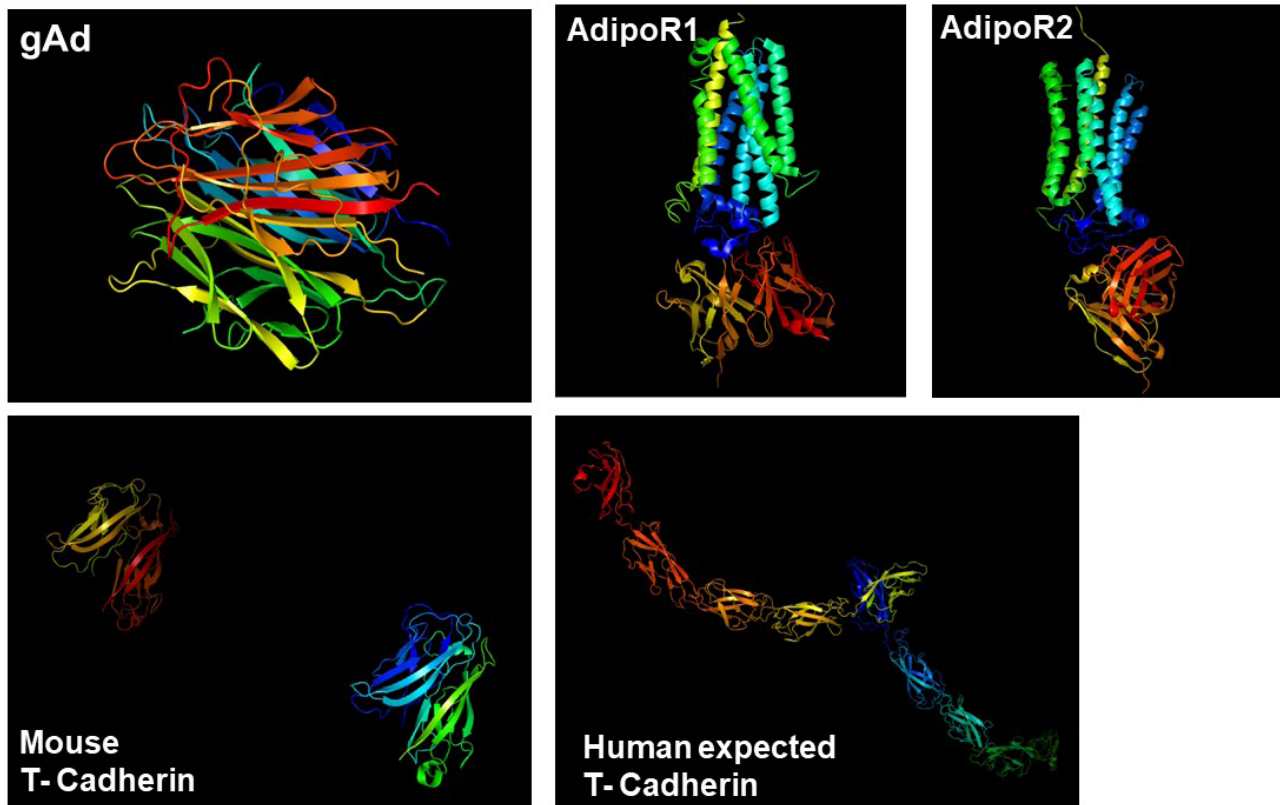


Fig. 1. Structure of globular adiponectin and adiponectin receptors. gAd, globular adiponectin.

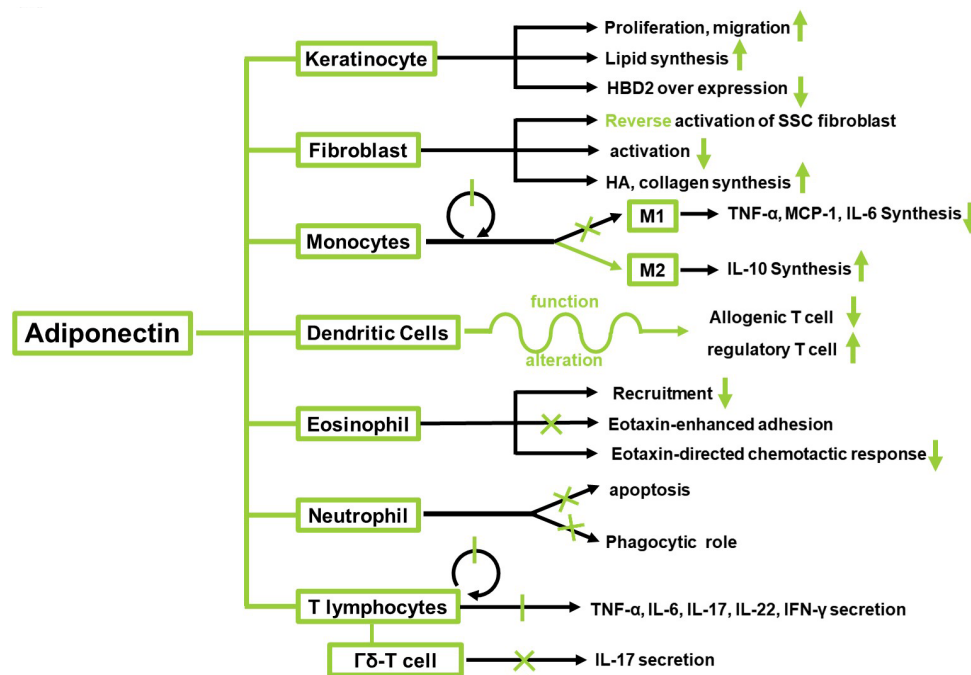
survival (Scherer, 2006; Deng and Scherer, 2010). Following the discovery of Ad as a fat-derived factor, researchers soon focused their attention on characterizing the Ad receptor. Kadowaki and colleagues succeeded in this goal. Through a series of classifications of fluorescent-activated cells, it was determined that the cDNA clone could act as a binding receptor of gAd. This molecule, termed AdipoR1, is generally expressed in the skeletal muscle and liver. After AdipoR1, another homologous sequence, termed AdipoR2, was isolated; its expression was relatively limited to within the liver. The two receptors showed a remarkably high degree of similarity. Both R1 and R2 are intact membrane proteins. According to the Scatchard diagram and ligand-binding analysis, AdipoR1 can serve as a binding receptor for gAd and full-length Ad (fAd). AdipoR2 shows medium affinity toward gAd and fAd molecules (Yamauchi *et al.*, 2003). In the past 20 years, Ad has been widely investigated and studied. It is established that Ad plays various roles in several organs, and these roles are mainly realized through the interaction between the two receptors of Ad. However, challenges in the field persist, and there are several unknown aspects of Ad that need to be elucidated (Wang and Scherer, 2016). In the present review, we focused on the interaction between Ad and skin based on existing experiments and studies. On this basis, four types of cells are described in detail: melanocytes, fibroblasts, keratinocytes, and immune cells.

ADIPONECTIN

Ad is an adipocyte-derived cytokine, also referred to as Acrp30 and AdipoQ. It is encoded by ADIPOQ in humans (Maeda *et al.*, 1996). Ad is composed of 247 amino acids. There are four different domains, the first being a signal sequence for the extracellular secretion. The second is the hypervariable region that varies among species. The third is a collagenous stalk region consisting of 65 amino acids. The last is a globular domain (Shapiro and Scherer, 1998). Ad exists both as a 30 kDa full-length molecule and a small-sized fragment containing the gAd (Fig. 1) (Wang and Scherer, 2016). fAd resembles the complement 1Q (C1Q) factors, whereas the tertiary structure of the globular domain shows a high degree of similarity with members of the tumor necrosis factor (TNF) family (Shapiro and Scherer, 1998). Ad comprises an asymmetric trimer of three identical monomers. There are three distinct complex forms, namely HMW, MMW, and LMW in native Ad. The distribution of complexes may contribute to different downstream biological effects. Ad may directly interact with its receptors through the interface at the apex, which is mostly hydrophilic (Pajvani *et al.*, 2003). Certain receptors bind to Ad (Table 1). Two receptors, namely AdipoR1 and AdipoR2, are homologous to the G protein-coupled receptors; one receptor resembles CDH13, a cadherin family receptor (Yamauchi *et al.*, 2003; Hug *et al.*, 2004). The receptors possess different affinities toward diverse forms of Ad and have distinct tissue specificities (Fang and Sweeney, 2006). When the receptor binds to Ad, it impacts the downstream target AMP kinase

Table 1. Adiponectin receptors

| Receptor | Affinity toward adiponectin | Expression site | Feature |
|------------|--|---|--|
| AdipoR1 | High affinity toward globular adiponectin Can bind to full-length adiponectin | Ubiquitous Especially skeletal muscle and liver | Integral membrane protein |
| AdipoR2 | Intermediate affinity toward both globular adiponectin and full-length adiponectin | Restricted to liver | Integral membrane protein |
| T-cadherin | Binds to the MMW and HMW forms of adiponectin | Endothelial cell Smooth muscle cell Attached to the plasma membrane by glycosyl phosphatidylinositol anchor | Interacts with eukaryotic post-translational modified adiponectin Does not interact with globular or bacterial-produced adiponectin |

**Fig. 2.** Effects of adiponectin on various types of cells in skin.

(Bonnard *et al.*, 2008). Ad is known to modulate numerous metabolic events such as regulation of glucose and fatty acid (Díez and Iglesias, 2003). However, the role of Ad in skin cells is relatively unknown. Therefore, in the present review, we focused on the function of Ad in keratinocytes, melanocytes, fibroblasts, and immune cells in the skin (Fig. 2, Table 2).

RELATIONSHIP BETWEEN ADIPONECTIN AND SKIN CELLS

Effects of adiponectin on keratinocytes

Keratinocytes constitute more than 90% of the cell population of the epidermis, the outermost part of the skin (Zeng *et al.*, 2017). The main function of keratinocytes is the establishment of a physical barrier against environmental stresses to protect our body (Yuki *et al.*, 2011). Therefore, it is important to repair the wounds in the skin to fill the gap created by the wound. Ad regulates multiple biological activities under various disease

conditions of the whole body (Chandran *et al.*, 2003; Achari and Jain, 2017) also known to influence cutaneous wound healing. Ad regulates wound healing in the skin through promotion of proliferation and migration of keratinocytes. Ad receptors are expressed in keratinocytes; Ad promotes the proliferation and migration of keratinocytes by activating ERK. The Ad-induced ERK signaling pathway is mediated by AdipoR1 and AdipoR2 (Shibata *et al.*, 2012). Ad also impacts keratinocyte lipid synthesis from the viewpoint of skin barrier function. Researchers determined that Ad facilitates an increase in keratinocyte intracellular and reconstructed epidermal lipid content, using lipid staining. The levels of ceramide and sphingosine, the downstream lipid-derivative metabolites, were also elevated. They attempted to define the underlying metabolic pathway of Ad by suppressing SIRT1 and inhibiting Ad receptors. Finally, they determined that Ad enhances the expression of the Ad signaling molecule, SIRT1, as well as nuclear hormone receptors such as peroxisome proliferator-activated receptors and liver X receptor- α , thereby enhancing lipid synthesis and

Table 2. Effects of adiponectin on various types of cells present in the skin

| Cell | Effects of Adiponectin on cells | References |
|--------------------------|---|--|
| Keratinocyte | Promotes cell proliferation and migration via ERK activation Effects on differentiation through enhancing lipid synthesis Anti-photoaging effect via downregulation of p38 and JNK/SAPK MAPK signaling | Shibata <i>et al.</i> , 2012 Hong <i>et al.</i> , 2019 Kim <i>et al.</i> , 2016 |
| Melanocyte | Full-length adiponectin inhibits melanogenesis via AMPK activation Globular adiponectin stimulates melanogenesis via AMPK-p38 MAPK, CREB signaling | Bang <i>et al.</i> , 2017 Kim <i>et al.</i> , 2018 |
| Fibroblast | Increasing HA and collagen production in a concentration-dependent manner and HA synthases 1,2,3 gene expression Attenuating CTGF-induced keloid fibroblast progression by inhibiting AMPK, p38 MAPK, ERK signaling Decreasing the activation of fibroblasts and reversing the activation phenotype of systemic sclerosis fibroblasts | Yang <i>et al.</i> , 2013 Iwayama <i>et al.</i> , 2012 Marangoni <i>et al.</i> , 2017 |
| Macrophage | Suppressing macrophage proliferation Activating M2 instead of M1 differentiation | Hui <i>et al.</i> , 2015 Tsatsanis <i>et al.</i> , 2005; Park <i>et al.</i> , 2007 |
| Dendritic cell | Role in DC differentiation remains controversial Alters DC phenotype Alters DC function to reduce allogenic T-cell proliferation | Tsang <i>et al.</i> , 2011; Jung <i>et al.</i> , 2012; Li <i>et al.</i> , 2012 Li <i>et al.</i> , 2012 Tsang <i>et al.</i> , 2011; Li <i>et al.</i> , 2012 |
| Neutrophil | Full-length adiponectin blocks neutrophil phagocytosis Inhibits neutrophil apoptosis | Wensveen <i>et al.</i> , 2015 Rossi and Lord, 2013 |
| Eosinophil | Negatively regulates recruitment of eosinophils Eotaxin-enhanced adhesion is inhibited by adiponectin pretreatment Eotaxin-directed chemotactic responses are diminished | Rossi and Lord, 2013 Yamamoto <i>et al.</i> , 2013 |
| Natural Killer (NK) cell | Still controversial | Takemura <i>et al.</i> , 2007; Shibata <i>et al.</i> , 2015 |
| T lymphocytes | Suppresses TNF- α , IL-17, IL-22 secretion Inhibits IL-17 producing activation of $\gamma\delta$ T cells | Takahashi and Iizuka, 2012; Jasinski-Bergner <i>et al.</i> , 2017 Shibata <i>et al.</i> , 2015 |

keratinocyte cell differentiation. This would aid in maintaining the homeostasis of the skin barrier (Hong *et al.*, 2019). There is also evidence of a link between Ad and psoriasis. Psoriasis is a chronic inflammatory disease that is influenced by various factors. It is characterized by hyperproliferation and modified differentiation of keratinocytes (Krueger and Ellis, 2005; Nestle, 2008). Researchers focused on adipokines and evaluated the relationship between adipose tissue cytokines and disease severity. In a study researchers enrolled 42 psoriasis patients, in addition to 42 healthy individuals, who constituted a control group. Ad levels in the psoriasis patient group were significantly lower than those in the control group. The results showed that the anti-inflammatory effects of Ad are diminished in psoriasis patients, possibly accelerating the inflammatory process. In addition, a significant linear relationship between Ad levels and Psoriasis Area Severity Index (PASI) score—an indicator of disease severity—was observed. However, the relationship between Ad and psoriasis severity, as well as the cause-effect relationship between psoriasis and adipokine levels, needs to be clarified (Sereflican *et al.*, 2016).

The anti-inflammatory effects of Ad also impact the inflammatory response-mediated premature senescence of keratinocytes. hBD2 overexpression was found in older individuals

and under conditions of UV exposure (Gläser *et al.*, 2009). UV irradiation influences calcium influx in keratinocytes and induces the production of intracellular reactive oxygen species (ROS) (Masaki *et al.*, 2009). ROS mediate various cellular events, including the mitogen-activated protein kinase (MAPK) activation and the induction of DNA damage, leading to cellular senescence and hBD2 overexpression. Therefore, the ROS-scavenging ability of Ad could contribute to the prevention of oxidative stress-mediated DNA damage and the attenuation of unregulated production of hBD2.

Effects of adiponectin on melanocytes

Melanocytes are skin cells—located in the human epidermis—that are involved in producing the human skin pigment melanin (Cichorek *et al.*, 2013). Tyrosinase and tyrosine-related protein 1 and 2 are involved in melanogenesis; adenosine monophosphate kinase, cyclic adenosine monophosphate response element-binding protein (CREB), p38 mitogen-activated protein kinases, and mitogen-activated protein kinase regulate *MITF* expression.

A few years ago, it was reported that Ad impacts melanocytes, regulating both their stimulation and inhibition. Interestingly, fAd exerts an anti-melanogenic effect; in contrast, gAd

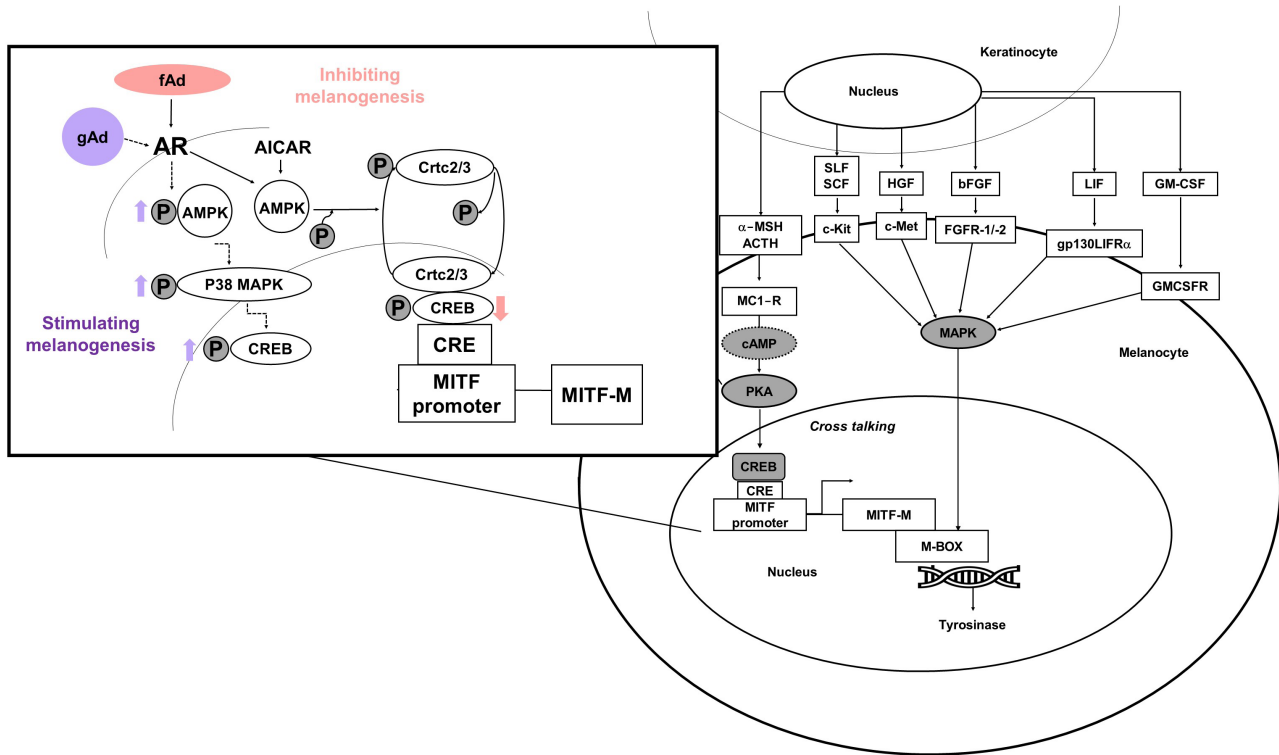


Fig. 3. Simple scheme of adiponectin action mechanisms in melanogenesis.

enhances melanogenesis (Fig. 3) (Bang *et al.*, 2017; Kim *et al.*, 2018).

Ad inhibits melanin synthesis via AMP-activated protein kinase (AMPK) activation. Furthermore, Bang *et al.* (2017) clearly demonstrated that CRTC2/3 and CREB co-operatively regulate *MITF* mRNA expression. They also reported that AMPK activation—through the induction of CRTC inhibitory phosphorylation—inhibits MITF expression (Bang *et al.*, 2017).

In contrast, the globular domain of Ad induces melanogenesis and melanin synthesis is mediated by AMPK-p38 MAPK and CREB signaling. However, PKA signaling is independent of gAd (Kim *et al.*, 2018). In addition, Mantzoros *et al.* (2007) observed a significant inverse relationship between serum Ad levels and melanoma risk in a case-control study, although this was not significant. Ad exerted anti-carcinogenic effects on other carcinoma cells, whereas it did not influence on melanoma cell proliferation in *in vitro* studies (Sun and Lodish, 2010). On the contrary, inhibition of tumor growth has been demonstrated for melanoma in animal studies. Ad has also been implicated in negative regulation of the growth of melanoma xenografts. The underlying mechanism of Ad may involve infiltrating macrophage into tumor tissue because tumors from Ad knockout mice exhibit reduced macrophage numbers (Sun and Lodish, 2010). Nevertheless, it remains unclear whether there is any impact on skin pigmentation in individuals with variations in AdipoR1 or AdipoR2 at the genetic level. Follow-up experiments are also necessary in *ex vivo* and *in vivo* models of hyper pigmentary disease (Tobin, 2018). Revealing the mechanisms governing the regulation of melanogenesis by Ad represents an important strategy for identifying therapeutic

targets for hyperpigmentary skin disorders. These targets can then be leveraged in skin-whitening products, which are one of the major driving forces in the biocosmetic market.

Effects of adiponectin on fibroblasts

Fibroblasts are the most common cells in the connective tissue; each subgroup of fibroblasts is distinguished by its unique function (Driskell and Watt, 2015). One of the most important functions of fibroblasts is to synthesize the extracellular matrix (ECM), which contributes to maintaining the structural integrity of most tissues (Yang *et al.*, 2013; Lynch and Watt, 2018). Type I collagen is the major component of the ECM in the skin and is composed of two $\alpha 1$ (I) chains and one $\alpha 2$ (I) chain, encoded by *COL1A1* and *COL1A2*, respectively (Woodley, 2017). Hyaluronan (HA) is abundantly expressed in the dermis and contributes to a wide range of cellular functions, including proliferation, migration, adhesion, and differentiation.

It has been reported that Ad boosts HA and collagen production by dermal fibroblasts. Additionally, increase in HA synthases (*HAS2*) expression has been observed (Yang *et al.*, 2013). Moreover, Luo *et al.* discussed the role of Ad in keloid progression (Iwayama *et al.*, 2012). The key phenotypic characteristics of keloid fibroblasts includes cell migration, hyperproliferation, and excess ECM accumulation. The authors proposed that Ad inhibits CTGF-induced keloid fibroblast proliferation, migration, and ECM production by attenuating CTGF-induced phosphorylation of p38 MAPK, ERK, and AMPK. Moreover, it was discovered that the AMPK, p38 MAPK, and ERK signaling pathways are involved in Ad-mediated CTGF-induced keloid fibroblast proliferation, migration, as well as

ECM production (Iwayama *et al.*, 2012).

In another experiment, it was confirmed that Systemic sclerosis (SSC) skin fibrosis was related to the injury of Ad signal in the injured tissue (Marangoni *et al.*, 2017). SSC is a chronic fibrodegenerative disease, characterized by dermal fibrosis, which eventually leads to the destruction of organ structure. Ad is the most abundant circulating fat factor in SSC patients. The level of Ad is decreased in diffuse cutaneous SSC patients, which is negatively correlated with disease activity, severity, and course. Ad simultaneously diminished the activation of fibroblasts and reversed the activation phenotype of SSC fibroblasts. These results revealed that the expression and dysfunction of endogenous Ad is a key pathogenic mechanism underlying skin fibrosis, with a strong negative regulatory effect on fibrosis. Enhancing cell Ad signaling may be employed as a novel strategy for treating SSC. Based on their tolerability and favorable pharmacokinetic properties, peptides that activate the Ad pathway may prove to be a feasible tool for further development of anti-fibrosis therapy.

RELATIONSHIP BETWEEN ADIPONECTIN AND SKIN AGING

Skin aging is influenced by intrinsic and extrinsic factors. Intrinsic (natural) aging is a gradual decrease in collagen production, decreased elastin elasticity, and decreased turnover rates. The criteria for intrinsic aging include fine wrinkles, loss of fat, and thin skin. Extrinsic aging is caused by external energies, forces, and factors such as ultraviolet violet radiation, gravity, and smoking (Sjerobabski-Masnec and Šitum, 2010). Urban particulate matter and blue light have also recently emerged as causes of skin aging (Kwon *et al.*, 2018; Yoo *et al.*, 2020).

The relationship between aging and Ad has been investigated (Iwabu *et al.*, 2015). Ad and AdipoR expression is skin aging-dependently reduced and an Ad deficiency promotes skin aging (Akazawa *et al.*, 2011). This indicates that Ad is related to skin aging. Young skin is characterized by low trans-epidermal water loss (TEWL), and aging skin gradually loses moisture (Ngatu *et al.*, 2017). Hyaluronic acid, which is mainly associated with TEWL, is supplied by keratinocytes and fibroblasts, and helps to maintain homeostasis by retaining moisture in the skin (Papakonstantinou *et al.*, 2012). Full-length Ad plays an important role in fibroblast HA metabolism and increases HA expression in the dermis (Akazawa *et al.*, 2011), which also helps to retain moisture in the skin (Papakonstantinou *et al.*, 2012).

The response to external wound healing becomes slower as skin ages (Wang and Dreesen, 2018). Wounds to the skin result in increased Ad generation, which slows the rate of keratinocyte proliferation in the epidermis during healing and promotes recovery (Kawai *et al.*, 2008). Photoaging accounts for a large proportion of extrinsic aging. Photoaging results in increased MMP-1 expression in the skin (Pittayapruek *et al.*, 2016). This can be suppressed by increased Ad production that attenuates skin aging via suppressing p38 and JNK/SAPK MAPK signaling in UVB-mediated premature senescent keratinocytes. These results indicate that Ad might act as an anti-photoaging agent in the skin (Kim *et al.*, 2016). Overall, the beneficial effects of Ad are improved skin health and inhibited skin aging.

ADIPONECTIN AND IMMUNITY

Immunity of skin

The skin acts as an excellent physiological barrier to external invasive factors, such as viruses, bacteria, and even small dust particles. As the skin is the first shield against pathogen infection, it is easy to presume that it is only involved in innate immunity, i.e., macrophages, neutrophils, etc. However, the skin also serves as a platform for recruiting components of the adaptive immune system, namely T cells—in particular CD4+, CD8+—and skin-resident memory $\gamma\delta$ T cells. Further, there are skin-specific immune cells, Langerhans cells, which are a mass of dendritic cells only located in the epidermis, and CLA+ memory T cells, which differentiate into either the T helper cells (Th) 1 or Th2 subtype depending on cytokine stimulation (Clark *et al.*, 2006).

Innate immunity and adiponectin

Innate immunity is the first line of defense against pathogens and it is distinguished by a rapid, non-specific response. It comprises several types of cells, including most antigen-presenting cells (APCs), neutrophils, natural killer (NK) cells, dendritic cells (DCs), macrophages, and ILC families. These cells are key regulators of energy and glucose homeostasis (Brestoff *et al.*, 2015). Ad colocalizes with TLR1, 2, and 4 proteins in human adipocytes, and TLR4 is the most abundantly expressed among the TLR families in human adipose tissue (Vitseva *et al.*, 2008). In addition, Ad regulates inflammasome activation via the AMPK signaling pathway, and gAd inhibits lipopolysaccharide (LPS)-primed inflammasome activation in macrophages via autophagy induction (Kim *et al.*, 2017). Ad can similarly abolish NLRP3 inflammasome activation via the AMPK-JNK/Erk1/2-NF- κ B/ROS signaling pathways (Dong *et al.*, 2020). These results suggest that Ad plays a dynamic role in the regulation of inflammation and innate immunity via the NF- κ B signaling pathway.

RELATIONSHIP BETWEEN C1Q AND ADIPONECTIN

Complement component 1q (C1q) participates in the classical pathway as a component of the innate immunity system. The CLR (collagen-like region) of C1q is the scaffold for C1s and C1r, which comprise a calcium-dependent C1 complex. Complement component 1q recognizes and binds to immunoglobulin, which induces the complement cascade to start. Ad contains a C1q-like globular domain. The structural similarity between Ad and C1q indicates that Ad participates in innate immunity. In fact, C1q and Ad both promote the removal of apoptotic cells by activating Mer tyrosine kinase, which regulates autoimmunity (Galvan *et al.*, 2014).

PRO- OR ANTI-INFLAMMATORY FUNCTION OF ADIPONECTIN

Ad usually acts as an anti-inflammatory factor exerting anti-apoptotic, inflammatory, and oxidative effects (Cappellano *et al.*, 2018). However, when LPS infiltrates, it helps cells to produce pro-inflammatory stimuli. Following LPS stimuli, Ad shows pro-inflammatory effects during the initial response (Yamaguchi *et al.*, 2005; Mandal *et al.*, 2011). Ad induces the

expression of pro-inflammatory cytokines and nitric oxide synthase in human cartilage cell chondrocytes (Lago *et al.*, 2008), indicating that it possesses both anti-inflammatory and pro-inflammatory properties (Monks *et al.*, 2019). Ad expression is linked to other adipokines, leptin, resistin, or other endothelial factors, including endothelin-1 (Stochmal *et al.*, 2020). They up- or downregulate each other, enhancing or inhibiting the activities of immune cells (Gerkowicz *et al.*, 2012; Li *et al.*, 2012; Takahashi and Iizuka, 2012; Stochmal *et al.*, 2020). From this section onward, we have summarized the roles of Ad in regulating innate immunity and adaptive immunity, especially T cells.

MACROPHAGES AND MONOCYTES

The relationship between macrophages and Ad has been well investigated, with the most studied aspects being the functions of Ad in innate immunity. M1 macrophages—classically activated macrophages—promote both the production of pro-inflammatory cytokines and obesity-induced insulin resistance and type 2 diabetes (Nguyen *et al.*, 2011; Mantovani *et al.*, 2013). Otherwise, M2 macrophages, alternatively activated macrophages, are polarized by IL-4 and IL-13 and contribute to induction of tissue repair, blockade of inflammatory responses, and the promotion of oxidative metabolism (Wolf *et al.*, 2004; Wulster-Radcliffe *et al.*, 2004). Numerous studies have demonstrated that Ad exerts anti-inflammatory effects. First, it downregulates M1 markers, such as MCP-1, IL-6, and TNF- α (Ohashi *et al.*, 2010; Odegaard and Chawla, 2011; Hui *et al.*, 2015). Differentiation of macrophages—which are activated by the classical pathway—is triggered by Ad deficiency (Hui *et al.*, 2015). Moreover, Ad blocks inflammatory effects by suppressing macrophage proliferation and by promoting the apoptosis of myelomonocytic progenitors. Second, it induces M2 proliferation by alternative activation (Tsatsanis *et al.*, 2005). fAd mediates the shift in macrophage polarization toward the M2 phenotype via the IL-4/STAT6 pathway (Li *et al.*, 2012). Because M2 macrophages play an important role in the browning of white adipose tissue (WAT) through secretion of norepinephrine, thereby providing a novel mechanism by which Ad promotes a cold-induced browning effect in (subcutaneous) adipose tissue (Park *et al.*, 2007), thus demonstrating a metabolic relationship.

Ad receptors play different roles in macrophages depending on their type. Macrophages bear AdipoR1, AdipoR2, and CDH13, with a high abundance of AdipoR1 (Mandal *et al.*, 2011). AdipoR1 primarily binds to gAd and suppresses pro-inflammatory cytokine expression, thereby mediating NF- κ B Ad suppressing activation (Chedid *et al.*, 2012). AdipoR2 is required for fAd-mediated M2 polarization (Medoff *et al.*, 2009). CDH13, especially activated by cold exposure, is required for M2 proliferation (Park *et al.*, 2007). However, suppression of these receptors does not result in a prominent effect on THP-1 cell uptake, although macrophages and their progenitors, monocytes, bear all these receptors, hence implicating other intermediate mechanisms. Further studies are required because AdipoR1 expression in monocytes remains a contentious topic (Jung *et al.*, 2012; Jasinski-Bergner *et al.*, 2017). The opposite conclusion may be derived from the low number of samples, which requires additional studies to define the properties of Ad in monocytes.

DENDRITIC CELLS (DCS)

DCs are one of important APCs. DCs exert a strong effect on psoriasis. DCs secrete IL-20, IL-23, TNF- α , and IL-23, thereby promoting the differentiation of Th17 cells, which stimulate keratinocyte proliferation and secrete IL-17A, IL-17F, and IL-22 (Gerkowicz *et al.*, 2012; Takahashi and Iizuka, 2012; Shibata *et al.*, 2015). DC counts are enhanced by Th17 through the boosting of IL-1, IL-8, and TNF- α levels via the upregulation of keratinocyte IL-8 secretion, which in turn upregulates IL-17 and IL-22 production (Shibata *et al.*, 2015).

The effects of Ad on dendritic cells remain controversial (Tsang *et al.*, 2011; Jung *et al.*, 2012; Li *et al.*, 2012). A prior study on Ad involving the blocking of DC activity revealed impaired activation of allogenic T cells following Ad treatment (Tsang *et al.*, 2011). A similar study showed that Ad directly impacts the DC phenotype, without considerable change in differentiation; conversely, the indirect effects alter DC function to reduce allogenic T-cell proliferation and enhance regulatory T-cell production (Li *et al.*, 2012).

Another study postulating the opposite theory specified DC activation via C γ /JNK/NF- κ B, resulting in Th1 and Th17 polarization depending on the Ad receptor type (Jung *et al.*, 2012); this indicates that Ad exerts a dose- and time-dependent effect (Luo and Liu, 2016). Other studies have shown low levels of Ad in psoriasis (Takahashi and Iizuka, 2012), which may indicate that Ad downregulates DCs. To clarify the action of Ad on DCs, further studies with well-considered models and experimental designs are needed.

BLOOD CELLS

Neutrophils

Blood cells are rich in neutrophils, of which granulocytes are the most abundant type. The mechanism of their response to bacteria involves antimicrobial granules that fuse with phagosomes and cause neutrophils to engulf and kill bacteria. Adiponectin negatively regulates neutrophils since most of them express AdipoR1 and AdipoR2, (Amulic *et al.*, 2012). Specifically, fAd AMPK-dependently blocks the phagocytic role of neutrophils through the suppression of NADPH oxidase and ROS production (Wensveen *et al.*, 2015). Ad also suppresses neutrophil apoptosis by activating ERK 1/2 MAP kinase, PKB, and AMP kinase (Rossi and Lord, 2013). Skin transplantation into Ad-knockout (KO) mice results in an expanded neutrophil population that induces an inflammatory response, indicating that an Ad deficiency impairs granulopoiesis (Li *et al.*, 2012; Masamoto *et al.*, 2016). Furthermore, Ad cleavage results in the production of gAd fragments in monocytic THP-1 and U937 cell lines (Wilk *et al.*, 2013). This process is notably mediated by leukocyte (neutrophil) elastase.

Eosinophils

Eosinophils are the second most abundant type of granulocytes; they protect against parasites and modulate innate and adaptive immunity through various mechanisms including the initiation and propagation of various inflammatory responses, the induction of T cell activation, and the secretion of cytokines such as IL-6, IL-12, and TNF- α (Rothenberg and Hogan, 2006) Human eosinophils express AdipoR1 and AdipoR2 (Yamamoto *et al.*, 2013), and Ad negatively regulates

eosinophil recruitment (Rossi and Lord, 2013). Although Ad does not affect eosinophil survival or CCR3 expression, Ad suppresses eotaxin-induced adhesion and decreases eotaxin-directed chemotactic responses, which results in reduced calcium signaling rather than altered surface receptor expression (Yamamoto *et al.*, 2013). However, AMPK activation in Ad KO mice first slightly decreased and then increased eosinophil counts, suggesting a relationship between Ad and AMPK (Li *et al.*, 2012). Eosinophils comprise a source of Ad (Withers *et al.*, 2017). Impaired adipocyte enlargement in eosinophil-deficient mice indicates a relationship between eosinophils and adipocyte maturation (Lee *et al.*, 2018).

NATURAL KILLER CELLS

NK cells are lymphocytes that play major roles in innate immunity as they can differentiate self from non-self and exert cytotoxicity against target cells (infected and tumorous cells). These cells do not need prior antigen exposure to exert anti-tumor actions, and their major responses target tumors and viruses. Natural killer cells function *via* unique signaling pathways that provide exclusive methods of genetic manipulation that enhance their effector functions (Abel *et al.*, 2018). Natural killer cells also mediate pro-inflammatory responses by promoting M1 activation (Waki *et al.*, 2005).

Human NK cells expressing CD56^{dim} also express AdipoRs, while CD56^{high} NK cells are AdipoR-negative. A small population of murine NK cells expresses surface AdipoR, whereas most murine NK cells store AdipoRs intracellularly (Wilk *et al.*, 2013). A modulating role of Ad in NK cells has not yet been clarified (Shibata *et al.*, 2015). That is, whether Ad enhances or reduces NK cell counts remains controversial (Takemura *et al.*, 2007; Shibata *et al.*, 2015). In addition, evidence has yet to show that AdipoRs contribute to the role of Ad in the regulation of NK cells (Kim *et al.*, 2006).

ADAPTIVE IMMUNITY: T CELL

T cells express the AdipoR1 and AdipoR2 (Cheng *et al.*, 2012), confirming that Ad has a strong relationship with adaptive immunity, especially with certain types of T cells. Ad inhibits the secretion of TNF- α , IL-17, and IL-22 by T lymphocytes; this phenomenon highlights the anti-inflammatory role of Ad (Takahashi and Iizuka, 2012; Jasinski-Bergner *et al.*, 2017). It also inhibits the enhancement of T-cell proliferation via the AMPK/p38 MAPK inhibitor (Li *et al.*, 2012). In Th, Ad specifically regulates Th1 cells, which express high levels of ADIPOR1 (Jasinski-Bergner *et al.*, 2017) and Th22 depending on its situation (Yamashita *et al.*, 2018). Regulatory T lymphocytes (Tregs)—the differentiation of which varies depending on whether they express a specific set of cytokines or not—inhibit the inflammatory reaction and antigen tolerance (Gerkowicz *et al.*, 2012). Ad may regulate Tregs by mediating the expression of TGF- β , which affects Tregs (Yamashita *et al.*, 2018).

IL-17 production by $\gamma\delta$ -T cells is inhibited by Ad; furthermore, the rate of infiltration of $\gamma\delta$ -T cells into dermal tissue is accelerated in Ad KO mice through direct interaction with AdipoR1, resulting in upregulated IL-17 (Shibata *et al.*, 2015). Cytotoxic T lymphocytes express ADIPOQ, and high levels of

Ad population may imply a correlation with Ad, which warrants further research (Jasinski-Bergner *et al.*, 2017). In response to LPS, Ad inhibits the expression of three T-lymphocyte chemoattractants that LPS-derived macrophages express (Steffens and Mach, 2008).

CONCLUSIONS

In the present study, we reviewed the functions of Ad in various types of cells of the skin. Ad is known to upregulate ECM production by dermal fibroblasts and anti-fibrotic factors concomitantly. It has been proved that Ad plays an essential role in renal fibrosis, periodontitis, and fibrosis diseases. In particular, a strong negative regulatory effect on fibrosis facilitates the development of novel anti-fibrosis therapy. Ad also enhances skin barrier function in keratinocytes. The proliferation and migration of keratinocytes, as well as lipid synthesis by keratinocytes, are regulated by Ad. Clinical studies on psoriasis patients have shown a cause–effect relationship, which needs to be investigated further in future studies.

Indeed, it has been determined that melanogenesis is regulated by Ad under *in vitro* conditions, and its regulation could be leveraged in the development of skin-whitening products and therapeutic agents for hyperpigmentary skin disorders. Ad is also linked to immunity, as skin is the foremost barrier in contact with pathogens. Although it remains controversial whether Ad application is efficacious in certain types of immune cells, it is clearly known that Ad can act as an anti- and pro-inflammatory factor under spatial and temporal conditions in macrophages, and that it has a strong relationship with T cells. The immune system works with sophisticated mechanisms; thus, further studies are required.

In conclusion, although the physiological roles of Ad are not fully understood, the present review demonstrates that Ad is involved in various aspects of cellular biology in the skin, indicating that it could be used as a molecular biomarker to treat skin disorders.

CONFLICT OF INTEREST

The authors have declared no conflicting interests.

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