Editorial

Editorial on "*PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis*"

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Many things have occurred in Oncology since the discovery of programmed death-1 (PD-1) and PD-1 ligand 1 (PD-L1) (1,2). PD-1/PD-L1 interaction appeared to be another one of many regulatory ligand-receptor interactions between antigen presenting cells (APCs) and T cells (3). But it turned out that this interaction was not like any other, at least from a clinical point of view with possibly the exception of CTLA-4/CD28. PD-L1 is a B7-related type I transmembrane protein belonging to the immunoglobulin superfamily constitutively expressed by the myeloid lineage and other cell types. Moreover, PD-L1 expression was found to be up-regulated by pro-inflammatory stimuli such as TNFs and IFNs and its expression represents a survival mechanism against pro-apoptotic stimuli (4-6). Its receptor PD-1 is a CD28-related type I transmembrane protein also belonging to the immunoglobulin superfamily that acts as PD-L1's receptor. PD-1 is mainly expressed by lymphoid cells including T, B and NK cells.

Preclinical studies showed that PD-L1/PD-1 interaction negatively regulates T cell proliferation and effector activities (3). Indeed, it was also demonstrated that cancer cells expressed PD-L1 as a means to counteract T cell-mediated killing by engaging with PD-1 (4,7). Nevertheless, the results from pre-clinical models in which this interaction was blocked showed rather promising although not spectacular results. Therefore, at this point PD-1 was just another negative regulator of T cell activation.

Then, in 2012 the results of PD-L1/PD-1 antibody-mediated blockade in human clinical trials were published, and it was found that blockade of this interaction led to a significant increase in survival with efficacious long-term anti-tumor responses (8,9). Since then, many clinical trials have been carried out and corroborate the potency of PD-L1/PD-1 blockade as an anti-cancer therapy. This explosion of efficacious immunotherapies has completely reshaped Oncology. While a few years back most of the research was directed to the designing of chemical inhibitors of oncogenic pathways (mainly kinases), now immunotherapy and biological therapies have taken over.

Curiously, although PD-1 and PD-L1 have become priority targets in Oncology, we know relatively little of the molecular and cellular mechanisms regulated by this interaction. In fact, although PD-L1/PD-1 is important to maintain immunological tolerance (10), there are surely other key physiological roles played by these molecules just to be discovered. And that is precisely what Wartewig and collaborators show in their recent letter to *Nature* (11). Rather surprisingly, the authors clearly demonstrate that PD-1 is indeed a tumor suppressor gene in non-Hodgkin T cell lymphoma. That was clearly unexpected.

PD-1 signal transduction pathways in T cells

When engaged with PD-L1, PD-1 interferes with T cell receptor (TCR) signal transduction through yet poorly characterized molecular mechanisms, which are reviewed in detail elsewhere (12,13). Briefly, PD-1 contains in its cytoplasmic domain immunoreceptor tyrosine-based inhibitory (ITIM) and immunoreceptor tyrosine-based switch (ITISM) motifs, which recruit SHP-1 and SHP-2

phosphatases. Most of the evidence points to SHP-2 as critical for PD-1 inhibitory activities. When bound to PD-1, SHP-2 may directly dephosphorylate or at least inhibit the phosphorylation of the TCR-associated kinases such as ZAP-70, LCK and PI3K (14,15). This process terminates TCR signal transduction by stopping the kinase cascade pathways which lead to phosphorylation of AKT, PCKθ and MAPKs. PD-1 ligation also switches T cells from a high-energy consuming metabolism to a low energy, fat-consuming state similar to that found in memory T cells (16). PD-1 also prevents the expression of CK2 leading to non-phosphorylated active PTEN that removes the intracellular messenger PIP3, terminating PI3K-dependent signal transduction (12,17). Finally, engaged PD-1 causes the up-regulation of E3 ubiquitin ligases of the CBL family that ubiquitylates TCR chains and CD28 (18). In this way, the TCR is endocytosed and does not signal any more.

PD-1 as a tumor suppressor gene

All of these pathways have as an ultimate goal to inhibit T cells by terminating TCR signal transduction. Hence, from a point of view of anti-cancer immunotherapies, PD-1 could in fact be considered an oncogene. However, this is not the case in some lymphoid malignancies that utilize sustained oncogenic activation of TCR signal transduction pathways to induce T cell proliferation and escape from apoptosis (19). Hence, anything that can stop TCR signal transduction pathways will act as tumor suppressor proteins in these T cell lymphomas.

Wartewig and collaborators were looking for the molecular mechanisms that promoted non-Hodgkin T cell lymphoma. The authors observed in a murine model that expression of the oncogenic fusion gene IKT-SYK in T cells led to the expansion of oligoclonal lymphoma T cells (11). That was also certainly unexpected, since strong widespread polyclonal proliferation of cancer cells would be predicted. This result strongly suggested that most T cells intrinsically expressed strong tumor suppressor genes and only a fraction of T cells develop into oncogenic clones. These clones would have selected somatic mutations disrupting the anti-tumor activities of the mysterious tumor suppressor gene. Therefore, the authors looked for potential novel tumor suppressor genes in this subset of cells by means of a genome-wide transposon mutagenesis assay. Surprisingly, the locus encoding PD-1 came up as the top common insertion site, leading to abrogation of PD-1 expression in these T cell clones. Their data was strongly reinforced by the high proportion of homo and heterozygous deletion of the *PD-1* gene (amongst other alterations) in clinical cases of T cell lymphoma (11). Indeed, Wartewig and colleagues demonstrated that PD-1 was up-regulated following IKT-SYK expression, and served as a negative feedback regulator by inhibiting AKT, PKCθ and elevating PTEN expression.

Scientific, clinical relevance, and beyond

The study by Wartewig and collaborators is the first one to demonstrate tumor suppressor functions for PD-1, and possibly it will not be the last to find novel roles for this key regulatory protein. Moreover, their results show that widespread PD-1 ligation probably occurs very frequently in physiological conditions although the authors do not go into much detail on this subject. Otherwise, PD-1 would not restrain most T cells from becoming cancerous. Undoubtedly, their results go also beyond the scientific and clinical relevance. Nowadays, an increasing number of clinical trials are undergoing with immune checkpoint inhibitors despite the relative lack of detailed scientific background on the biology of these critical interactions. Interestingly, the authors demonstrate in their study that PD-L1/PD-1 blockade transiently accelerated the growth of lymphoma cells (11). These results highlight the importance of deciphering and understanding the molecular mechanisms of cellular malignancies for the proper application of immunotherapies.

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Footnote

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