Overview of cytokine and growth factor review focus on Australia

Paul J. Hertzog and Niamh E. Mangan

Centre for Innate Immunity and Infectious Diseases, Monash Institute of Medical Research, Monash University, Clayton, Victoria 3168, Australia
This special edition of CGFR focuses on the significant and substantial contributions of Australian researchers to cytokine and growth factor research. This is by no means a comprehensive collection of all the cytokine research in the country, but a representative selection. We apologise to those not included, many of whom are mentioned in the Nicola historical overview. We have elected to cover a range of cytokines and growth factors: GM-CSF/IL-3/IL-5 (Nicola, Hercus), IL-6 (Mansell), IFNs (Hertzog, Campbell), BAFF/APRIL (Vincent), mechanisms of regulation of production (Stow) and action (Linossi); and their impact, e.g. chemokines (Comerford) in immune function, growth factors in bone remodelling (Chim), activins and follistatins in inflammation and fibrosis (Hedger).

Cytokines and growth factors are important not only in the maintenance of homeostasis but are important mediators in a range of disease processes including cancer, autoimmunity, obesity and acute and chronic inflammation, as outlined in the reviews presented here. The survival and activity of almost every cell in the body is regulated by growth factors and cytokines. A well-documented example is the cytokine regulation of the initiation and effector functions of immune cells. Such is the importance of these proteins that many of the known influences of cytokines and growth factors on biological processes have and are being harnessed for clinical and translational outcomes, and more functions and translational applications are undoubtedly yet to be discovered.

Professor Nicos Nicola (WEHI, Melbourne, VIC) provides an eloquent historical synopsis of the major inputs of Australian researchers to the discovery and description of cytokines and growth factors, most notably starting with colony stimulating factors (CSFs) in 1964, to bring us up-to-date with Australian research in this complex biological field. We are fortunate to have Prof. Nicola provide this reflection, as he was a key player in the seminal research resulting in the discovery and characterisation of multiple CSFs, LIF, their receptors and suppressors of cytokine signalling (SOCS). The structural interactions of these cytokines and growth factors with their receptors led to the discovery of the common beta chain (βc) receptor and resolution of the crystal structure of receptor-cytokine interactions delineated the structural confirmations required for downstream signalling. The biological significance of this signalling axis of the GMCSF/IL-3/IL-5 (βc) family in stimulating and regulating cell functions, is reviewed here by Hercus and colleagues (Centre for Cancer Biology, Adelaide, SA).

The TNF family member, BAFF is a B cell survival and maturation factor. The negative role for BAFF in systemic lupus erythematosus (SLE) has been well characterised, with the targeting of BAFF (Belimumab) in ongoing clinical trials. However, the impacts of BAFF are not limited to SLE and Vincent et al. describe potential functions of BAFF in other autoimmune conditions as well as cancer, inflammation and infection.

Hertzog and Williams (Monash Institute of Medical Research, Melbourne, VIC) discuss the fine tuning of Type I IFN responses, from the questions of when, where and which one is produced, to the role of each receptor component in interacting with its ligands and transducing one of many signalling pathways that include classical JAK/STAT as well as so-called “alternative” pathways. Fine-tuning of this response averts the potential toxic/lethal effect of excessive IFN signalling, and SOCS1 is a key inhibitor. These authors also discuss the harnessing of genome-wide assessments of signalling/IRG induction on understanding type I IFN signals and their pathophysiological consequences.
Cytokines and growth factors can elicit pro- and anti-inflammatory responses dependent on the timing of induction, levels of production, cell source, secretion and regulation of cytokine signalling. Stow and Murray (IMB, Brisbane, QLD) demonstrate how the magnitude of the cytokine response can be varied even within cells depending on the different physiological stimuli in a context-dependent manner. They discuss many cytokines reviewed in this volume including TNF, IFN and IL-6. Different cells appear to have differing cytokine trafficking machinery (granules and endosomes) and secretory pathways for the directional release of stored or newly synthesised cytoplasmic cytokines, as described in depth for TNF. The complexities of this delivery network are being unravelled through the use of better technologies enabling real time live cell and in vivo imaging.

Not only the production, but also the actions of cytokines are tightly controlled by proteins such as the SOCS family which are well defined for their role as negative regulators of cytokine signalling, through inhibition of the cytokine receptor associated JAK/STAT signalling pathway (as reviewed by Linossi et al., WEHI, Melbourne, VIC). These authors summarise the literature on SOCS proteins from the initial discovery of SOCS1 by Doug Hilton and colleagues (WEHI, Melbourne, VIC) to our current knowledge of the biological regulation of cytokine signalling (e.g. suppressor of IL-6 signalling as well as Type I and II IFN signalling) by the known SOCS proteins.

SOCS3 been shown to be important in the regulation of IL-6 and IL-11 responses (Mansell and Jenkins, Monash Institute of Medical Research, Melbourne) acting via the gp130 signal transducer. Mice with a transgenic knock-in mutation of Tyr757 to phenylalanine in the IL-6 receptor component gp130 thus preventing SOCS3 recruitment and inhibiting JAK signalling, have increased susceptibility to LPS induced septic shock and also incidence of gastric cancer due to aberrant STAT3-dependent IL-6 signalling. These authors discuss the cross-talk of these cytokine signalling pathways with TLR2 which also drives carcinogenesis in this model. This provides an elegant demonstration of how deregulated signalling can have detrimental pathological consequences.

Deregulated cytokine and growth factor responses contribute to autoimmunity, chronic inflammatory diseases and cancers. Indeed, Stow, Mansell, Campbell, Hertzog and Linossi all discuss the importance of regulating cytokine responses for a timely controlled production and action of cytokines dependent on the stimulus, whether it be pathogenic in origin or host-derived sterile inflammation versus maintenance of homeostasis. Production of cytokines is driven by upstream signalling emanating from sensing of a danger signal via intracellular and extracellular pathogen recognition receptors (PRRs). This is currently an explosive field of research which impacts on cytokine and growth factor biology whose discovery was acknowledged by award of the 2011 Nobel Prize to Beutler, Hoffman and Steinman (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2011). Although not reviewed specifically in this edition, it continues to be an active area of research in Australia and is discussed in many chapters in this volume.

Cross-talk between cells through the production of cytokines and chemokines by haematopoietic and non-haematopoietic cells enables the rapid migration of immune cells from the bone marrow or blood to sites of inflammation (often initiated by PRRs) and thus orchestration of the innate and adaptive immune responses. For example, the chemokine signalling axis CCR7/CCL19/CCL21, in concert with other chemokine pathways, enables DC and T cell migration from the periphery to the
lymphoid organs where they can then stimulate or repress cellular responses, and the production of cytokines and growth factors (Comerford et al., University of Adelaide, SA).

We are constantly evolving and redefining our understanding of the complex interaction, functioning and magnitude of cytokine and growth factor responses. Transforming growth factor-β superfamily members, activin A and activin B, initially characterised for their activation of hypothalamic/pituitary/adrenal axis and impact on the reproductive tract, may also be used as diagnostic indicators of disease progression and severity in acute and chronic inflammation, as reviewed by Hedger and deKretser (Monash Institute of Medical Research, Melbourne, VIC). Furthermore, inhibition of these cytokines via the activin-binding follistatin offers considerable therapeutic potential in many inflammatory conditions including LPS-induced septic shock and liver inflammation and fibrosis.

Chim et al. (Molecular Laboratory, Perth, WA), present a thorough review of the role of epidermal growth factor family members (such as vascular endothelial GF and fibroblast GFs) in angiogenesis in skeletal development and bone remodelling. Aberrant angiogenesis is associated with many bone pathologies including osteoarthritis.

The pathological consequences of dysregulated type I IFN signalling is emphasised by Campbell (University of Sydney, NSW), who describes how aberrant chronic IFNα production in the central nervous system mediates some of the neuro-pathological inflammatory outcomes of Aicardi-Goutieres Syndrome and the systemic effects observed in SLE. While type I IFNs can also be protective in other neurological conditions such as Multiple Sclerosis where therapeutic administration of IFNB can improve clinical disease, the conflicting evidence for pathological and beneficial roles for IFN demonstrates our ongoing need to better understand the regulation of this and other cytokines.

A common thread across all the reviews is that cytokines and growth factors are key players in maintaining homeostasis and the innate and adaptive immune responses, whereas dysregulated cytokine and growth factor production has detrimental impacts on the individual. Thus, regulation of cytokine and growth factor production by specific cell populations and in a timely manner holds the balance in check. The key to harnessing the therapeutic potential of cytokines and growth factors lies in understanding the global impact of cytokine networks in coordinating the immune response and how we adapt the strength and magnitude of the response appropriate to the stressor or stimulus.

Major questions remain in identifying the upstream regulators and the downstream molecular targets of cytokine responses, as well as their roles in the promoting pathophysiological responses. In the post-genomic era, the question, could be asked: What is left to be discovered? Are major discoveries like those of Nicola, Hilton and Metcalf still possible? Do we know all the cytokines, growth factors, chemokines and receptors and are we now just redefining the functions of known cytokines and GFs? Much of the answers lie in current and future technologies. It appears that we have the near full list of genes encoding proteins. However we still have to annotate the functions of many – including secreted, plasma membrane and intracellular signalling molecules. Exciting questions also remain about discovering their functions which again will be facilitated by high throughput technologies using genome-wide approaches (as were indeed used to discover the JAK/STAT pathway by Stark and Kerr group; and SOCS1 by the Hilton group). Cytokine production in
homeostasis and immune function will also help identify and define new cell populations (such as innate lymphoid cells, nuocytes), and their function. Next generation sequencing technologies now allow us to use a systems-wide biology approach to determine the global map of a particular cytokine or growth factor regulation and signatures in specific cell populations. Bioinformatics and cross-disciplinary approaches to support these key biological questions are now more essential than ever, as the amount of data becomes enormous.

Historically, the cytokine field has been driven by the target of translation. Cytokines like IFNs were some of the first proteins to be cloned by recombinant DNA technologies of the 1980s and the production of large amounts of pure cytokines with tantalising functions fuelled the biotechnology boom. Cytokines such as IFN, CSFs are in clinical use, monoclonal antibodies have been developed to block their dangerous, pro-inflammatory effects (e.g. anti-TNFα, anti-BAFF) and small molecule drugs have been developed as in the case of JAK inhibitors. The continued development of the cytokine field will undoubtedly see more refined use of cytokines, and their “signature” changes in cells in diagnosis, prevention, genetics and targeted therapy.

Corresponding author. Tel.: +61 3 9594 7206/9902 4827; fax: +61 3 9594 7211.

Paul J. Hertzog is Director of the Centre for Innate Immunity and Infectious Diseases at Monash Institute of Medical Research. His research interests are in understanding the molecular control of signalling in the innate immune response. His focus is in interferon signalling where current projects address structure:function of receptors, negative regulation of signalling, characterisation of interferon ε function in reproductive tract immunity and disease. He has a particular interest in signal transduction and gene regulation in innate immunity and is using systems biology to address to understand the control of immune response in infectious and inflammatory disease and cancer.
Niamh Mangan is a research fellow in the Centre for Innate Immunity and Infectious Diseases at Monash Institute of Medical Research. Her research is focussed on using cellular and molecular immunology approaches to understand innate and adaptive immune response to infectious diseases. She is also interested in the characterisation of how new cytokines regulate mucosal immune responses. Her projects currently include the characterisation of the physiological role of newly discovered interferon epsilon and its role in regulating immune responses to viral and bacterial infections of the female reproductive tract. She is also working on the new IL1 family members. She is supported by funding from the National Health and Medical Research Council, the Australian Research Council and the Victorian Government's Operational Infrastructure Support Program.