IL-2: More Than a T Cell Growth Factor

Joost J. Oppenheim

J Immunol 2007; 179:1413-1414; doi: 10.4049/jimmunol.179.3.1413
http://www.jimmunol.org/content/179/3/1413

References
This article cites 14 articles, 5 of which you can access for free at:
http://www.jimmunol.org/content/179/3/1413.full#ref-list-1

Subscription
Information about subscribing to The Journal of Immunology is online at:
http://jimmunol.org/subscription

Permissions
Submit copyright permission requests at:
http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts
Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
IL-2: More Than a T Cell Growth Factor

Joost J. Oppenheim

The 1976 and 1977 reports of the discovery of T cell growth factor (TCGF) by Francis W. Ruscetti, Doris A. Morgan, and Robert C. Gallo sparked great interest in lymphocyte growth factors (1, 2). Although there were a number of prior reports of the detection of factors mitogenic for lymphocytes, this discovery, featured in Pillars of Immunology (2), made it possible to grow and expand normal lymphocytes long term using TCGF. A blastogenic factor (BF) capable of inducing lymphocyte mitogenesis was first detected by Kasakura and Lowenstein in the supernatants of antigen and alloantigen-stimulated leukocyte cultures in 1965 (3). Also in 1965 Gordon and McLean demonstrated that in vitro generation of BF in response to lymphoproliferative mitogens could be inhibited by puromycin or 5-fluorouracil, suggesting that BF was lymphocyte derived (4). Dumonde et al. (1969) identified lymphocytes as the source of these mitogenic factors and termed them “lymphokines” (5). Several years later, Gery et al. reported that macrophages also produced a “lymphocyte-activating factor” that could only support short-term growth of thymocytes and lymphocytes (6). Chen and DiSabato discussed a number of studies investigating short-term thymocyte-stimulating factor (7).

Ruscetti et al. were apparently unaware of these immunological laboratory efforts. Robert Gallo was aiming to identify a means of growing myeloid cell lines long term to discover and culture human retroviruses. They therefore obtained human bone marrow cells as a source of myeloid precursors and cultured them with repeated additions of supernatant of PHA-stimulated human blood lymphocytes (1, 2). To their surprise, rather than the usual EBV-positive B lymphocytes, this yielded a long-term growth of T lymphocytes that could be maintained and expanded for 9 months only by the repeated addition of TCGF.

Nevertheless, Bob Gallo was initially very disappointed that this approach yielded only the “wrong” cell for the purpose of cultivating human viruses. Despite a variety of attempts, bone marrow-derived granulocytes and myeloid cells died during the first week of culture, leaving only the E-rosette-forming mononuclear lymphocytes (i.e., T cells) capable of responding to TCGF. This led them to report TCGF as a factor capable to generate normal T cells in large quantities. As predicted in their report, these “immortalized” normal T cells have provided an excellent tool for molecular immunological studies of the growth and differentiation of T cells and for use in the treatment of cancer patients.

The availability of TCGF made it possible to study cloned T cells with a single antigenic specificity. This led to an understanding of how T cells recognize Ags and to the identification of receptors for TCGF and Ags. It also led to the unanticipated identification of Th1- and Th2-polarized T cell types. TCGF has also proven to be of great benefit to virologists by providing the necessary culture methodology that led to the discoveries of human T cell leukemia virus type 1 and HIV-1.

The immunologists became very unhappy with the plethora of terms used to describe endogenous lymphocyte-derived lymphoproliferative factors and proposed to use the more abstract term of IL-2 (8). Scientists who favored TCGF resented this apparent expropriation of their discovery by immunologists. However, this resistance was overcome by reports that IL-2 acted on non-T cells and was also a growth factor for NK cells (9) and B cells (10).

Since then, the multitudinous and complex activities of IL-2 have repeatedly surprised investigators. In addition to promoting the survival and growth of T cells, IL-2 terminally differentiates T cells for activation-induced cell death (11). The development of technology for inactivating the IL-2 gene led to observations that IL-2 null mice paradoxically developed progressive lymphoid hyperplasia (12). The mice also developed autoimmune syndromes such as hemolytic anemia and in a conventional environment they subsequently developed autoimmune enteritis as well (13, 14). These consequences are now understood to be based on the more recent surprising observations that IL-2 is a potent stimulator of T regulatory cells (15).

IL-2 is a necessary signal for the development, survival, and expansion of regulatory T cells that down-regulate self-reactive lymphocyte responses, thus preventing anemia, enteritis, and other autoimmune sequelae. Consequently, the unintended discovery of Ruscetti, Morgan, and Gallo has led to our appreciation of T cell growth factors not only as promoters of the survival and proliferation of immune effector and killer cells but also as the pivotal inducers of T regulatory cells.

Acknowledgments

I am grateful to Drs. Scott Durum, Giorgio Trinchieri, and Francis Ruscetti for their constructive discussions of this essay and to Cheryl Fogle-Lamb for producing multiple drafts.

References

