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Interleukins and large domestic animals, a bibliometric analysis

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Abstract

Interleukins have been well described in mice and humans. In large domestic animals the situation is drastically different and there is still a need for further researches aiming at identifying all the homologous interleukins and comparing their functions among species. We performed here a bibliometric analysis of all interleukins described in the literature in various large animal species to identify what is known so far and to underline where there is a need for new studies. Using indicators such as H index but also M quotient, A index, G index, GH ratio, and HG index we ranked 39 interleukins identified so far in bovine, caprine, equine, ovine, and porcine, the main large domestic animals. Indexes and ratio under investigations were higher for IL1, IL2, IL4, IL5, IL6, IL8, IL10, IL12, and IL18 than for other interleukins, particularly in bovine and porcine species and to a certain extent in equine species. Recently discovered interleukins presented low values for the different indexes, quotient, and ratio. Even some "old" interleukins showed low values highlighting the need for further developments in comparative immunology. For instance an interleukin such as IL4 demonstrated variation in its functions between species. In conclusion, this study provides the first bibliometric analysis dedicated to large domestic animal interleukins and underlines the need for more studies to fully determine the structure and the functions of interleukins in other mammal species.

Keywords: Immunology, Veterinary medicine, Veterinary science, Cell biology, Information science

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1. Introduction

Immunology has known major developments in the last years. In mammals, most of our knowledge comes from the murine model and human. Besides, in large domestic animals the situation is quite different (Montoya and Meurens, 2015; Summerfield, 2009). Indeed, basic or applied immunology studies dealing with large domestic animals constitute less than 5% of the publications in major immunology journals. However, some specialized journals like Veterinary Immunology and Immunopathology, Veterinary Microbiology and Developmental and Comparative Immunology are dedicated to animal immunology and infectious diseases and several studies about large domestic animal immunology were published in the last years.

Interleukins are proteins enabling communications between the various cell populations. Some of them such as interleukin 1 (IL-1) and IL-6 have pro-inflammatory actions while some other ones such as IL-4, IL10 and IL-37 are clearly anti-inflammatory compounds making them interesting targets to diagnose or treat various conditions (Carinci et al., 2016; Conti et al., 2017; Lin et al., 2016; Mahdavi-Roshan et al., 2016; Wu et al., 2016). The word interleukin, created in 1979, derives from Latin *Inter*- ("between, amid") and −*leukin* because many interleukins are produced by leukocytes and stimulate these cells (di Giovine and Duff, 1990). Logically the first interleukin to be identified was interleukin 1 (di Giovine and Duff, 1990). Since then many interleukins were described in various species including human, mouse and large domestic animals. However, papers related to specific interleukins in a determined species are not so frequent and there are significant variations in the knowledge of interleukins between species.

The measure of the scientific productivity and quality of a particular researcher has been widely used by managers, research institutions, and funding agencies to evaluate professional promotions or to rank projects and grants. Created in 2005 (Hirsch, 2005), the H index, which is the number of published papers (N) that have been cited N or more times, became quickly popular to assess researchers at different stages of their career. Originally used to assess scientists the H index was then proposed to evaluate countries (Csajbók et al., 2007), journals (Braun et al., 2006), and even, more recently, animal and human pathogens (Cox et al., 2016; Díaz et al., 2016; Ducrot et al., 2016; McIntyre et al., 2011). Regarding pathogens these studies were particularly interesting in identifying the hot and/or neglected topics. Because H index has some drawbacks most of these studies also used other bibliometric indicators such as A index, G index, HG index, GH ratio, M quotient, and Deciphering Citations Organized by Subject (Dcos) index which measure the contribution that a given author, institute or country would have in a specific research area or subject (Díaz et al., 2016; Ducrot et al., 2016). A simultaneous use of the various indicators could provide a more accurate view of the situation for a

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specific subject. So far, no studies applied bibliometric indexes to immune mediators such as cytokines, interleukins, and chemokines. With the development of comparative immunology there is a need for complementary approaches to assess what has been done and what needs to be done.

In the current study, interleukins were compared using H index scores and other indexes in 5 large domestic animals including four artiodactyls (bovine, caprine, ovine, and porcine) and one perissodactyl (horse). This bibliometric analysis enabled us to globally assess the present situation regarding research on interleukins in large animals.

2. Materials and methods

2.1. Selection of interleukins and animal species

The current study comprises all identified interleukins so far in mice and humans (IL1 to IL39). Because some interleukins, especially the first ones, have been described under various names, searches were done using several names, synonymous, and acronyms used for every interleukins. Most of these alternative "names" are listed in Table 1. Some interleukins such as IL12 and IL23 required further bibliometric analyses as they are heterodimeric and share the subunit p40. Furthermore, other interleukins such as IL1 or IL17 are described as families of compounds instead of unique molecules. Indeed, IL1 family includes, amongst others, IL1α, IL1β, and IL1Ra and IL17 family IL17A to F. Because in many publications, especially the oldest ones, there was no information regarding the exact nature of the considered interleukin we did not distinguish between themselves the different members of the interleukin families and instead considered the families as a whole. Regarding selected animal species we focused especially on large domestic animal which are mostly livestock animal (see Table 2).

2.2. Calculation of the H index for the interleukins in the selected species

To calculate H index we used the software package developed by Web of Science (WOS). The work was carried out from May 2016 to June 2016 included ("Thomson Reuters: Overview-Web of Science v.5.22.2," 2016). All searches were restricted to the title of articles published in English between 1956 and 2016. Because there are multiple synonyms, names, and acronyms for interleukins and large domestic animal names, the selection of the terms used in the multiple searches had to be done very carefully. Various sources such as general English dictionaries, NCBI databases, Immunology text books were used to generate a list of terms (see Tables 1 and 2). For instance, for pig we used the terms: "porcine or pig or *Sus scrofa* or swine or boar or piglet or sow" and for IL2: IL2 or IL-2 or

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Table 1. Interleukin names or abbreviations used to perform the analysis.

IL1	or IL-1 or interleukin 1 or lymphokine activating factor or lymphocyte-activating factor or B-cell activating factor or catabolin or endogenous pyrogen or epidermal cell-derived thymocyte-activating factor or mononuclear cell factor
IL2	or IL-2 or interleukin 2 or T cell growth factor or T cell stimulating factor
IL3	or IL-3 or interleukin 3 or multipotential CSF or mast cell growth factor or P cell stimulating factor or histamine-producing cell stimulating factor or hematopoietic growth factor
IL4	or IL-4 or interleukin 4 or B cell growth factor 1 or B cell stimulatory factor 1
IL5	or IL-5 or interleukin 5 or T cell-replacing factor or BCGF II or eosinophil colony stimulating factor or eosinophil differentiation factor
IL6	or IL-6 or interleukin 6 or IFN B2 or BSF2 or hybridoma growth factor or plasmocytoma growth factor or myeloid blood cell differentiation-inducing protein or hepatocyte stimulating factor
IL7	or IL-7 or interleukin 7 or LP-1 or lymphopoetine 1
IL8	or IL-8 or interleukin 8 or neutrophil activating factor or neutrophil chemotactic factor or NAP-1 or GCAP or CXCL-8 or CXCL8
IL9	or IL-9 or interleukin 9 or TCF III or TCF3
IL10	or IL-10 or interleukin 10 or CSIF or cytokine synthesis inhibitory factor
IL11	or IL-11 or interleukin 11
IL12	or IL-12 or interleukin 12 or NKSF or natural killer cell stimulatory factor or CLMF or cytotoxic lymphocyte maturation factor
IL13	or IL-13 or interleukin 13 or P600
IL14	or IL-14 or interleukin 14 or HMW-BCGF
IL15	or IL-15 or interleukin 15
IL16	or IL-16 or interleukin 16 or LCF
IL17	or IL-17 or interleukin 17 or CTLA-8 or CTLA8
IL18	or IL-18 or interleukin 18 or IGIF or interferon gamma inducing factor
IL19	or IL-19 or interleukin 19
IL20	or IL-20 or interleukin 20
IL21	or IL-21 or interleukin 21
IL22	or IL-22 or interleukin 22 or IL-TIF
IL23	or IL-23 or interleukin 23
IL24	or IL-24 or interleukin 24 or IL-10B or MDA7 or melanoma differentiation association protein 7
IL25	or IL-25 or interleukin 25 or IL-17E or SF20
IL26	or IL-26 or interleukin 26

IL27 or IL-27 or interleukin 27

IL28 or IL-28 or interleukin 28 or IFNλ2 or IFNλ3 or interferon lambda

IL29 or IL-29 or interleukin 29 or IFNλ1 or interferon lambda

IL30 or IL-30 or interleukin 30 or IL27p28 or IL27 p28

IL31 or IL-31 or interleukin 31

IL32 or IL-32 or interleukin 32 or NK4

IL33 or IL-33 or interleukin 33 or NF-HEV

IL34 or IL-34 or interleukin 34

IL35 or IL-35 or interleukin 35

IL36 or IL-36 or interleukin 36

IL37 or IL-37 or interleukin 37

IL38 or IL-38 or interleukin 38

IL39 or IL-39 or interleukin 39 or IL-23p19/Ebi3

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Table 2. Terms used to describe the different large animal species.

Bovine	or Bos Taurus or calf or cow or cattle or bull or heifer
Caprine	or goat or billies or kids or wethers or *Capra hircus* or *Capra aegagrus*
Equine	or horse or *Equus ferus* or mare or stallion or foal or yearling
Ovine	or sheep or ewe or *Ovis aries* or mouton or lamb or ram
Porcine	or pig or *Sus scrofa* or swine or boar or piglet or sow

interleukin 2 or T cell growth factor or T cell stimulating factor. Consequently, especially for interleukins, possible changes in the terminology have been taken into consideration. The Boolean options "AND", "NOT", and "OR" were used to organize the terms of the search. For instance, in pigs, "NOT" option was necessary to exclude all the papers related to the guinea pig. Besides H index, the first year of publication and the total number of citations were also collected. Searches were performed twice by two independent operators.

2.3. Comparisons of the H index with others indices

To assess and challenge H index other indicators – M quotient, A index, G index, GH ratio, and HG index- were generated for all the interleukins in the different species. M quotient was created to overcome the fact that H index was directly proportional to the career length of the scientists who were assessed. Hirsch proposed that index to enable a comparison of scientists with different scientific career length (Hirsch, 2005). To calculate this indicator H index is divided by the number of years of research activity. Since there are also significant differences regarding the year of the first description of interleukins, M quotient was also applied to interleukins to evaluate "research productivity outcome" of interleukins. To do that, H index of a given interleukin was divided by the number of years since publication for the oldest paper included in the H index. A index is the mean number of citations of the papers included in H index (Jin et al., 2007). This indicator was generated simultaneously to H index using WOS software package. To calculate the G Index a new list of publications for each interleukins was required. This list was generated applying same terms than for H Index calculations. G index is as described by his creator: "For a set of papers, ranked in decreasing order of the number of citations they received, G index is the highest number of papers that received H or more citations" (Egghe, 2006). Then, using G and H indexes, the HG index was established ($HG = \sqrt{(HxG)}$) (Alonso et al., 2010). This index reduces the influence a highly cited paper has on the G index. The GH ratio ($GH = G/H$) shows the relative increase of G index with respect to H (Egghe, 2006).

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2.4. Statistical analyses

All statistical analyses were done using computer software Prism 6 for Windows (version 6.02; GraphPad Software, San Diego, CA, USA). One-Way ANOVA was used to detect differences amongst the groups. To account for the non-normal distribution of the data, all data were sorted by rank status prior to ANOVA statistical analysis. Tukey's test was used to compare the means of the ranks among the groups. P values less than 0.05 were considered significant.

3. Results

3.1. Article selection and first analyses

Fig. 1 presented the number of articles found for every interleukin and animal species. The number of articles is highly variable between interleukins (Fig. 1) and within them between species (supplementary Table 1). Because of this high variation, no statistically significant differences were identified between the 39 interleukins. However, it can still be observed that a higher number of articles were found for interleukins 1–18 than for other interleukins. After an analysis of the found articles, we identified several articles which were not linked to the interleukin assessed in the search. These articles can be considered as false positive results and were consequently excluded for further analyses. A list of selected articles was then constituted for each interleukins and each species (supplementary Table 1). In some cases, the difference in the number of articles was quite important. For instance, in bovine IL1, from 271 articles, 223 were kept. These differences illustrate the necessity to check articles one by one.

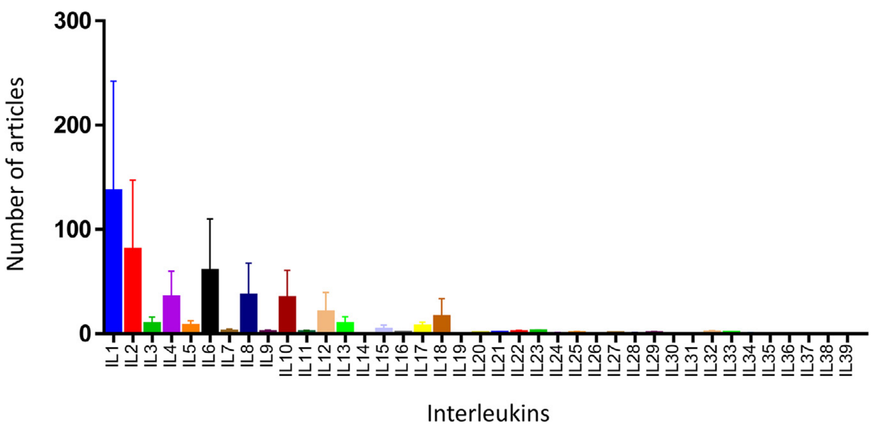

Fig. 1. Number of articles found for all the interleukins considered in our study. Variable numbers of articles were identified for the 39 interleukins. For each interleukin, all the selected species were considered together. The search was carried out in titles and was based on specific terms listed in Tables 1 and 2. Median values +/− SD are presented.

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3.2. Top 9 interleukins in terms of selected papers

The 9 interleukins showing the highest number of selected papers are presented in Fig. 2. For each interleukin, the total number of selected papers is provided at the centre of the circles and the contribution of each species is illustrated using different colours. Additionally, for each species, the year of publication of the first published paper is identified. Except for IL5, most of the time bovine and porcine species are dominating. The number of selected papers rapidly decreased from IL1-IL2-IL6 to IL12-IL18-IL5 and only 26 articles were kept for IL5, essentially from equine and ovine species. The first articles were published in the seventies for IL1 in small ruminants and less than ten years ago in the caprine species for IL18. Globally interleukins were first studied in the pigs and in the bovine species and later in ovine, caprine and equine species.

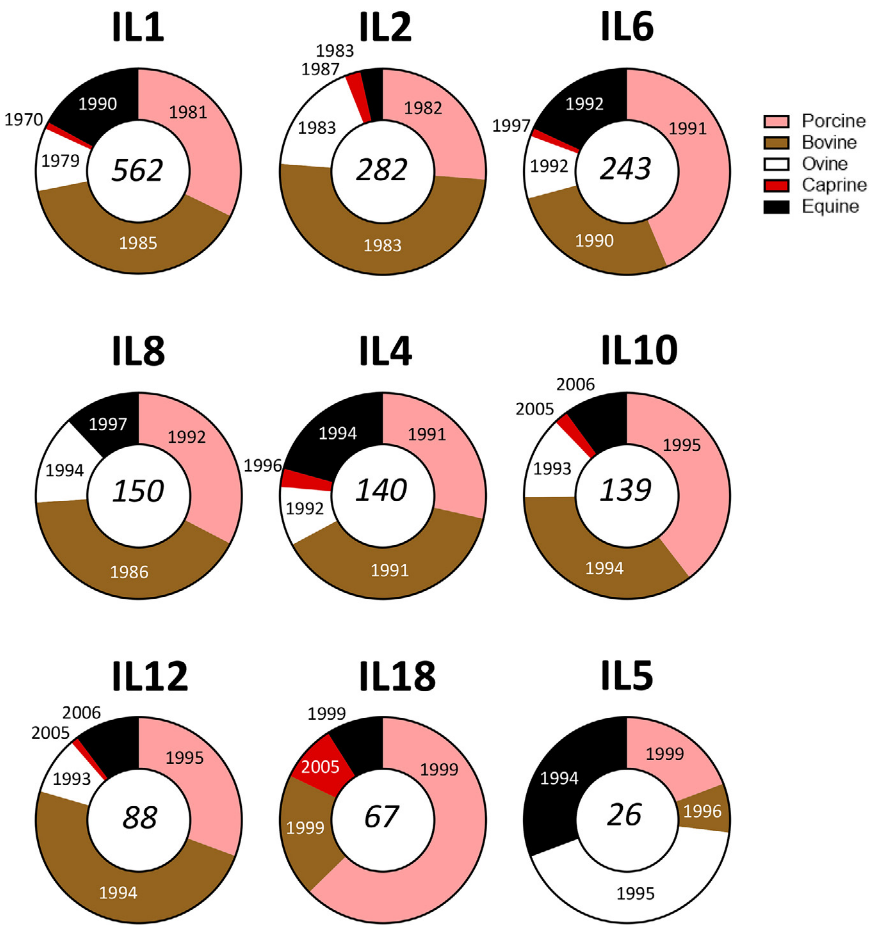

Fig. 2. Total number of papers and first years of publication in the different species for the 9 interleukins (IL1, IL2, IL4, IL5, IL6, IL10, IL12, IL18) presenting the highest numbers of selected articles. For the 9 interleukins, the contribution of every species is visualized using different colours and for every single species the first year of publication of an article dealing with the interleukin is provided.

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3.3. Interleukin ranking by H index

Regarding H index, the distribution of the interleukins was similar to the one observed for the number of selected papers. Highest H indexes were observed in IL1, IL2, IL4, IL6, IL8, IL10, IL12, and IL18 with again a strong variation between species (Fig. 3 and supplementary Table 1). The two highest H indexes were calculated for IL1 in bovine (36) and porcine species (32) meaning that 36 papers about bovine IL1 were cited more than 36 times and 32 papers dealing with porcine IL1 were cited more than 32 times (supplementary Table 1). For recently identified interleukins, H indexes were low or equal to 0. For instance, for IL23, H index was 3 in horse, 2 in sheep and 1 in bovine. Again and similarly to previous observations with the number of selected papers, the variation between species within interleukins H index was high preventing statistical comparisons to reach significance.

3.4. Assessment of H index, M quotient, A index and G index for the main interleukins in domestic large animal species

In Fig. 4, the different indexes and M quotient are presented for the most studied interleukins in the different species. H index is high in all the species, especially in porcine and bovine species, except caprine species (Fig. 4). IL5 was one of the only interleukins where H index was higher (5) in the horse than in other species (Fig. 4 and supplementary Table 1). Horse IL4 H index was also quite high compared to other species H indexes. Regarding IL18, it can be observed there is no H index for ovine species. With the calculation of M quotient, the ranking of the interleukins is modified and IL6 and IL10 have globally higher values than IL2 and IL4 for instance (Fig. 4). The differences between species are lower regarding M quotient than H index. For instance, ovine IL1 M quotient or equine IL10 M quotient are very similar to their bovine and porcine counterparts. Moreover, some interleukins such as IL22, IL23, and IL29 showed values ≥0.4 in bovine, ovine, and porcine species

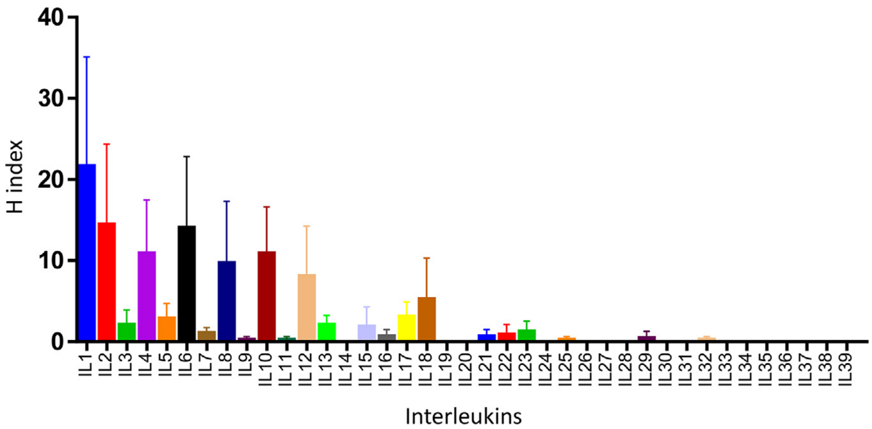

Fig. 3. Global H index for the 39 interleukins in the different species. A global H index for all the species is illustrated for every interleukins. Median values +/− SD are presented.

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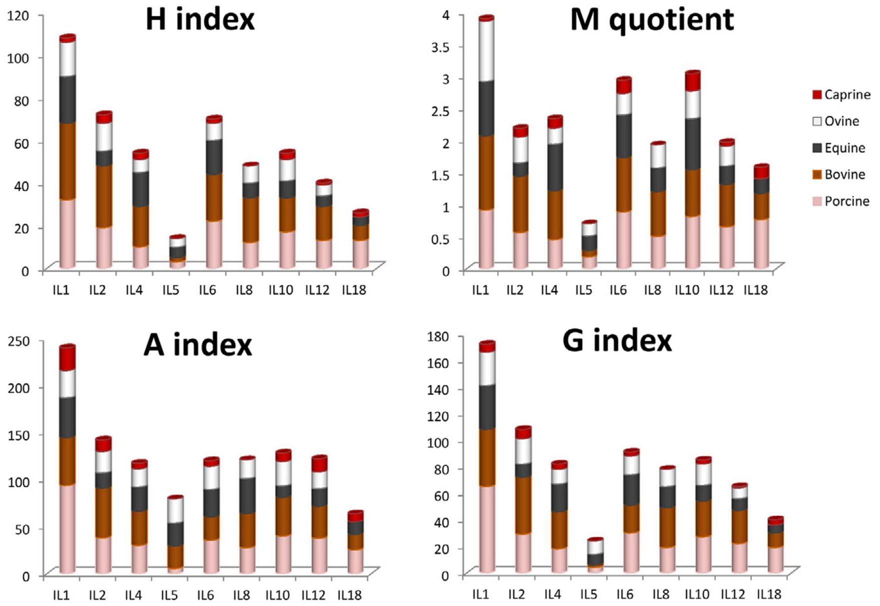

Fig. 4. H index, M quotient, A index, and G index in the different species for the 9 interleukins (IL1, IL2, IL4, IL5, IL6, IL10, IL12, IL18) presenting the highest numbers of selected articles. For the 9 interleukins, the contribution of every species is visualized using different colours.

(supplementary Table 1). A index is the mean number of citations of the papers included in H index. Using that index, IL6, IL8, and IL12 in the different species show increased values compared to H index graph. Differences between H and A indexes within one species are important. For instance, bovine IL5 H index is low (2) compared to ovine or horse (4 and 5, respectively) but IL5 A indexes are similar between these 3 species (24 to 25.75). On the contrary the profile of G index graph is extremely similar to what was observed with H index graph showing the same ranking for the main interleukins (Fig. 4).

3.5. GH ratio and HG index for the main interleukins in domestic large animal species

GH ratio shows the relative increase of G index with respect to H. Using that ratio, the main change is observed for caprine and ovine species which are presenting values similar to the ones observed in other species (Fig. 5). Regarding the HG index, an index established to reduce the influence of highly cited papers on the G index, the profile was very similar to what was observed with G index (Fig. 5) suggesting a low influence of highly cited papers.

4. Discussion

Most of our knowledge about interleukins is coming from studies performed in rodents and humans. However, several papers dedicated to these important

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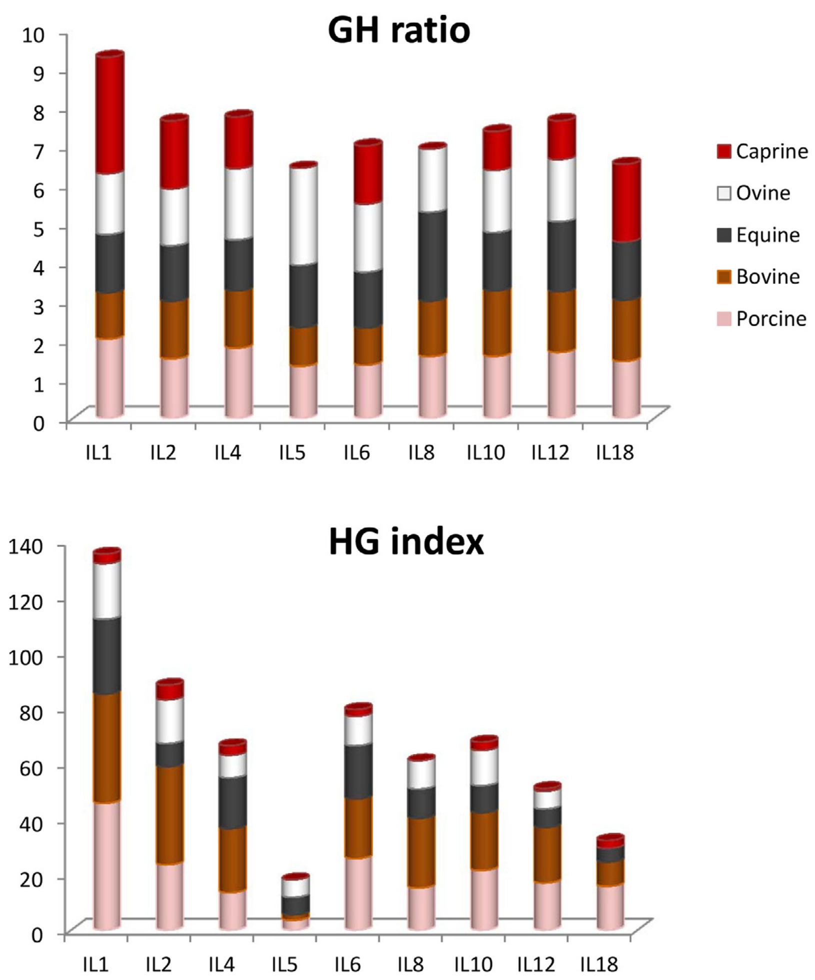

Fig. 5. GH ratio and HG index in the different species for the 9 interleukins presenting the highest numbers of selected articles. For the 9 interleukins, the contribution of every species is visualized using different colours.

mediators in other mammal species such as large domestic animals have been published in the last thirty years. In order to get a view of the situation at the front of the research about interleukins in large domestic animals, it was decided to carry out a bibliometric analysis on all the identified interleukins in the five major large animal species, i.e. bovine, caprine, equine, porcine, and ovine. To perform the bibliometric analyses, different indicators were measured including H index which is generally used to assess researcher productivity (Hirsch, 2005).

The first issue we had to overcome in the bibliometric analysis was related to the accuracy of the performed search using the selected terms for each individual interleukin. Indeed several searches in our study generated biased lists potentially introducing errors. Some interleukins names have changed since their discovery, even sometimes repeatedly (see for instance IL1 in Table 1). Consequently in order

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to obtain accurate results, search terms were modified to include a maximum of alternative and/or complementary names (Table 1). A second issue was the absence of detection of relevant papers caused by a title choice strategy where there is no mention of the involved species or interleukin. For instance, several very relevant and interesting studies about IL17 in bovine have been published in the last years (Rainard et al., 2013; Roussel et al., 2015). However, because the species of interest was not mentioned in the titles, the papers failed to be selected in our analysis. It is also probably the case in the other selected species of our bibliometric analysis. Furthermore, molecular techniques such as RT-qPCR and microarray have been developed to study interleukin and others molecules involved in immunity. These techniques allow the simultaneous study of many targets (23 genes in (Magiri et al., 2016)) in a same experiment contrary to older experimental approach like ELISA for instance. Thereby, it was not possible to indicate all the interleukins assessed in the paper title and authors preferred to relate their study as “interleukin expression” (Deplanche et al., 2016), “response of immune response genes” (Magiri et al., 2016) or “immune response” (Zbinden et al., 2015). It is difficult to accurately assess the impact of this bias as the missed papers are by nature hidden. However, it can be assumed that in most of the major articles reporting studies focusing on an interleukin in a particular species, there is mention of the interleukin name and the animal species in the article title. Thus, except for less studied interleukins, the percentage of missed papers is probably lower than 10 percent. Performing the search not only based on title but also on abstract and general text could have solved that problem. This approach was not selected since it would have generated drastically longer output list with massive background.

Another possible error is the retrieval of several papers not related to the topic in the generated list. For instance the paper entitled “Interleukin-22: a sheep in wolf's clothing” was dedicated to IL22 in the mouse model and did not use any sheep in any experiment (Laurence et al., 2008). Similarly, a term such as kids refer to juveniles of both sexes in goat and can bring many papers unrelated to goat in the output list. To improve the database accuracy and to minimize the impact of potential mistakes all the references in the generated lists were revised one by one by both authors and in some searches up to 48 papers were removed (see IL1 in bovine, supplementary Table 1). Because the amount of work can become quickly important the research topic has to be well determined from the beginning. After analysis of the number of selected articles, it appears clearly that many papers have been dedicated to the study of most of the first described interleukins in the different species assessed in our report. On the contrary when newly described interleukins are considered a very low number of selected papers or even an absence of papers is observed (see for instance interleukins IL19 to IL32). Since there is a growing interest for the development of more predictive models for the study of various conditions in human biology (see for instance (Aigner et al., 2010;

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Gerdts et al., 2015; Meurens et al., 2012; Montoya and Meurens, 2015; Perrin, 2014)) it underlines the need for more research in comparative immunology to support these alternative models. The case of IL4 in pigs well illustrates the requirement for further research about interleukins in other mammal species. Indeed, studies about porcine IL4 demonstrated a replacement of IL4 by IL13 for some specific functions related to the development of monocyte derived dendritic cells (Bautista et al., 2007) and no role as a stimulatory factor in the development of B cells for this interleukin (Murtaugh et al., 2009). We can postulate similar situations for some other interleukins in other large animal species.

As mentioned before there is basically no paper focusing on the newly described interleukins in large domestic animals. Because our bibliometric analysis was based on title information, we could have missed some papers dealing with these recent interleukins. Indeed, this is the case for instance for porcine IL28B (Interferon λ1) and IL29A (Interferon λ3) in a recent paper (Delgado-Ortega et al., 2014). In that paper, mRNA expressions of these two newly described interleukins were assessed but because the main topic of the paper was not directly related to these interleukins or their characterizations we could not find it in our bibliometric research. As reagents are available for these two interleukins we can postulate the existence of more publications reporting data related to it. Regarding interleukins 24 to 39, only 5 papers were published in large domestic species, in pig, bovine, and ovine, underlining the paucity of studies dedicated to new interleukins in these species. IL23 was quite an exception with a total of 10 publications available in all the selected animal species. It is most probably linked to its major role in the Th17 response (Iwakura and Ishigame, 2006) which has been a hot topic recently. Moreover, the number of selected papers for IL23 could be slightly underestimated, especially for old papers, as this heterodimeric interleukin shares p40 subunit with IL12.

Considering the different species separately, various trends are observed (see supplementary Table 1). Indeed, even if the most studied interleukin is invariably IL1, there is a large variation between species regarding other interleukins. In the pig, IL6 and IL10 have also been highly studied and generated several papers and numerous citations. When we look at M quotient and A index, we can observe high values for IL10 showing the more recent interest for this interleukin particularly involved in the pathogenesis of a major viral disease of the pig caused by the porcine reproductive and respiratory syndrome virus (Díaz et al., 2016; Ducrot et al., 2016; Lunney et al., 2016). Research on this interleukin started more than ten years later than research on porcine IL1 and IL2 but accelerated in the last years modifying quotient and indexes. In the bovine, IL4, IL6, IL8, IL10 and IL12 were particularly studied after IL1 and IL2 generating high values for H index, A index, and M quotient. In sheep, there are the special cases of IL13 which generated a high number of citations (102 citations from 2005; A index = 55.5) and IL5 with 11 selected articles and a A index of 25.75, more than in the others species and the

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others interleukins (IL1, IL2, IL6, IL8, and IL10). The sheep model has been used to study asthma and parasite infections which are associated to a Th2 response (Bao et al., 1996; Kasaian et al., 2007; Liravi et al., 2015; Pernthaner et al., 2005). However, only a few papers among the selected articles concentrated most of the citations (100 citations for 2 articles for IL13 (Kasaian et al., 2007; Liravi et al., 2015) and 89 citations for 2 articles for sheep IL5 (Bao et al., 1996; Pernthaner et al., 2005). In goat, highest H indexes are observed for IL2, IL4, IL10, IL1, IL6, and more surprisingly IL18. This interleukin has been studied for its role in the modulation of ovarian steroids in the goat reproductive tract (Lei et al., 2015; Liu et al., 2005; Qi et al., 2012). In horses, IL4 and IL6 were particularly high after IL1. Equine IL4 was associated to pulmonary diseases (Cordeau et al., 2004) and IL6 to various inflammatory conditions (Barton and Collatos, 1999; Fumuso et al., 2003).

The indexes, ratios and quotient used in our study illustrate different aspects of the bibliometric analyses such as, for instance, the interest for one specific interleukin, the number of papers dedicated to it, the amount of associated citations, and the number of years it has been studied. As for researcher or institution evaluation, simultaneous use of different indicators was needed to assess the interest of the scientific community for a specific subject. For example, even if ovine IL13 H index was low (2), the A index (55.5) and the GH ratio (3) clearly indicated the interest developed in the researcher community for this specific interleukin. Comparing these indicators enabled interesting observations in old interleukins. For instance, M quotient revealed an important and quite recent interest for IL18 in pig with papers having a higher number of citations than papers related to most other interleukins. In more recent interleukins, indicators failed to generate comparisons as the number of selected papers was too low.

To our knowledge this is the first report dedicated to a bibliometric study focusing on interleukins. The analysis was carried out with large domestic animal interleukins to get a first idea of the current situation regarding the study of these immune mediators in these species. Our analysis emphasizes the need for more studies dealing with comparative immunology between species. This is of high importance today when there are many voices asking for the development of new alternative and more relevant animal models in biomedical research.

Declarations

Author contribution statement

Emmanuelle Moreau, François Meurens: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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