European Journal of Pharmacology 778 (2016) 90–95

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Basophils in inflammation

Christian Schwartz, Joerg U. Eberle, David Voehringer*

Department of Infection Biology, University Hospital Erlangen and Friedrich-Alexander University Erlangen-Nuremberg (FAU), 91054 Erlangen, Germany

ARTICLE INFO

Article history:
Received 19 December 2014
Received in revised form
8 April 2015
Accepted 21 April 2015
Available online 7 May 2015

Keywords:
Basophils
Atopic dermatitis
Allergic asthma
Anaphylaxis
Food allergy

ABSTRACT

Basophils are functionally closely related to mast cells. Both cell types express the high-affinity IgE receptor (FcεRI) and rapidly release preformed mediator from intracellular stores upon IgE-mediated activation. However, in contrast to mast cells basophils finish their maturation in the bone marrow and have a lifespan of only 2–3 days. Basophil numbers increase in response to IL-3 or TSLP and migrate into tissues to promote type 2 immune responses. Here we review recent advances regarding the pro- and anti-inflammatory functions of basophils in murine models and human allergic inflammation of the skin, lung and intestine.

1. Introduction

Inflammatory responses are classically characterized by the presence of swelling (tumor), redness (rubor), heat (calor), pain (dolor) and loss of function (functio laesa). They are evoked by various noxious stimuli including chemical irritants, toxins, physical injury, trauma, and infections. Recruitment of effector cells depends on the site of inflammation and is regulated by inflammatory mediators released from cells present at the site of injury, such as epithelial cells, macrophages, dendritic cells or granulocytes. Thus, a complex network of cells collaborates to counteract the entry of infectious or harmful agents. Parasites generally evoke a so-called type 2 immune response which is characterized by high IgE titers, eosinophilia, basophilia, and increased numbers of IL-4-producing CD4 T cells. However, dysregulation of this network may lead to allergic reactions, like dermatitis, asthma, or food allergy, against otherwise harmless substances. It is still largely unclear which factors induce type 2 immune responses.

Already discovered more than 130 years ago by Paul Ehrlich, basophils have long been ignored due to their rare abundance in the blood (Ehrlich, 1879). In the 1970s it was observed that they can release histamine upon cross-linking of the high-affinity receptor for IgE (FcεRI) (Ishizaka et al., 1972). Only in the 1980s basophils were discovered in mice (Dvorak et al., 1982) and a decade later they were recognized as source of the Th2-associated cytokine IL-4 (Brunner et al., 1993; Seder et al., 1991). With the generation of IL-4-reporter mice it was discovered, that basophils constitutively express IL-4, facilitating their identification and characterization (Min et al., 2004; Mohrs et al., 2001; Voehringer et al., 2004). Deletion of basophils by monoclonal antibodies revealed many non-redundant functions, some of which were confirmed later with the generation of basophil-deficient mice. To date several mouse models to study basophil function are available and summarized in Box 1. Whether basophils serve as antigen-presenting cells during type 2 immune responses is still highly debated but recent studies indicate that they are dispensable for priming of Th2 cells in most conditions (Eckl-Dorna et al., 2012; Hammad et al., 2010; Kim et al., 2010; Kitzmuller et al., 2012; Nakanishi, 2010; Ohnmacht et al., 2010; Otsuka et al., 2013; Perrigoue et al., 2009; Phythian-Adams et al., 2010; Sharma et al., 2013; Sokol et al., 2009; Yoshimoto et al., 2009). Further studies demonstrated that basophils contribute to the pathogenesis of allergic skin and airway inflammation, and contribute to immunity against parasites both in the gut and the skin (Mukai et al., 2005; Obata et al., 2007; Ohnmacht et al., 2010; Sawaguchi et al., 2012; Wada et al., 2010).

Here, we will highlight recent advances made on the function of basophils when the barrier integrity of skin, lung and gastrointestinal tract is impaired and inflammatory responses unfold (Fig. 1).

2. Role of basophils in tissue inflammation

2.1. Skin inflammation

2.1.1. TSLP-mediated skin inflammation

Early studies with guinea pigs already revealed basophil recruitment to the skin during cutaneous basophil hypersensitivity

* Corresponding author. Tel.: +49 9131 8532735; fax: +49 9131 8532733.
E-mail address: david.voehringer@uk-erlangen.de (D. Voehringer).

http://dx.doi.org/10.1016/j.ejphar.2015.04.049
0014-2999/

Box 1–Genetically engineered mouse models of basophil-deletion.

Mcpt8^{DTR} (Wada et al., 2010)	The human DT receptor was inserted in the 3′ UTR of *mcpt8*. Diphtheria toxin injection depletes more than 90% of basophils within two days.
Mcpt8Cre (Ohnmacht et al., 2010)	BAC-transgenic mice express Cre recombinase under the control of regulatory elements of *mcpt8*. Cre toxicity constitutively deletes >90% of basophils.
Basoph8 (Sullivan et al., 2011)	An IRES-YFP-Cre cassette was inserted before the *mcpt8* start codon. Cross to R-DTA mice constitutively deletes >90% basophils.
Bas-TRECK (Sawaguchi et al., 2012)	The human DT receptor was inserted under control of the 3′ proximal enhancer in the *il4* locus. DT injection deletes >90% of basophils.
Runx1$^{P1N/P1N}$ (Mukai et al., 2012)	Disruption of the P1 promoter of *runx1* by the insertion of a neo-cassette leads to constitutive deletion of >90% basophils.

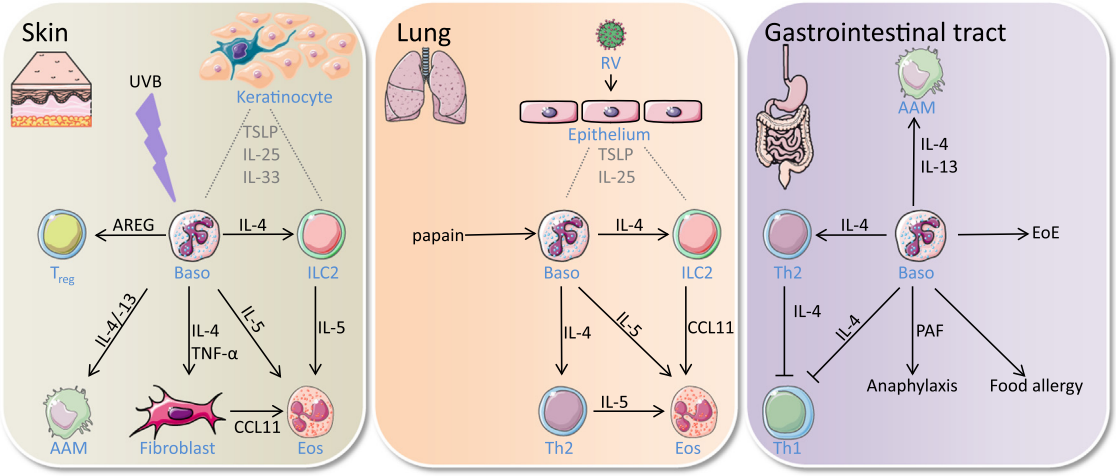

Fig. 1. Illustration of basophil functions during inflammatory response in skin, lung and intestine. Symbols are derived from Servier medical art (Servier, Suresnes, France).

(Dvorak et al., 1970). Basophils were detected in the skin of patients suffering from various skin diseases such as allergic contact dermatitis, atopic dermatitis, prurigo, urticarial, eosinophilic pustular folliculitis and bullous pemphigoid (Dvorak and Mihm, 1972; Ito et al., 2011; Mitchell et al., 1982; Ying et al., 2002). The pathogenesis of these inflammatory conditions is orchestrated by complex interactions between different cell types.

Atopic dermatitis (AD) is characterized by skin inflammation, impaired barrier function, and subsequently leads to an elevated risk of acquiring bacterial infection and allergic sensitization. Reportedly, patients with polymorphisms in the gene encoding thymic stromal lymphopoietin (TSLP) have an increased risk of developing AD and TSLP was detected in skin lesions of AD patients, highlighting the potential role of TSLP in the initiation of AD (Gao et al., 2010). Interestingly, TSLP promotes IL-3-independent basophilia (Siracusa et al., 2011).

One of the most widely used mouse models mimicking AD, involves the topical application of the low-calcemic vitamin D3 analogon MC903 (also named calcipotriol), a treatment regimen for psoriasis (Staberg et al., 1989). TSLP-overexpression in and MC903-triggered TSLP release from keratinocytes leads to leukocyte infiltration and inflammation (Li et al., 2009, 2006). Basophils and group 2 innate lymphoid cells (ILC2s) are among the first infiltrating cells in the skin, though basophils enter the skin before the ILC2s and both cell types accumulate in close proximity of each other (Kim et al., 2014). Using diphtheria toxin (DT)-mediated depletion of basophils in BasTRECK mice, it was shown that basophils were required for optimal IL-33-independent ILC2 responses. However, others have reported a non-redundant role of IL-25- and IL-33-dependent ILC2s for the pathogenesis of MC903-induced AD (Salimi et al., 2013).

Opposing this model, another report demonstrated that basophils, dendritic cells and CD4 T cells cooperate in order to induce inflammation in the MC903 model (Leyva-Castillo et al., 2013). Leyva-Costillo et al. proposed that TSLP-activated dendritic cells activate T cells via OX40L which then release IL-3 to recruit basophils into draining lymph nodes where basophils release IL-4 to induce Th2 polarization. However, the role of Th2 cells in this model remains unclear since RAG1$^{-/-}$ mice develop full-blown AD (Kim et al., 2013). Epidermal Langerhans cells were also reported to mediate inflammation in the MC903 model via stimulating release of CCL17 and CCL22 from keratinocytes (Elentner et al., 2009). So far, it remains unclear whether basophils respond directly to TSLP and which downstream mediators are released. Therefore, studies with conditional deletion of TSLP and the TSLP receptor in different cell populations should be performed to uncover the cellular interactions during the pathogenesis of AD.

Basophils were shown to recruit eosinophils to inflamed skin. Topical application of croton oil which contains phorbol 12-myristate 13-acetate (PMA) induces irritant chemical dermatitis (ICD) by the