

Marking the 50th Anniversary of *Immunology*

## Special regulatory T cell review: The suppression problem!

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**Summary**

The concept of T-cell mediated suppression evolved more than 30 years ago. At that time it spawned many claims that have not stood the test of time. The rediscovery of suppression phenomena and regulatory T cells over the past 15 years created schizophrenic responses amongst immunologists. Some claimed that the new proponents of suppression were, once again, bringing immunology into disrepute, whilst others have embraced the field with great enthusiasm and novel approaches to clarification. Without faithful repetition of the “old” experiments, it is difficult to establish what was right and what was wrong. Nevertheless, immunologists must now accept that a good number of the old claims were overstated, and reflected poor scientific discipline.

“I speak not to disprove what Brutus spoke, But here I am to speak what I do know”

*Shakespeare. Julius Caesar Act 3, Scene 2.*

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**Introduction**

Here is an extract from a recent article which reflects a disturbing viewpoint.

“It is worrying that there has been overemphasis of what may be exceptional cases of immunological phenomena. Recently there has been an enthusiastic renaissance not only of signal theories, but also about regulatory T-cells, negative (suppressive) T-cell mechanisms, and idiotypic networks, as if they had not misled (or even ruined) entire generations of immunologists during the past 40 years.”<sup>1</sup>

The above remarks from an eminent immunologist demonstrate how emotive the subject of suppression has been from its first description in the 1970s, leading that author to dismiss a whole recent decade of overwhelming evidence on the existence of CD4 T-regulatory cells!

Why did the suppression research of the 1970s create this loss of confidence in the subject? There is no doubt that immunologists of that era lacked technologies and tools (e.g. monoclonal antibodies) to finesse the experiments. The lack of transferable tools meant that the community could not distinguish poorly executed science from good science. It would be easy, as some have done to stop the analysis there. However, in my view, this situ-

ation (lack of tools) also spawned a significant level of indiscipline and poor training. Consequently, a number of laboratories generated data that (for sure) has not stood the test of time (for example T-cell antigen-specific suppressor factors, and hierarchies of suppressor cells). If I had to point blame, it would be at the laboratory heads who were too quick to align themselves to colourful explanations, and often approached experiments with pre-conceived notions. Young trainees trying to cut their teeth in the subject might, in that climate, have not been trained to be open minded and critical of their data. For example, on the issue of ‘antigen-specificity’, many of the early claims of antigen specific suppression lacked the discipline cultivated by the classical serologists, in not performing criss-cross experiments. In other words to claim antigen-specificity in a population of cells or extracts thereof, one had to show that A-type T-cells primed to B would suppress responses to B but not C, but also (and critically) that A T-cells primed to C would suppress responses to C and not B. This might easily have misled them into concluding specificity on insufficient data!

This sentiment has been long felt but rarely stated. I think it important that the notion of some very poor science in that period be recognized, lest we spend too long

trying explain many of those early experiments that simply do not merit the generous view.

The strong views I express above should not be taken to dismiss all papers of the period. The original papers of Gershon<sup>2,3</sup> and McCullagh<sup>4</sup>—the early proponents of suppression—were compelling reading, and could well be compatible with current dogma. At some point it would be useful for their experiments to repeated using the modern tools. Only then could we be satisfied that the phenomena of the 1970s were the ‘prior art’ that justifies proper precedence.

### The modern era?

On the good side, the new era has identified markers (e.g. FoxP3, CD25), genetically manipulated models and reporter systems that enable reproducible manipulation of suppression. The identification of natural regulators formed in the thymus, and induced-regulators (convertes from naïve T-cells) has, in part, clarified roles for antigen. The symmetry of data from transplantation, autoimmunity and immunopathology also gives confidence to their existence and roles. The demonstration of a role for transforming growth factor- $\beta$  in their conversion, and the ability to culture lines of induced regulatory T-cells (Treg), all provide for reproducible systems for analysis.

Having said that, there are still major knowledge gaps that need filling to complete the credibility gap:

- We still lack sufficient model systems for analysis of antigen specificity and function of Treg in lymphocyte-replete recipients. Lymphopenic recipients might mislead by favouring homeostatic proliferation phenomena.
- There remain too few high-quality criss-cross experiments to demonstrate antigen specificity
- We have minimal understanding of mechanism for regulation. There are many possible candidates but no overwhelming proof for any one of them.

- We cannot be sure about the fidelity of the regulatory lineage, in particular, the extent to which induced Treg remain committed to that function indefinitely.
- We lack knowledge on where Treg operate. Is it in the lymphoid organs, the tissues or both?

### Conclusion

Although asked by the editor to write an article with reference to the early literature, I must admit to not wanting the responsibility of arguing about which of the old papers were correct and which were incorrect. What I do feel though, is that someone does need to say that many claims of the 1970s were not based on high scientific standards, and this has corrupted a proper historical analysis of the evolution of the subject. Hopefully, the field will learn from this difficult time and ensure higher standards in the published works.

Despite the advanced tools we now have, it is surprising just how difficult it has been to pin down mechanisms of suppression. What is reassuring is that the field of suppression is now highly popular and respectable for aspiring scientists and funding agencies. Even Nobel Laureates can get it badly wrong sometimes!

### References

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