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Models of human psoriasis: Zebrafish the newly appointed player

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ABSTRACT

Psoriasis is a human chronic, immune disease with severe cutaneous and systemic manifestations. Its prevalence, among the world population, highly varies with ethnicity and geography, but not sex from remarkable low levels in Asia to 2.3% in Spain, or an impressive 11.5% in Norway. The pathogenesis of psoriasis derives from complex genetic and environmental interactions, which creates aberrant crosstalk between keratinocytes and variated immune cell, resulting in open amplified inflammatory and pro-proliferative circuits. Both, innate and adaptive immune systems are known to be involved in the response at the cellular and humoral levels. Nevertheless, the exact molecular mechanisms are still under debate. Therefore, discovering useful therapeutic targets to stretch the molecular gaps in psoriasis pathogenesis and its associated comorbidities is still mandatory. So far, some mutagenic or pharmacological studies *in vitro* or using comparative vertebrate models have provided critical molecular insights and directed the human research. Although highly feasible in rodents, the versatile physiology, genetic similarity to humans and outstanding molecular toolbox available, suggest that elaborate forward genetic screenings are far easier to be conducted using the zebrafish model. Thus, in this review, we intend to briefly overview psoriasis and revise in a digested fashion the preclinical research models available, emphasizing the zebrafish as a powerful tool in the study of immune effectors on the same, and how it supports the discovering of new therapies that may help in controlling this widespread disease around the globe.

1. Introduction

Autoimmune and autoinflammatory disorders are a newly expanding concept in most medical areas, but with substantial relevance in the field of human dermatology (Murthy and Leslie, 2016). Among the several non-pathogenic skin disorders reported so far, one of the most recurrent is psoriasis. Psoriasis is a chronic, immune-mediated skin-disease with strong inflammatory and systemic manifestations which possess a complex genetic architectural background (Greb et al., 2016a; Woo et al., 2017). The increasing public concern about psoriatic elements is recurrently observed in the several research papers published yearly on this topic, and hence the urgent necessity to increase our knowledge of the mechanisms governing this widespread disease. So far, the pathogenesis of psoriasis is inferred to be triggered by traumatic, environmental or pharmacological mediators which induce susceptible individuals to aberrant crosstalk between keratinocytes and diverse immune cell types resulting in open amplified inflammatory and pro-proliferative circuits. Such elaborated characteristics provide the disease with extensive plasticity that allows it to manifest diverse phenotypes. Clinical manifestations include psoriasis vulgaris, plaque psoriasis, scalp psoriasis, guttate psoriasis, inverse psoriasis, erythrodermic psoriasis, palmoplantar psoriasis, and pustular psoriasis (Lebwohl, 2018; Raposo and Torres, 2016; Renton, 2014; Syed and Khachemoune, 2011). However, despite the particular phenotype expressed at a time, the pathophysiology in all psoriasis variants is characterized by an abnormal keratinocyte proliferation and strong immune cell infiltration among the different layers of the skin causing shared symptoms that include: intense itching, burning, and soreness (Ippagunta et al., 2016) (Fig. 1A). These symptoms mostly result from the open recruitment of immune cells to specific skin sections, which together with keratinocytes release potent inflammatory mediators, like interleukins (Fig. 1B and C). All psoriatic phenotypes have been reported worldwide with a global prevalence within adult populations, regardless of sex, estimated at 3% of the total world population (Lebwohl, 2003). However, prevalence estimates are strongly affected by marked variations observed among ethnic groups and geographical locations. In fact, reported incidence of psoriasis in Taiwan (0.19%) (Chang et al., 2009) and Japan is low (0.30%) (Kubota et al., 2015),

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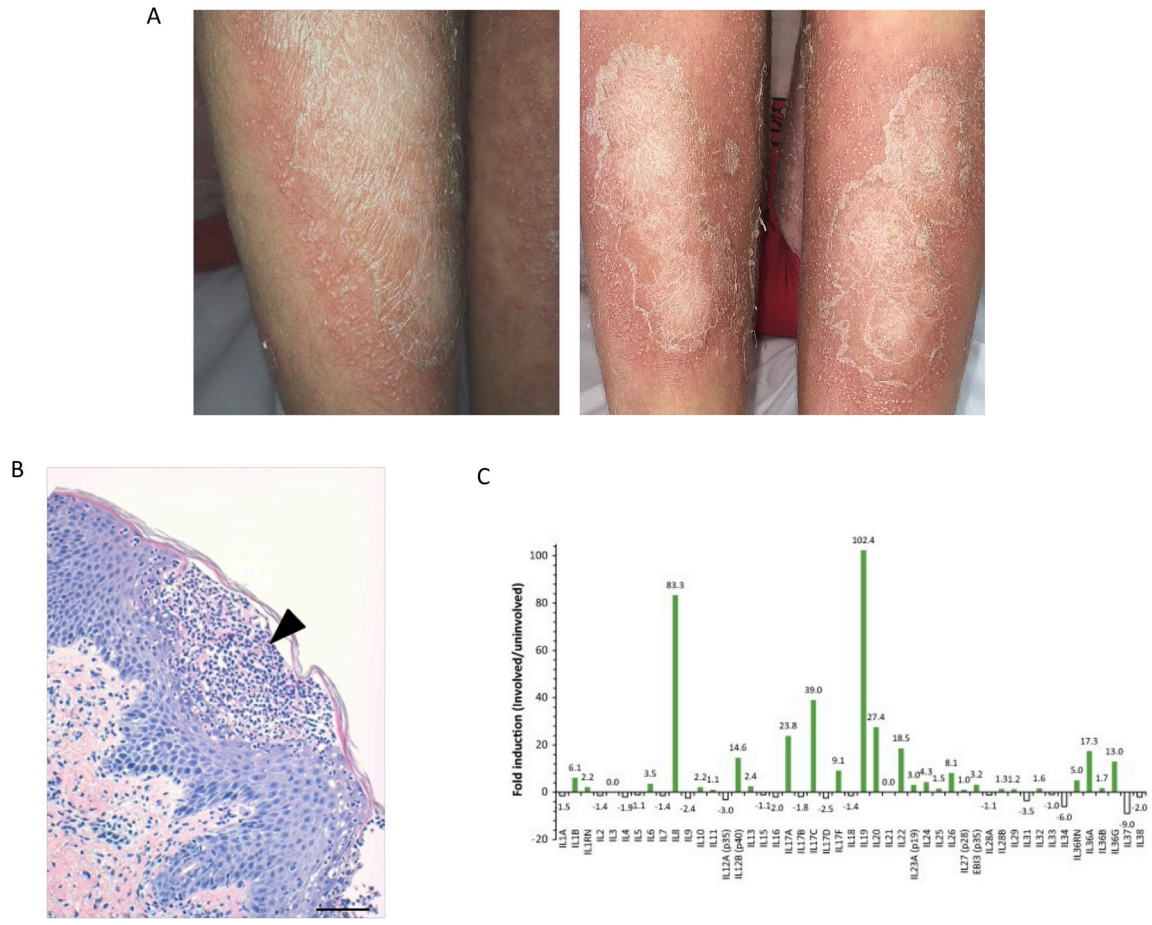

Fig. 1. General characteristics of psoriasis in humans. A) The abnormal keratinocyte proliferation produces characteristic sterile pustules overlying erythematous skin in the extremities of an adult patient. Redness areas denote inflammation signs. **B**) Classical histologic biopsy of lesional pustular psoriasis. The black arrowhead is pointing to an intense infiltration of immune cells affecting the different skin layers. (H&E, 30×). Scale bar 80 μm. **C**) RNA-seq data fold change showing differential regulation of interleukins 1 to 36 in psoriatic lesions compared with healthy skin (Baliwag et al., 2015).

moderate in Spain (2.31%) (Ferrándiz et al., 2014) or USA (2.50%) (Gelfand et al., 2005), and impressively high in Norway (11.43%), indicating that different races had diverse genetic backgrounds that profoundly affect the disease output (Danielsen et al., 2013). Patients affected with psoriasis suffer not only the externally exposed physical condition but, given its systemic characteristic, additional severe pathologies expressed as comorbidities use to be present as well (Parisi et al., 2013). Arthritis, autoimmune disease, cardiovascular disease, chronic obstructive pulmonary disease, inflammatory bowel disease, liver disease, metabolic syndrome, migraine, obesity, sleep apnea, psychiatric illness, sexual dysfunction, and addictive behavior have been repeatedly reported to promote a remarkably complicated disease loop in psoriatic patients (Capo et al., 2018; Greb et al., 2016b; Molina-Leyva et al., 2018). Moreover, patients suffering the combination of extreme visually exposed psoriatic lesions, linked to a complex comorbidity ultimately can trigger an uncontrolled, strong emotional stress burden, that in the worst scenario shall lead to suicidal behaviors (Wu et al., 2017; Wu and Armstrong, 2018).

To understand the mechanisms associated with psoriasis, *in vitro*, *ex-vivo*, and *in vivo* preclinical models of the human disease have been described (Bocheńska et al., 2017; Danilenko, 2008; Hawkes et al., 2018; Wcisło-Dziadecka et al., 2018). Notably, the murine models have proven to be extremely valuable in investigating critical molecular mechanisms that underlie the complex interplay between epidermal keratinocytes, and the innate and adaptive immune system in human psoriasis (Bezdek et al., 2018; Chuang et al., 2018; Nakajima and Sano, 2018). Nevertheless, this far, not any one of the systems mentioned above are neither homologous nor isomorphic and do not entirely phenocopy the human disease, suggesting the urgent necessity of searching for alternative relevant matching models. In this regard, a new player with particular characteristics has emerged in the last decade to complement the research efforts achieved so far in understanding intimate mechanisms of inflammatory skin diseases, such as, psoriasis. The zebrafish (*Danio rerio*) has striking similarities between cells, tissues, and physiological functions to those of humans (Galindo-Villegas, 2016). After its complete genome assembly, it was recognized that more than 70% of all human genes have at least one ortholog in zebrafish (Howe et al., 2013). Thus, by using the latest mutagenesis resources diverse human disease models have been produced in this model animal (Santoriello and Zon, 2012). Here, we briefly overview psoriasis and review in a digested fashion relevant research models, emphasizing on those using zebrafish that have been developed for the study of immune effectors on the same, and thus to provide support on discovering new therapies that may help on controlling this widespread disease around the globe.

2. Pathogenesis of psoriasis

In all vertebrates, the skin consists of two multilayered regions, the dermis, and the epidermis that is in contact with the environmental factors. Keratinocytes constitute both layers, differentially represented and stratified according to the taxonomic level of the host (Fig. 2A and B) human and zebrafish, respectively. However, despite the species represented, the basic morphology is always present and continuously

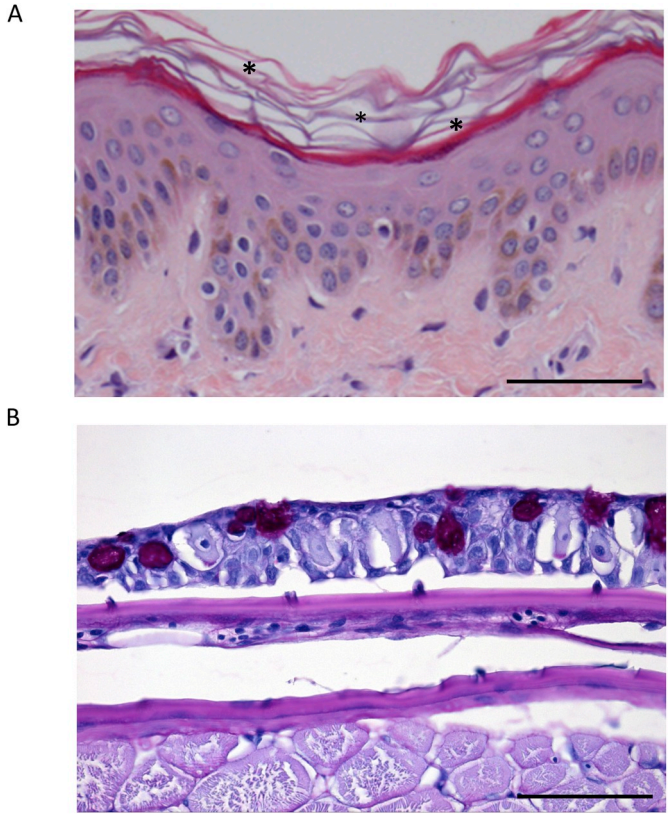

Fig. 2. Representative histologic differences between human and wild-type zebrafish adult healthy skin. A) Human skin, when compared with **B**) zebrafish skin, displays the presence of mature keratinocytes containing fibrous proteins (keratin) and forming the stratum corneum (black asterisk) at the outer layer. Nevertheless, both species share several characteristics at the epidermal and basal layers. (H&E classical staining) Bars, 50 μm.

renewing (Chermnykh et al., 2018). Keratinocytes are versatile cells which perform diverse essential mechanical protective functions while providing an immunological defense to the host (Johansen, 2017). Thus, understanding the regulation of keratinocyte proliferation, their complex functions, and the multiple interactions with immune cells is fundamental to get track of the pathogenesis of psoriasis.

Despite psoriasis disease results from an immune disorder, at the very early stage, a puzzling issue is that neither innate nor adaptive cells are present in high numbers to produce the cytokines and related chemokines required on site to activate an exacerbate the immune response. Therefore, it has been proposed that environmental factors via innate immune effectors, like the Toll-like receptors (TLRs), activate keratinocytes to release potent inflammatory mediators and active signaling molecules to recruit further macrophages, neutrophils, and mast cells that will amplify the inflammatory network and trigger the disease (Albanesi et al., 2018; Candel et al., 2014; Schubert and Christophers, 1985). Indeed, psoriasis etiology is based on an increased epidermal keratinocytes turnover that produces a focal coalescing raised cutaneous plaque with consistent scaling and variable erythema in connection to the presence of excessive infiltrating immune cells (Büchau and Gallo, 2007). Using human biopsies and last generation microarray technology, Pasquali et al. (2018), just recently characterized the keratinocyte-specific transcriptome signature of psoriasis lesional and non-lesional skin in psoriatic patients. Results revealed that keratinocyte-specific gene expression in psoriatic disease is mainly enriched for genes related to the cell cycle, innate immunity, DNA repair/replication, and keratinocyte development and differentiation, unequivocally supporting the notion that keratinocytes are significant contributors to molecular changes in psoriasis skin.

Some causes of increased keratinocytes proliferation and disturbed cell maturation have been suggested. Among them, the excessive presence of cAMP, the disturbed metabolism of vitamins and calcium, or modifications in the arachidonic acid downstream signaling (Andrés et al., 2017; Cubillos and Norgauer, 2016; Kharaeva et al., 2009; Setkowicz et al., 2015). These theories may in part explain some of the events occurring in psoriasis pathogenesis. However, due to critical overlapping mechanisms and the variated immune cellular elements occurring in the development of the disease, several aspects could be overlooked, and much more research, particularly at the innate level is still missing. In contrast, identification of expanded infiltrates of T-cells in psoriatic lesions (Cai et al., 2012), composed of polarized T helper (Th) cells populations, particularly Th1 and Th17 cells, and plenty pro-inflammatory mediators strongly put front the adaptive T-cells as crucial effectors in psoriasis (Greb et al., 2016b; Yamaguchi et al., 2018). However, the imbalance among Th subsets shown by the Th1 and Th17 cell increments, but not the regulatory Th2 and Treg is a matter of interest which deserves further clarification. Whatever the case, several excellent reviews published so far have analyzed in detail the role and particularities of the adaptive effectors in psoriasis pathogenesis under variated scenarios (Karczewski et al., 2016; Krueger and Bowcock, 2005; Singh et al., 2018). Nevertheless, despite the notorious advances on the contribution of T-cells in psoriasis, up to date the complete set of elements present in the pathogenesis of the disease is still unraveling and far of being completely understood. Our attention here faces the primary innate leukocytes present in the skin, namely neutrophils. On the sequence of inflammatory events triggered at the epidermis, keratinocytes initiate the response, and later the myelocytes, notably neutrophils take center stage in the pathogenesis of psoriasis (Ikeda et al., 2013). This controversial notion has been extended support by the histologic changes observed in variated animal models which resemble psoriasis lesions, with a high detection of the archetypal pro-inflammatory cytokine interleukin-1 (IL-1), but with a limited presence of T-cell infiltrates. To clarify it, Nakajima et al. (2010), following an elegant approach using Il1rn$^{-/-}$ mice, clearly demonstrate the development of cutaneous inflammation without the involvement of T-cell-mediated immunity, confirming that T cells are not required for the early pathogenesis of skin diseases. After that, variated information supporting the role of innate immunity in the developmental pathogenesis of psoriasis has emerged (Sweeney et al., 2011).

The clinical efficacy of compounds blocking the tumor necrosis factor (TNF), a critical cytokine that induces cell survival, apoptosis, and necrosis and contributes to both physiological and pathological process, highly suggests a vital role of the innate immune system in psoriasis (Boehncke and Schön, 2015; Zenz et al., 2005). TNF is considered a key messenger within the network of pro- and anti-inflammatory cytokines that have the capacity of triggering even its production, as well as that of other essential cytokines in inflammatory diseases (Kim and Moudgil, 2017). Consequently, anti-TNF therapy has become a mainstay treatment for autoimmune diseases (Li et al., 2017). Interestingly, despite the significant adaptive differences known between mice and human immune system, responses at the innate level are functionally fully comparable. Using relevant murine mutant lines to test the role of proinflammatory cytokines in the pathogenesis of skin inflammation, was demonstrated that TNF, but not IL-6 or IL-17, is crucial in this process (Nakajima et al., 2010). Likewise, clinical development of early lesions in psoriasis link to periodic waves of autoinflammation, represented by a burst of neutrophils and their associated cytokines related to the interleukin-1 (IL-1) family, such as IL-1α, IL-1β, and IL-36, that along with TNF all possess a full capacity of initiating the disease (Christophers et al., 2014). Mahil et al. (2017), using knockout individuals with IL1RL2 mutations validate IL-36 as a viable psoriasis target, proposing the development of IL-36 blockade as a therapeutic strategy. Interestingly, the IL-36 dependent genes signature profile in keratinocytes was extensive but particularly attractive among them is the high production of IL-17, IL-8, and CXCL1 which are

inflammatory elements closely related to neutrophils and were all three cytokines over expressed in psoriatic patients. Besides, Wang et al. (2018), confirmed that increased production and activation of IL-36 might act on neutrophils and further exacerbate neutrophilic inflammation. To round the concept, Swindell et al. (2018), using RNA-seq evaluated the gene expression response of primary epidermal keratinocytes to stimulation by IL-1β, IL-36A, IL-36B, and IL-36G. Strikingly, applying CRISPR/Cas9 mutagenesis, they demonstrate that shared IL-1B/IL-36 responses depend entirely upon MyD88 adaptor protein. Together, these results strongly emphasize the critical role of innate immunity in epidermal keratinocytes and neutrophils on triggering an exacerbated inflammatory response in psoriatic patients.

Here, we put forward a major question requiring an integrative approach. Which is the role of innate immunity in the IL-23/IL-17 pathway? So far, using murine models and human psoriatic lesional biopsies with elevated levels of IL-17 and IL-22 was demonstrate that anti-IL17 treatment dramatically improves the psoriatic skin lesions, regulates IL-23 and reduce inflammation by normalizing the levels of IL-17 (Malakouti et al., 2015; Paek et al., 2018). However, the cell types related were not identified. To do so, Reich et al. (2015), demonstrate that a single dose of the anti-IL-17A antibody Secukinumab resulted in skin normalization as soon as two weeks after injection, a finding paralleled by the disappearance of IL-17$^+$ neutrophils population, but not the T-cells. Meanwhile, several different immune cells, out of Th17 have been recognized as IL-17 producers. Whether being still debated, granulocytes like neutrophils and mast cells appear to synthesize IL-17 actively and release it through the formation of extracellular traps (Brembilla et al., 2018). Strikingly, this granulocytes behavior seems to expand well beyond psoriasis, and it extends along the vast majority of inflammatory diseases. As an example, Lunding et al. (2016), searching after the mechanisms underlying asthma observed that experimentally exacerbated mice released high amounts of several proinflammatory cytokines. Strikingly, this behavior was further associated with increased IL-17 and infiltration of variated IL-17 + immune cells in animals deficient either for IL-23p19 or the transcription factor RORγt, suggesting the crucial role of neutrophils in the response. However, caution should apply when evaluating the interrelation of these cytokines and neutrophils due to several isoforms exist, and further functional analyses are warranted.

3. Types of models for psoriasis research

3.1. In vitro

Several studies have evaluated psoriatic keratinocytes to identify intrinsic defects, differentiation, proliferation, and gene expression profile in cell culture or transplant systems (Dombrowski et al., 2011; Piskin et al., 2006). Keratinocytes used *in vitro* are from diverse origins, from intact or lesional human skin to established cell lines, like the normal human epidermal keratinocytes (NHEK) and immortalized human keratinocytes line (HaCaT) (Borowiec et al., 2013; Büth et al., 2007). *In vitro* keratinocyte research has provided valuable information. By themselves, however, these studies do not match *in vivo* psoriatic lesions entirely, and high variability among studies is observed turning quite tricky to draw comparisons. So far, several factors have been proposed as the source of variation (e.g., culture temperature, serum quality and quantity, calcium content, or lack of cell-cell interactions, and the intraspecies variability in the biological response due to cells commonly are isolated from individual members of the species). Despite clarifying the controversy, recently a transcriptomic study was conducted applying RNA-seq technology in a primary confluent keratinocytes monolayer culture grown from full-thickness punch biopsies, and the full-thickness skin biopsies itself from psoriasis patients, and control subjects (Swindell et al., 2017b). Results are puzzling, due to transcriptomic findings from the *in vitro* study, agreed only partially with results from full-thickness skin biopsies. These findings suggest that analysis of full-thickness skin biopsies may obscure functionally significant expression declines in psoriatic and normal patient keratinocytes which can, in contrast, be detected from *in vitro* analysis of patient-derived cells. Outcomes like this highlight the intrinsic constraints of the *in vitro* keratinocyte models of psoriasis produced at least due to the lack of blood and cell-cell interactions in the test system and suggest the use of direct physiological relevant models instead.

3.2. Ex-vivo

Ex-vivo models are invaluable research tools and have been used to investigate psoriasis. In general, *ex-vivo* human or rat skin is excised by abdominal surgery followed by removal of the adhering fat and visceral tissues. Eventually, (considered as a source of variation) the skin is rinsed thoroughly with NaCl solution before using it in the study of skin permeation and deposition. Hydrophobic or formulated compounds delivered by niosomes or liposomes containing gels are assayed for percutaneous absorption studies using Franz diffusion cells (Abu Hashim et al., 2018). *Ex-vivo* skin is particularly suited to address topical treatments of psoriasis or sun protection with dedicated biomarkers, such as pyrimidine dimers, p53 activation, caspase activation, and sunburn cells, based in histology and immuno-labeling (Agarwal et al., 2001; Bocheńska et al., 2017). However, the effect of topic treatments assayed for permeation *ex-vivo* could be affected by numerous combined reasons like the adsorption and fusion efficiency of niosomes, the nanosized particles, penetration rate, the richness of lipid in the environment, solubility and stability of compounds, or some other factors.

3.3. Pre-clinical

Despite useful, *in vitro* and *ex-vivo* systems are by far not capable of modeling whole-body physiology. As such, research into the pathogenesis of psoriasis has been severely hampered by the lack of a naturally occurring disorder in laboratory animals that mimic the complex phenotype and pathogenesis of the human disease. Throughout time, primates, dogs, pigs and several murine models related to the research process of psoriasis have been described (Bocheńska et al., 2017; Danilenko, 2008; Hawkes et al., 2018; Wcisło-Dziadecka et al., 2018; Yang and Wu, 2018). The approach clearly shows the longstanding practice of using animals for scientific purposes in biological research and medicine. Nevertheless, now this practice turns the issue an ordinary matter of debate by the radical supporters of the 3R's concept (replacement, reduction, and refinement) in our societies (Barré-Sinoussi and Montagutelli, 2015; MacArthur Clark, 2018). Nowadays, most current *in vivo* studies is conducted using one of the more than 40 unique mouse models of psoriasis described so far (Hawkes et al., 2018). However, while many mouse models of psoriasis have been proposed, a standardized validation criterion encompassing most models is not widely applied. On the aim to do so, Swindell et al. (2011), performed a whole-genome transcriptional profile study to compare gene expression pattern manifested by human psoriatic skin lesions with those that occur in five classical psoriasis mouse models displaying phenotypes associated to the TLR-imiquimod, TGFβ, endothelial tyrosine receptor, amphiregulin or Stat3. Results revealed that while cutaneous gene expression profiles associated with each mouse phenotype exhibited statistically significant similarity to the expression profile of psoriasis in humans, each model displayed unique sets of similarities and differences in comparison to human psoriasis. Several many other studies show the double-edged pattern associated with mice research as a model of psoriasis. A recent study demonstrates that one of the most used mouse model of psoriasis, the TLR-imiquimod does not produce psoriasis only, but triggers a core set of pathways active in different skin diseases (Swindell et al., 2017a). From these reports, we can conclude that mice are quite useful in the study of psoriasis and have been the predominant animal bridge between the bench and the

bedside in the past. Nevertheless, now is time to look forward and open the door to a new complementary animal model of psoriasis, the zebrafish.

4. The zebrafish as a model of skin inflammation

The use of zebrafish to investigate the genetic causes and molecular mechanisms of psoriasis is rapidly gaining popularity. Zebrafish is a small freshwater fish taxonomically positioned in the Cyprinid family. Compared to rodent models, zebrafish exhibit much more efficient reproduction, rapid external development, and undefeatable optical transparency throughout the early larval stages. Besides, zebrafish provides infinite possibilities of experimental reproducibility due to a daily high progeny availability (Meshalkina et al., 2017). Also, zebrafish enables the characterization of gene function via overexpression, transient depletion, or genome editing by applying variated gene editing technologies, including the latest CRISPR/Cas-based method (Ablain et al., 2018; Varshney et al., 2015). Zebrafish are not only embryo/larvae with robust phenotypes or genetically tractability, but they also present accessibility optically for intravital real-time *in vivo* imaging and display a fully functional innate immune system where myeloid cells are present as soon as 24 h post fertilization (hpf) mimicking their mammalian counterparts (Gurevich et al., 2018; Henry et al., 2013; Torraca and Mostowy, 2018). Besides that, the zebrafish genome is fully sequenced, highlighting a remarkable similarity with humans, with at least 71.4% human coding genome having a direct ortholog in zebrafish (Howe et al., 2013; Shim et al., 2016). The Zebrafish Model Organism Database (ZFIN https://zfin.org) is the central resource where genetic, genomic, and phenotypic data on zebrafish research is curated and run (Bradford et al., 2017). Similar to the mouse, the zebrafish epidermis is a multilayered tissue composed by keratinocytes, separated from the dermis by a basal membrane. In fish, this structure is much simpler than the mammalian one, and in contrast to terrestrial vertebrates, the skin does not function to prevent dehydration due to the lack of *stratum corneum* (Webb et al., 2008). However, several physical similarities exist. Among them, at 24 hpf different skin layers representing the epidermis and the dermis are separated from the underlying tissue stroma by a basal membrane, and at 2 days post fertilization (dpf) the lamina lucida densa can be identified (Le Guellec et al., 2004). Interestingly, it has been observed *in vitro* and *ex-vivo* that alteration of these elements forming paracellular barriers for solutes and inflammatory cells, together with proinflammatory cytokines are related to the early events in psoriasis (Kirschner et al., 2009). These unique features present in the zebrafish model provides a unique platform to further understand *in vivo* their functionality in the psoriatic disease. Last but not least, in zebrafish, the lipid-rich cornified layer observed in higher mammals is not present, and epidermis remains metabolically active and readily available as a live substrate for experimentation throughout all life stages (Glover et al., 2013). As a consequence, relevant zebrafish disease models of psoriasis have been developed to aid in unraveling the complicated pathogenesis in the human disease (Table 1).

4.1. Mutant models

Zebrafish with its extensive toolkit for genome modification and its capacity for recapitulating human disease has found a niche among the preclinical models of psoriasis to study and validating genetic variants, as well as to identifying previously unrecognized disease-associated genes. The first zebrafish model generated to study the development of the basal epidermis and the associated mechanisms were the mutant penner/lethal giant larva 2 (*pen/lgl2*). The *pen/lgl2* zebrafish has a defect which disrupts the basal localization of keratin cytoskeletons on epidermal keratinocytes. This effect in humans is mediated by the *lgl2* homolog, the Hugl-2 gene which is a crucial regulator of epidermal polarity, and, in turn, keratinocyte proliferation (Zimmermann et al., 2008). The mutant *pen/lgl2* zebrafish larvae shown overgrowth of epidermal cells leading to different morphological shapes and fail to form basal hemidesmosomes, which link the epidermis to the underlying basement membrane (Sonawane et al., 2005, 2013). Therefore, while in *pen/lgl2*$^{-/-}$ skin detaches from the basement membrane, epidermal cells hyperproliferate and migrate ectopically, resulting in a psoriasis-like phenotype. Deletion also removes an essential enhancer for keratinocyte differentiation, and the loss of this regulatory element allows

Table 1
Synopsis of relevant zebrafish models supporting the comparative study of human psoriatic disease.

Type	Name	Description	Advantage	Reference
(Mutant)	*Penner/lethal giant larvae 2*	The lack of *pen/lgl2* disrupts the basal localization of keratin cytoskeletons on fish keratinocytes.	Target the process of hemidesmosome formation, maintenance of cytoskeletal elements, and cellular morphology in the basal epidermis.	Sonawane et al. (2005)
	Hai1a/Spint1la	Keratinocytes acquire a mesenchymal-like characteristic, lose contact, become mobile and highly susceptible to apoptosis. Antagonistic roles between *Hai1* and *St1a* are produced.	Useful to uncover crucial signaling players on defects caused by the loss of Hai1 and Matriptase 1a.	Carney et al. (2007)
	Hai1	Fish embryos exhibit inflammation in areas of epidermal hyperproliferation.	Enable the study of chronic inflammation and visualization of immune responses with high resolution in real-time.	Mathias et al. (2007)
	Psoriasis/m14	This fish exhibits widespread over proliferation of the epidermis and a defect in keratinocyte differentiation	Allow the study of epidermal growth regulation and may point further insights into skin development in fish.	Webb et al. (2008)
(Morphant)	*Tnfa-Tnfr2*	Inhibition of the ligand *tnfa* and related receptor 2 results on neutrophil mobilization to the fish skin in response to H2O2 derived enzyme (DUOX1) released by keratinocytes	A robust platform to study the management of inflammatory molecular mechanisms resulting from oxidative stress.	Candel et al. (2014)
(Inducible)	*Trpv4*	Explores fish new immune mechanisms mediated by a *TRPV4/TAK1/NF-κB* signaling pathway that operates in skin keratinocytes.	A convenient model to study skin inflammation resulting from osmotic changes in the absence of commensal microbes and functionally mature immune cells.	Galindo-Villegas et al. (2016)
(Germ-Free)	GF	Fish generated following this procedure lack regular microorganisms that may contribute to achieving a psoriatic status.	Allow the experimental colonization with single or complex microbial association(s).	Galindo-Villegas et al. (2012)

DUOX1 Dual oxidase 1; **H2O2** Hydrogen peroxide; **Hai**1 Hepatocyte growth factor activator inhibitor 1; **NF-κB** Nuclear factor kappa B; **Pen/lgl2** Peener/Lethal giant larvae; **St1a** Serine protease matriptase; **TAK1** TGFb associated kinase 1; **TNFa** Tumor necrosis factor a; **TNFR2** TNF receptor 2; **Trpv4** Transient receptor potential vanilloid 4.

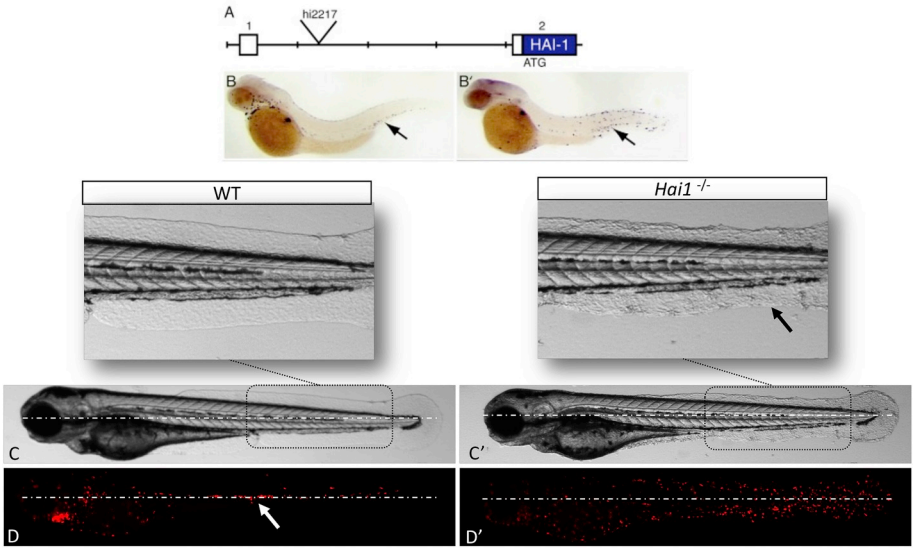

Fig. 3. Development, and assay process of a mutant zebrafish model of psoriasis disease. A) Genomic map of *hi2217* insertion and the start of the *hai1a* (*spint1a*) open reading frame (blue) is indicated (ATG); each section equals 500 bp. **B, B′)** *In situ* hybridization of zebrafish myeloperoxidase (*mpo*) at 2 dpf, arrows indicate the position of the intermediate cell mass (ICM), the location of neutrophil development in zebrafish embryos (Mathias et al., 2007). **C, C′)** Bright field and fluorescence images showing lateral views of (**C**) wild-type sibling (WT) and (**C′**) a homozygous *hi2217 larvae (hai1a* $^{-/-}$*)* mutant at 3 dpf. Ectopic keratinocyte aggregates are pointed by the black arrow in the magnified area. (**D, D′**) WT siblings or Mutant *hi2217* were crossed with the transgenic zebrafish line Tg (*lysC:DsRed2*)^{nz50} to visualize neutrophil (in Red) behavior in the resulting larvae at 3 dpf. (**D**) In WT fish, the white arrow indicates the basal state of neutrophils in the CHT. (**D′**) While in *hi2217* mutants the presence of Hai1 affects the matriptase producing an exacerbated behavior of neutrophils resulting in high proliferation and massive recruitment in the affected epidermal tissue. White dash-dot line act only as a visual guide. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

for the study of psoriasis association. In connection with the same, the *pen* function is revealed as specifically required for the process of hemidesmosome formation. However, suggested caution should be applied with this model due to the disruption of *lgl2* would lead to epidermal tumor formation.

Not long after the creation of the *pen/lgl2* mutant, two more lines carrying mutations in the serine peptidase inhibitor, Kunitz type 1 a (*Spint1a*), also known as *Hai1a* (Fig. 3A), and clathrin interactor 1a (*clint1a*) genes exhibited epidermal proliferation, and keratinocytes with mesenchymal-like characteristic (Carney et al., 2007; Dodd et al., 2009; Mathias et al., 2007). In both models, loss of *Spint1a* produces neutrophil skin infiltration and losing of contact among keratinocytes which become mobile and highly susceptible to apoptosis (Fig. 3 B, B' C, C'). In the *Spint1a* mutant, antagonistic roles between *Hai1* and its target matriptase 1a (*St1a*) are produced. The mutation over the *Spint1a* in zebrafish enable the study of chronic inflammation and visualization of immune responses with high resolution in real-time. These models demonstrate their utility in the identification of functional interactions between the keratinocytes and surrounding leukocytes (Fig. 3D, D'). At 24 hpf, the *Spint1a*$^{-/-}$ phenotype is characterized by an erratic localization of E-cadherin in epidermal cells, the fast expression of the damage phenotype, and a keratinocyte hyperproliferation in regions of cell aggregation.

An additional mutant model in this series is the *Psoriasis/m14*. This zebrafish mutant model was identified resulting from a large-scale ethylmethanesulfonate (EMS) mutagenesis screen for genes required for zebrafish embryogenesis (Webb et al., 2008). Mutants of this fish do not regulate cell proliferation in the epidermis late in embryogenesis and concomitantly accumulate aggregates of epidermal cells in the embryo surface, clearly resembling psoriasis. Besides, the late-stage epidermal keratin is significantly reduced in this mutant fish and acts non-cell autonomous, suggesting that it encodes an extracellular factor that controls keratinocyte proliferation and differentiation. A loss-of-function mutation in *atp1b1a*, encoding the beta subunit of a Na, K-ATPase pump, has been responsible for this phenotype (Hatzold et al., 2016). Blockade of the ensuing PI3K-AKT-mTORC1-NF-κB-MMP9 pathway activation in basal cells, as well as systemic isotonicity, prevents keratinocyte hyperproliferation and subsequent malignant transformation.

4.2. Morphant model (knock-down)

A recent study has approached the functionality of *tnfa*, its receptors (*tnfr*), and neutrophils behavior in the skin of zebrafish (Candel et al., 2014). Morpholino technology producing a transient gene knock-down cannot be used to study gene function in mice because antisense oligonucleotides are rapidly diluted during mouse development (Flynt et al., 2017). In a strict sense, morpholino is not a right genetic approach due to the possibility of producing unspecific reactions, but they have been used extensively in zebrafish research with a high degree of success (Kok et al., 2015). Candel et al. (2014), following elegant approaches, including morpholinos, demonstrate that the knock-down of *tnfr1* have little effect on the neutrophil trafficking in the developing larvae at 3 dpf, while *tnfa* and *tnfr2* had a strong effect in their mobilization (Fig. 4A). Additionally, in this study the use of the transgenic zebrafish Tg(*mpx:GFP*) in which neutrophils express green fluorescence under the promoter of myeloperoxidase allow these researchers to determine the particular geographical position of neutrophils. Besides, they supported this result by applying a novel fluorescence quantification technique and contrasted by visual inspection (Fig. 4B and C). The specificity of the observed phenotype for the *tnfr2* was confirmed by using a dominant-negative of Tnfr2 lacking the entire intracellular signaling domain, which phenocopy the results previously observed. To establish other cell types, intimately related in the response whole-mount immunohistochemistry against p63 (basal keratinocyte marker) was conducted in morphant fish with neutrophils expressing GFP. Results revealed that mobilized neutrophils in *tnfr2* deficient larvae were in close contact with skin keratinocytes. In addition to neutrophils mobilization, *tnfr2* or *tnfa* morphants triggers a steady production of master proinflammatory molecules (*tnfa*, *il1b*, and *ptgs2b*) through the NF-κB pathway, resembling the phenotype of mutant *spint1a* and *clint1a* mutant zebrafish where chronic inflammation triggers *il1b* production and neutrophil infiltration. To round their results, they sorted neutrophils from Tg(*mpx:GFP*) and keratinocytes from Tg(*-2.9krt18:RFP*) embryos revealing that both cell types overexpress inflammatory cytokines, reflecting a positive feedback loop between both cell types potentiating skin the inflammation. Strikingly, using an H_2O_2-detecting probe, it was observed that *tnfr2*-deficient larvae keratinocyte activate dual oxidase 1 (DUOX1) enzyme creating H_2O_2 gradients which were sensed by neutrophils through the tyrosine kinase Lyn (Yoo et al., 2011). Together, these results give strong support to the interplay between neutrophils and TNF-alpha which defines the immune pathology in psoriasis.

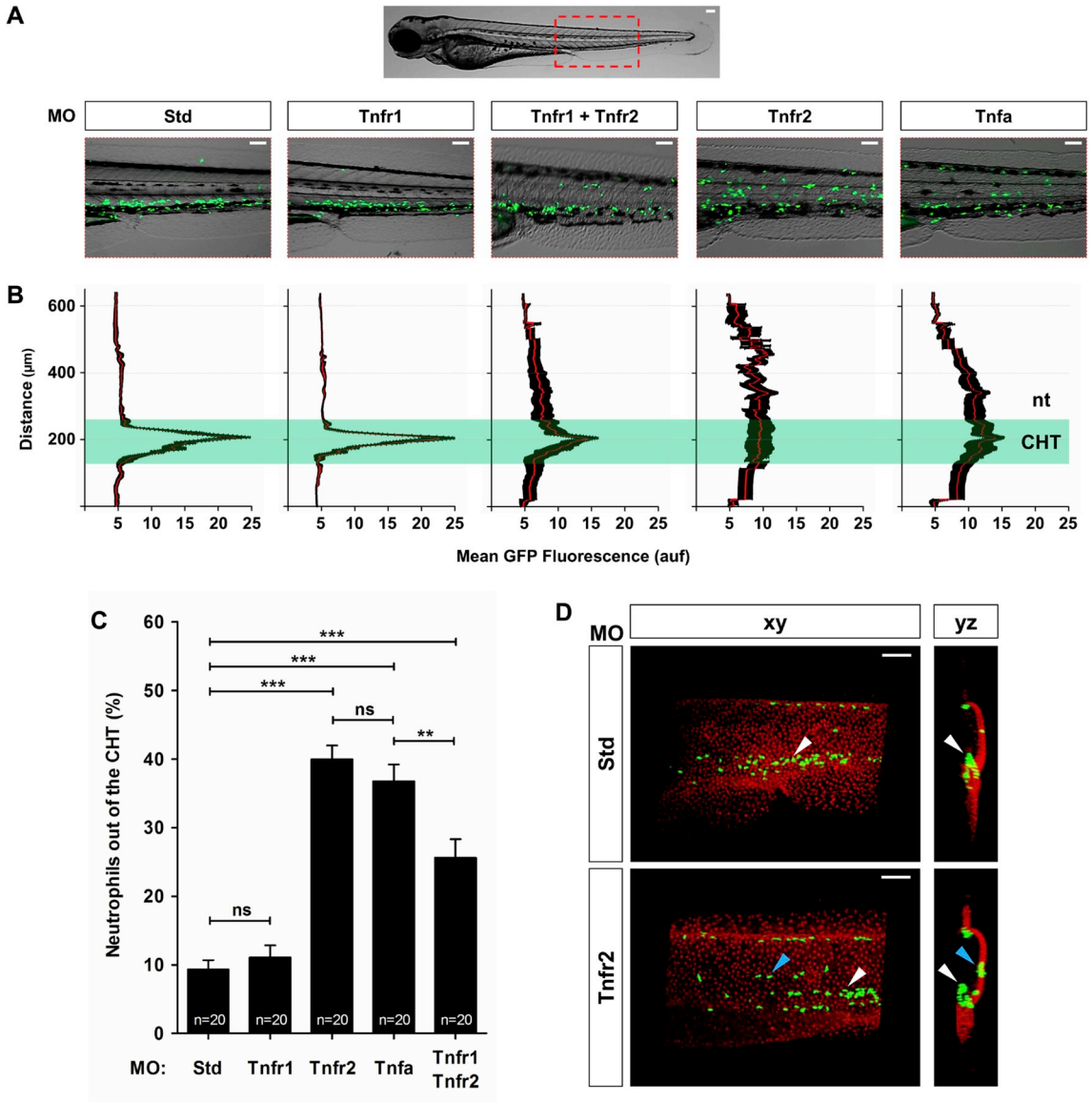

Fig. 4. Zebrafish allows the detailed *in vivo* study effect of key molecules and cells related to psoriasis. Transgenic zebrafish embryos microinjected with standard control (Std), ligand/receptors of tumor necrosis factor (*tnfr1*, *tnfr2*, *tnfa*, or *tnfr1* + *tnfr2*) morpholinos (MO) were microscopically analyzed in real-time. (A) Bright field and green channels, of the morphants at 3 dpf showing the differences in the neutrophils distribution. (B) Fluorescence intensity was measured for all the groups in the area indicated (A), the CHT. (C) The neutrophil mobilization from the CHT in *tnfa*- and *tnfr2*-deficient larvae was quantified. (D) Representative dorsal (*xy*) and lateral (*yz*) views of tridimensional reconstructions from confocal microscopy images of whole-mount immunohistochemistry of Tg(*mpx:GFP*) larvae stained at 3 dpf with anti-p63 antibodies (basal keratinocyte marker, red) showing the neutrophils' distribution in the CHT area of control and *tnfr2*-deficient larvae (Candel et al., 2014). Scale bars, 100 µm ns, not significant. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4.3. Environmental inducible models

Breaking the body balance by the environmental inputs and genetics is often considered among the major candidates directly affecting the onset and development of the psoriatic disease. Exploring however such environmental insults and their associated mechanisms is a significant challenge so far. Recent advances highlight the crucial role of the commensal microbiota in the pathophysiology of chronic multifactorial inflammatory disorders as well as its impact on the efficacy of therapeutic agents. The skin harbors complex communities of resident microorganisms loosely organized and highly variable between different locations among the epithelium. Recently, using state-of-the-art technologies, profound changes in DNA and RNA have been observed resulting directly from the effect of microbes in psoriatic individuals (Nibali et al., 2014). Microbiological analysis by 16S rRNA massive sequencing of psoriatic patients shows the existence of specific transcriptional signatures of microbial regulators common to both the skin and the gastrointestinal tract (Meisel et al., 2018). Moreover, the existence of a core intestinal microbiome with a particularly marked increase in *Firmicutes* and a decrease in *Actinobacteria*, compared to healthy individuals has been well characterized (Adams et al., 2015; Gao et al., 2008; Schommer and Gallo, 2013; Tett et al., 2017). Their

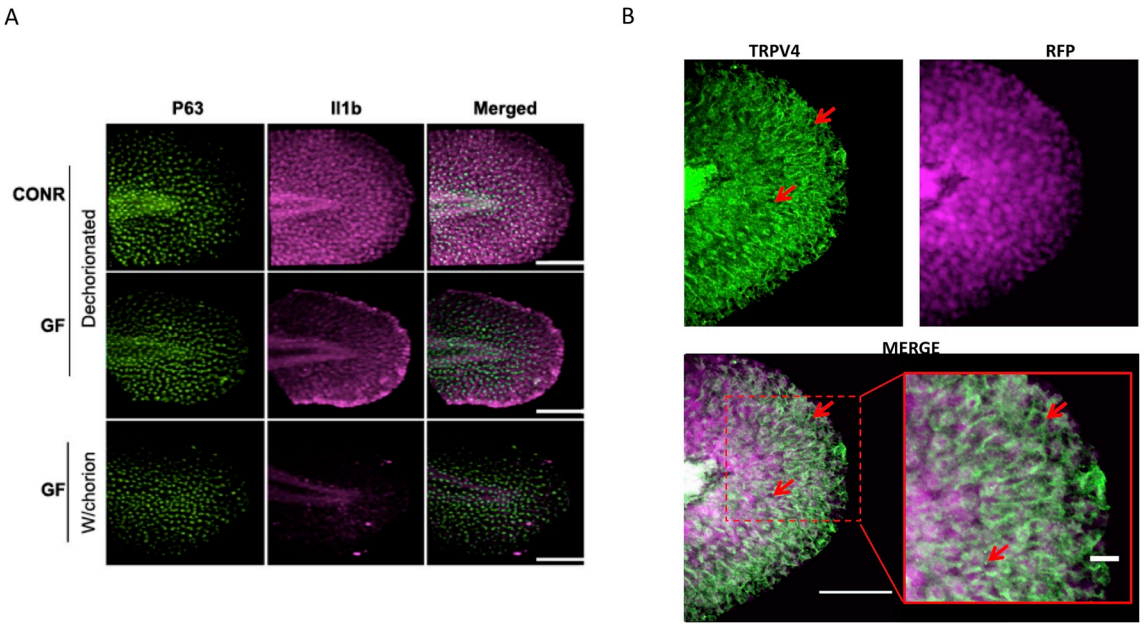

Fig. 5. Keratinocytes sense the presence of bacteria and osmotic changes to activate the immune system. Environmental insults trigger inflammation in the skin **A**) Tail views of tridimensional reconstructions from confocal microscopy images of whole-mount immunohistochemistry of 52 hpf germ-free (GF) or conventionally (CONR) raised zebrafish larvae subjected or not to hypoosmotic shock for 4 h, and then stained with anti-P63 (basal keratinocyte marker, green) or anti-Il1b (inflammatory marker, magenta) antibodies. **B**) Keratinocytes sense hyposmotic changes trough TRPV4. Confocal microscopy images of the tail from whole-mount 72 hpf CONR Tg(*-2.9krt18:RPF*) zebrafish, immunostained specimens for Trpv4 (green) and RPF (magenta). Merged image shows the Trpv4 signal colocalized over Krt18 positive keratinocytes (red arrows) (Galindo-Villegas et al., 2016). Scale bars, 100 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

physiological roles and the molecular mechanisms mediating the host-microbe interactions at mucosal tissues, including the skin or gut are still under debate (Sanchez et al., 2015). With this foundational approach, to close the present knowledge gap, the use of two environmental tractable zebrafish models recently generated by our group are proposed as novel tools to elucidate critical features in the pathogenesis of psoriasis. The germ-free (GF) zebrafish model which is based on the principle of the commensal microbiome exclusion has been proved as an excellent tool to perform accurately, manipulative studies with defined microbial constituents triggering inflammatory mediators from the early life stages that may lead to the development of immune-related diseases (Galindo-Villegas et al., 2012; Tobia et al., 2013). Recently, we and others have found that colonization by commensal microbes in newly hatched zebrafish primes innate immunity through TLRs and their central adaptor molecule Myd88 (Galindo-Villegas et al., 2012; Koch et al., 2018). These findings suggest the requirement, in addition to TLRs/Myd88 of the transcription factor NF-κB, MAPK, and PI3K for the regulation of critical immune genes. Undoubtedly, these data place the spotlight over the skin microbiota as an essential factor in the inflammatory response that may play a role in the pathogenesis of psoriasis.

Also, this disease often develops upon triggering events of mechanical nature leading to increased proliferation and damaged differentiation of epidermal keratinocytes. In this context, some studies highlight the impact of mechanical forces and mechano-transduction during triggering events of the disease, therefore inducing mechano-regulated signaling pathways in keratinocytes. Emerging pieces of evidence suggest that many polymodal transient receptor potential (TRP) channels are critically related to it, and consequently in the development and further regulation of psoriasis (Caterina and Pang, 2016; Malakou et al., 2018). Mainly, TRP vanilloid 4 (TRPV4) is an epidermal channel linked directly to barrier functions and cell proliferation (Olivan-Viguera et al., 2018). Recently, using zebrafish embryos, we have uncovered a previously unappreciated role of the skin in the activation of developmental immunity in keratinocytes mediated by the TRPV4 channel (Galindo-Villegas et al., 2016). In 24 hpf zebrafish embryos, positive immune cells are not present in high numbers to mediate an inflammatory response. Thus, keratinocytes "take the function of neutrophils" following the environmental insult and produce and release variated powerful inflammatory mediators (Fig. 5A). Of particular relevance in our model is that osmotic stress regulates the activation of immunity and host protection in newly hatched embryos. Mechanistically, skin keratinocytes were responsible for both sensing the hyposmolarity of the aquatic environment and mediating immune effector mechanisms. This effect occurred through a TRPV4/Ca^{2+}/TGFβ-activated kinase 1(TAK1)/NF-κB signaling pathway. Notably, in support of this appreciation, the combinatorial zebrafish model does not trigger an inflammatory process if embryos remain under the protection of their chorions. Thus, our findings suggest that drugs targeting the TRPV4 channel (Fig. 5B) or the associated signaling pathway together with the selective manipulation of commensal microbes may be useful in treating chronic inflammatory skin disorders, such as psoriasis (Galindo-Villegas et al., 2016; Montalban-Arques et al., 2015). Nevertheless, despite zebrafish embryos are highly promising as a powerful tool for high-throughput drug screening of TRPV4 antagonists, or some related pharmacological drugs, further studies should explore in much detail how hyposmolarity regulate the crosstalk between the skin, commensals attach and the immune cells.

5. Summary/future directions

Here, we have provided a short overview of many current vertebrate disease models developed so far as to understand psoriasis disease. Impressive findings have been achieved, many of them already applied in patients or under investigation in biomedical phase III. Nevertheless, substantial gaps remain to be sorted before providing definitive and

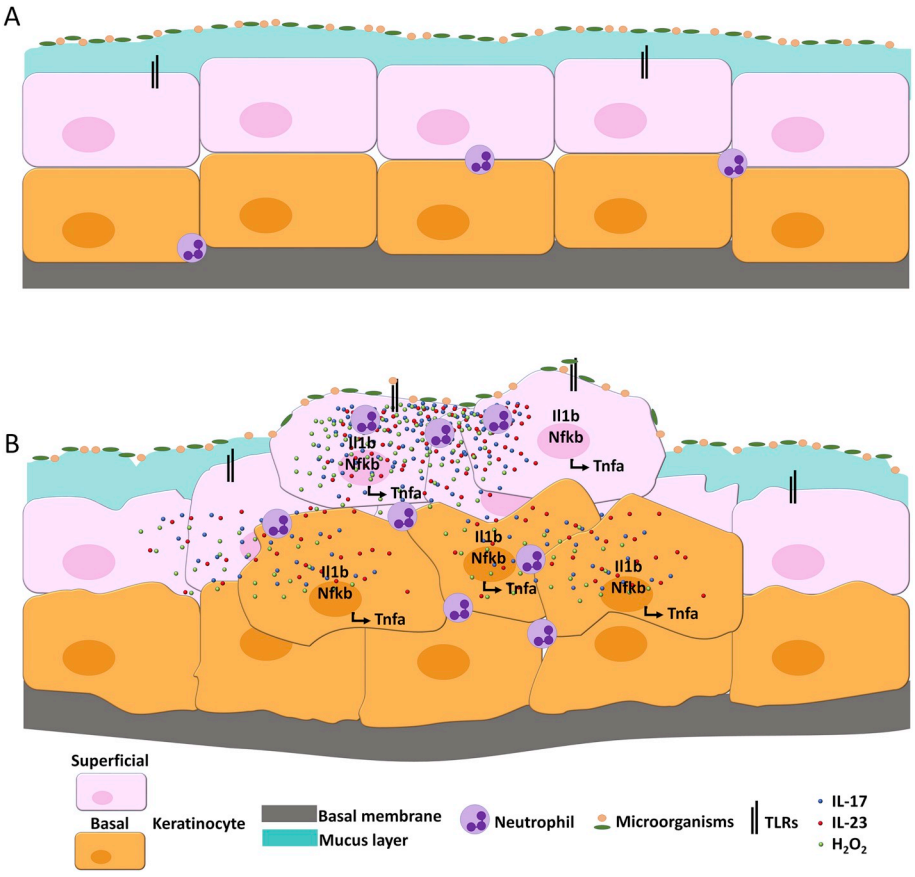

Fig. 6. Inflammation Model in Zebrafish Skin Larvae. A) Normal epithelium. Superficial and basal keratinocytes are correctly organized forming a uniform layer. B) Swollen epithelium. Superficial and basal keratinocytes over-proliferate and lose their organization and skin integrity. This behavior induces the production of different types of chemoattractants that heavily recruit neutrophils to the skin, resembling the human psoriasis disease.

universal conclusions on the pathogenesis of this disease. Notably, we illustrated significant advances obtained by using classical psoriasis models which partially recapitulate the human disease. However, further, we highlight the impressive features intrinsic to zebrafish, a novel organism that may provide fundamental advances on the molecular mechanisms associated with keratinocytes and neutrophils at the early stages of the psoriatic disease. The power of the model is solely based on the zebrafish simple skin structure, and the high similarity to the human epithelium and the potent immune mediators it produces in compromised conditions (Fig. 6A and B) On this perspective a myriad of environmental, genetic and drug screening tests can be conducted, and aid on enabling rapid discovery of possible chemical targets. Finally, in further research applying this model the identification and understanding of crucial aspects of epigenetic, post-translational modifications, host-microbe interactions, and trained immunity (all possible using zebrafish) could help on bridging the gap between genetic and environmental risk factors to understand the psoriasis disease.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dci.2019.03.018.

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