



## Tumour Infiltrating Lymphocytes: *Changing Trends*

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### Short Communication

The tumours are unique by virtue of their genetic instability and thus carry tumour associated antigens formed the basis of immune recognition of the cancers. An important link in the chain of host response to malignancies is the presence of Tumour infiltrating lymphocytes (TILs).

The TILs as the name suggests are the lymphocytes found within the tumour. Since many years, they have been used as tools to gauge immune-reactivity of malignancies of colon, ovary, lung, bladder, breast etc [1-4]. TILs have been noticed in both primary and metastatic tumours. Presence of TILs in tumours has been positively correlated with its prognosis and response to chemotherapy in many studies [5]. In some malignancies like triple negative breast cancer, TIL positive and TIL negative have been proposed to reflect tumour types with different response to immunotherapy. Moreover, the autologous TILs isolated from tumours and cultured with cytokines like IL-2 have been used as for immunotherapy of tumours [6]. However, other studies have shown no or a negative correlation between TILs and tumour prognosis [7].

Many past studies have emphasized upon the importance of systematic evaluation of quantity and quality of TILs as markers of outcome in different tumours. Degree of lymphocytic infiltration has been considered as predictor of favourable response in tumours in the past. In most of the studies TILs have been evaluated using immunohistochemistry, however, more recently techniques like, multicolour flow cytometry, TIL related genetic signatures and digital profiling are also gaining popularity [8,9]. Tumours are known to possess a mixture of lymphocytes, which may be present in different proportions. These include Th1, Th2, Th17, Tfh type cells, FoxP3+ T regulatory cells (Tregs) and T-cells with a memory phenotype [10]. Whereas the infiltration by effector CD4+ and CD8+ T-cells has been correlated with good prognosis in tumours, presence of Tregs has been associated with a bad prognosis [6]. CD8+ T-cells are cytotoxic to malignant cells and CD4+ T-cells being the central players in immune response to cancer are important in driving both CD8+ anti-tumour activity as well as antibody mediated response. Further, tumours have been found to reject subsequent challenge with the same tumour, which points towards the presence of memory against tumour antigens.

However, despite so much insight into immune surveillance of tumours, the performance of immunotherapeutic strategies was found to be less than anticipated. This has been attributed to several factors leading to dysfunction of TILs in tumour microenvironment (TME). Metabolic conditions prevalent in TME like hypoxia, aerobic glycolysis resulting in enhanced lactate generation, abundance of oxidised lipids, competition amongst TILs and tumour cells for essential nutrients like glucose and amino acids are believed to result in decline in TIL effector functions. As a result, there ensues an imbalance between co-stimulatory and co-inhibitory signals resulting in progressive anergy of effector T-cells [11,12].

The TILs in the above state are said to exhibit an exhausted phenotype. Based on their functional status three types of TILs have been proposed to exist in the TME: 1. Functionally active 2. Reversibly exhausted: Express PD-1<sup>med</sup>T-bet<sup>+</sup>/EOMES<sup>+</sup> 3. Irreversibly Hyper-exhausted: Express PD-1<sup>high</sup>LAG-3<sup>+</sup>TIM-3<sup>+</sup>T-bet<sup>+</sup>/EOMES<sup>-</sup> [13].

Novel strategies targeting co-inhibitory molecules especially anti-PD-1/PDL1 monoclonal antibodies are the focus of immune-based therapy in recent times [14]. However, the response to above therapy has been found to be 10-40% only [15]. It is believed that patients with tumours showing exhausted TILs are the ones benefitting maximum from anti PD1/PDL-1 therapy. In addition, strategies are being developed to target TME conditions, which push the TILs towards hypo-responsiveness. These include use of mTOR inhibitors or 2-deoxyglucose to reduce glycolysis

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in them, agents blocking esterification of cholesterol in TILs, oxygen supplementation or treatment with metformin to tackle hypoxia etc. The above may perhaps be successful in reducing the population of exhausted and hyper exhausted TILs present in TME [16].

Also, the location of TILs in stroma surrounding the nests of tumour cells or within the main tumour has been given significance. Whereas some studies show that, the tumours with immune cells within the tumour are better responders to anti-PD-1/PDL1 therapy others show that stromal but not intratumoral TILs are linked to a better prognosis [11].

In view of wide acceptance of cancer immunoediting theory the question that comes to our mind is: How do TILs behave in three Es of cancer immunoediting process? Do different functional subtypes characterize different phases of cancer immunity? As elimination stage is characterized by clearance of tumours by the immune system it is fair to presume that the TILs in this phase may mainly be of active subtype. During equilibrium phase, the TILs may enter into completely or partially exhaustive phenotype albeit with a possibility of reversibility of the same to active state provided proper conditions. Therefore, though they are present they are unable to remove the tumour. In the escape phase, they may be completely exhausted to hyper-exhausted and thus are largely irreversible from their anergic state. It will thus be fruitful to check for functionality related biomarkers of TILs in all three stages of cancer immunoediting process. These assumptions however further dictate that identification of factors prevalent in TME determining the functional status of TILs may serve as important targets for immunotherapeutic responsiveness. Also a question that comes to our mind is that: Is it worthwhile to classify the tumours as TIL rich and TIL poor? TIL rich tumours can then be evaluated for the functional subtypes of TIL and hence their fitness for immune checkpoint inhibitor therapy.

Modern era has seen a spurt of knowledge regarding TILs and has changed the concept of TILs from simplistic cells infiltrating the tumours to complex admixtures of cell populations that may or may not be functional. However lack of uniformity in criteria for assessing TILs and methods used for their evaluation have somewhat hindered the progress in using them as impeccable prognostic markers or as appropriately guided missiles of cancer immunotherapy. Functional categorisation of TILs and linking of factors prevalent in TME to their function is helping to unveil interesting facets, which carry promise for development of more efficient TIL based immune therapies in future.

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