An eruption of European B-cell biology

Michael P. Cancro

Volcanic ash clouds disrupted the 2010 ESF/EMBO meeting on B cells and protection. Nevertheless, the delegates who did make it to Catalonia put together their own programme of talks covering a range of themes from mutualism to epigenetics.

The 2010 ESF/EMBO meeting on 'B Cells and Protection: Back to Basics' had been impeccably planned. The organizers, Rita Carsetti (U. Rome 'Tor Vergata') and Deborah Dunn-Walters (King's College, London), had dotted each 'i' and crossed every 't' with care. The gathering was scheduled to take place in idyllic San Fileu de Guíxols on the coast of Catalonia with a globally representative cast of speakers and session organizers, and a near record number of registrants. The only thing left was for all participants to arrive in beautiful Barcelona on 17 April, board the shuttle buses to San Fileu, and convene the meeting with a plenary talk and a welcome drink overlooking the azure Mediterranean. What could possibly go wrong? In a word: *Eyjafjallajökull*.

Many of us attending from faraway places, including the USA, Brazil and Israel, boarded planes the previous evening and arrived safely in Barcelona. However, on our arrival we noticed ominous signs beginning to emerge: newscasts trumpeting an enormous plume of stratospheric ash spewed out by the aforementioned active Icelandic volcano; the steady southward march of European airport closures; massive numbers of displaced travellers straining European rail systems to capacity, and airport schedule boards peppered—if not filled—with the word "cancelled" (Fig 1). Even Barcelona itself, one of the southernmost European airports, closed briefly that afternoon. By early evening, fewer than 20 of the expected 200 attendees queued up for the shuttle buses. Ironically, few were Europeans. This meagre

Photo credit: Eric Klein

"... rather than give up, this small group of dyed-in-the-wool immunologists transformed the get-together into an intimate 1.5-day workshop..."

band arrived at the hotel in San Fileu de Guíxols to be greeted with uncertainty as to the viability of the meeting, but checked into their rooms for the night. By the next morning, it was clear that additional attendees were unlikely to make it, so the meeting—at least as originally planned—was cancelled.

However, rather than give up, this small group of dyed-in-the-wool immunologists transformed the get-together into an intimate 1.5-day workshop (see photo). Ramit Mehr, a mathematical modeller from Bar-Ilan University (Ramat-Gan, Israel), spearheaded the impromptu planning, with everyone's enthusiastic participation. Even Ramit's husband, Eric Klein, was pressed into service as the information technology, computing, audio and photographic consultant. The meeting thus began with brief overviews of B-cell differentiation and activation, after which the group settled into a full day of

thought-provoking talks from all invited speakers and poster presenters in attendance. Within this quickly fashioned but well-constructed framework, a series of timely and conceptually related themes emerged. Judging from the entirety of abstracts submitted for the originally planned meeting, these represented a solid cross-section of the blueprint originally envisaged by Rita and Deborah.

Several talks revolved around understanding the role of commensal microbiota in B-cell development and regulation, as well as how the immune system manages to avoid eliminating these beneficial microbes. Many of these suggested that normal microbiota could influence the balance of inflammatory responsiveness in a variety of scenarios, including tolerance and allergy models. Jenny Hansson (Nestlé Center, Lausanne) presented work suggesting that the establishment of normal peripheral B-lymphocyte numbers and subsets is independent of neonatal commensal colonization. Nonetheless, work described in the abstracts of several registrants who were unable to attend suggests that splenic architecture and B-cell subsets, as well as the species composition of gut microbiota, can influence one another. In a related presentation, François Leulier

"Several talks suggested that normal microbiota could influence the balance of inflammatory responsiveness a variety of scenarios, including tolerance and allergy models."

(IBDML, CNRS, Marseille) explored the basic principles of this balance by studying how mutualism is maintained in the nuclear factor- κ B (NF- κ B) system of *Drosophila* spp. His findings suggest molecular mechanisms for tuning NF- κ B-mediated signals on the basis of intervening molecular circuits. These prompt speculation that common molecular paradigms might be at work in tuning the adaptive and innate receptor systems of vertebrates. Together, the take-home message seems to be that setting this balance involves autonomously driven developmental and homeostatic programmes combined with cross-talk between the commensal niche, innate immunocytes and the adaptive immune repertoire.

A second cluster of talks centred on molecular and cellular aspects of B-lineage differentiation. Yehudit Bergman (The Hebrew U. Medical School, Jerusalem) presented an elegant series of studies showing that in haematopoietic stem cells (HSCs) the asynchronous replication time mode for each allele is not maintained in a clonal manner. Choosing one allele becomes fixed in pro-B cells. Once a clonal replication decision is established it acts as the basis for initially choosing one allele to rearrange. She also showed that both alleles are packaged in differential chromatin states, with the open conformation allele being the preferred target for rearrangement. As for the V_k genes, she has shown that they are opened in a mono-allelic way on both chromosomes. Yehudit suggests that this might afford a means for ensuring that different V_k genes are used on either allele during receptor editing. This intriguing observation also raises the question as to whether this is exemplary of a general differentiative mechanism, through

“... [TLR4] ligands afford both phenotypic and functional B-cell maturation from B-cell progenitors *in vitro*... [this] process involved the classical NF- κ B pathway and was BAFF ... independent.”

which epigenetic marks can be preserved at selected loci once lineage specification ensues. Representing the Nóbrega laboratory at the Federal University of Rio de Janeiro, Elize Hayashi and Alessandra Granato showed that Toll-like receptor 4 (TLR4) ligands afford both phenotypic and functional B-cell maturation from B-cell progenitors *in vitro*. Interestingly, this TLR4-mediated process involved the classical NF- κ B pathway and was BAFF (from the TNF family) independent. Moreover, when added together, BAFF and lipopolysaccharide (LPS) showed synergistic effects on the number of mature B cells generated. It is tempting to speculate that the classical NF- κ B-dependent, LPS-driven signals replace the role of B cell receptor signals in this differentiative scheme, and can be further augmented through the survival-promoting effects of BAFF. These observations underscore the suspicion that we have not yet fully unravelled the tangled web of cross-talk of the signalling systems downstream from innate, adaptive and BAFF receptor families.

Horas	Vol	Destinación	Observación
15:00	15:50 SAS	SAS 9580 MENORCA	CANCELLED
	15:55 LH	LH 4455 FRANKFURT	CANCELADO
	15:55 JKK	JKK 5710 P.MALLORCA	CANCELLED
	15:55 TAP	TAP 8610 P.MALLORCA	CANCELLED
	15:55 THY	THY 8224 P.MALLORCA	CANCELLED
	15:55 LH	LH 2536 P.MALLORCA	CANCELADO
	15:55 SN	SN 6267 P.MALLORCA	CANCELADO
	16:00 IBE	IBE 8560 NANTES	CANCELLED
	16:00 IBE	IBE 5652 SEVILLA	CANCELLED
	16:00 VLG	VLG 2278 SEVILLA	CANCELLED
	16:00 VLG	VLG 8055 PARIS ONLY	CANCELADO
	16:00 IBE	IBE 5760 PARIS ONLY	CANCELLED
	16:15 JKK	JKK 133 MUNICH	CANCELLED
	16:20 BTI	BTI 5876 ALICANTE	CANCELLED
	16:20 VLG	VLG 6106 ROMA	CANCELADO
	16:20 IBE	IBE 5710 ROMA	CANCELADO
	16:20 JKK	JKK 6716 ALICANTE	CANCELLED
	16:20 THY	THY 8218 ALICANTE	CANCELLED
	16:20 SAS	SAS 6253 ALICANTE	CANCELLED
	16:20 MSR	MSR 8845 ALICANTE	CANCELADO
	16:20 SN	SN 6253 ALICANTE	CANCELADO
	16:20 UX	UX 3929 ALICANTE	CANCELADO
	16:20 AUA	AUA 8845 ALICANTE	CANCELLED
	16:20 MSR	MSR 9398 ALICANTE	CANCELLED
	16:20 SAS	SAS 9866 ALICANTE	CANCELADO

Fig 1 | The Eyjafjallajökull ash cloud devastated European flight schedules.

A final area of interest centred on the dynamics of T-cell-dependent immune responses, particularly on events involved in the formation and evolution of germinal centres (GCs). A few of these talks occurred on the day after the main meeting, due to late arrivals that had made their way by a combination of boat, automobile and train across Europe. Among these, Yang Zhang—a PhD student from Kai-Michael Toellner's group at U. Birmingham—showed a series of cleverly designed experiments to assess the role of GC-associated antibody in affinity maturation. With a combination of careful *in vivo* histological studies and subsequent *in silico* analyses, she demonstrated that the immunoglobulin within GCs is in equilibrium with antibody outside, and that the replacement rate of GC-associated antibody relies on relative affinities. In related studies, work from Radhika Goenka (U. Pennsylvania, Philadelphia) suggested that BAFF receptor

TACI is downmodulated on GC B cells, thereby dramatically lowering levels of bound BAFF in the GC and making T_{FH} the primary source of BAFF in these regions. Considered together, these findings indicate that many layers of competition—for antigen, cognate interactions and survival factors—might underlie the process of affinity maturation within GCs.

All things considered, the telescoped version of this meeting provided an exciting glimpse of the originally planned four-day event. Indeed, given this preview of the breadth and strength of the field likely to be realized, I am certain nothing will prevent me from attending the soon-to-be rescheduled full version. Well, so long as it is not held too near Pompeii.

Michael P. Cancro is at the University of Pennsylvania School of Medicine, Philadelphia, PA, USA.

E-mail: cancro@mail.med.upenn.edu

Published online 20 August 2010

EMBO reports (2010) 11, 653–654.
doi:10.1038/embor.2010.128