

## Immunity and Pancreatic Cancer

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The pancreas has two morphologically and functionally distinct compartments: one comprising the exocrine cells, and the other comprising the endocrine cells [10]. The exocrine cells are the suppliers of various digestive enzymes to the upper small intestine through pancreatic duct, and the endocrine cells are the suppliers of various pancreatic hormones directly to the blood. Not surprisingly there are two broad divisions of Pancreatic Cancer (PC): the Exocrine Pancreatic Cancer, and the Neuroendocrine Pancreatic Cancer. The Exocrine Pancreatic Cancers are further divided into several sub-types that vary from each other histologically, and in symptoms and prognosis. Of these the Pancreatic Ductal Adenocarcinoma (PDAC), an Exocrine Pancreatic Cancer, is the most common amongst all the reported cases of PC. More than 90% of the PCs are found to be PDACs [12, 7]. From here on the term PC will be used to mean PDAC. PC is one of the deadliest cancers in the world because the PC is mostly detected when the tumor is not removable by surgery, and or the tumor has invaded the other organs of the body [9, 7, 3, 11].

There are three known precursor lesions of PC, without progressing through the various grades of which in steps PC does not develop [4, 2, 9]. These are Intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and pancreatic intraepithelial neoplasia (PanIN). Hence the early detection of these lesions is the key towards preventing PC. The PC is very rare amongst the general population, and the precursor lesions (of the PC) are mostly asymptomatic making the selection of the population eligible for screening difficult [4]. The precursor lesions are mostly detected when they are co-existing with a full-blown PC. As long as these hurdles remain PC will continue to remain a deadly disease. Surprisingly there has been very little study of Immunity in the context of PC and its precursor lesions. I discuss below Immunity with a vision to unlock the secret of early detection of PC.

### Immunity, PanIN, and PDAC

PanIn is the most frequent precursor lesion of PDAC. According to a simulation model [8], the percentage of the patients that develop PC from the lowest grade of PanIN lesion out of the total number of patients having the lowest grade of PanIN lesion is 1.43 in males and 1.31 in females. There are three break-ups in above calculation: the probability of PanIN1 lesion progressing to PanIN2 lesion, the probability of PanIN2 lesion progressing to PanIN3 lesion, and the probability of PanIN3 lesion progressing to PC. This means that in a vast majority of the patients of PanIN lesion, either the PanIN goes away naturally or the PanIN has been treated successfully. What is the cause of the successful eradication of the PanIn lesion to the order of 98-99%? The genetic mutation that is the most common in the PanIN lesion is that of the KRAS gene, and it occurs even in the lowest grade of PanIN lesion, PanIN1. In the work [5], it has been shown that the mutant KRAS, specifically KRAS<sup>G12D</sup> is responsible for the development of immunosuppressive environment around the cells of the PanIn lesion when a high-fat diet activates the peroxisome proliferator-activated receptor-delta, a lipid nuclear receptor. This development of immunosuppressive environment around the cells of the PanIn lesion accelerates the malignant transformation of the lesion. Hence the reason for the successful eradication of the PanIN lesion to the tune of 98-99% could be the active Immunity against the lesion.

## The Immunity Status of the Precursor Lesions of PC

The most obvious indicator of the activity of the immune system in human body is the WBC count (White Blood Cell count) in the blood [1]. Because a majority of the lesions do not develop into PC, and in one particular case [5] we have the experimental proof that the lesion develops into PC by beating immunity, it is likely that the Immune Surveillance takes care of the cells of the precursor lesions of PC and eliminates them. The other lesson that the particular case in [5] teaches us is that the Immune Surveillance against the lesion fails only and only when there is external stimulus to the cells of the lesion like that provided by smoking habit, alcoholic consumption habit, heavy fat diet, lack of sleep, over-sleeping, etc. KRAS mutation is the dominant genetic abnormality in the precursor lesions of PC, specially in the PanIN lesions. Hence the most probable molecule that triggers immune reaction against the lesions is the mutated KRAS molecule. KRAS is an intracellular molecule localized to the regions near the plasma membrane. Hence the Cell-Mediated Immunity, rather than the Humoral Immunity, is more likely to play role in eradicating the lesion. Moreover, fifty years after the Immune Surveillance Theory was proposed it was suggested that only the immune attack by the T lymphocytes does the job of surveillance [6]. From literature nothing can be said about the role of Natural Immunity in eradicating the lesion. Hence in this Editorial I propose WBC count, Lymphocyte count, T Lymphocyte count, CD4+ cell count, CD8+ cell count, CD4+ cell to CD8+ cellratio as the key components of the immunity status of the precursor lesions of PC. Clinical Studies need to be done to find the immunity status (as defined above) of various precursor lesions of the PC devoid of cancer cells. Only such a study will tell if a particular immunity status is unique to the precursor lesion of PC. If a particular immunity status is unique to the precursor lesion of PC, simple CBC test (Complete Blood Count test) will be the diagnostic test for the precursor lesions of PC and this will eventually lead to the prevention of PC.

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