Manage TB
Dr. Subash Babu
National Institute for Research in Tuberculosis, Chennai

Lecture – 05
Pathogenesis of Tuberculosis
Session 02

Welcome to the second session on the Pathogenesis of Tuberculosis.

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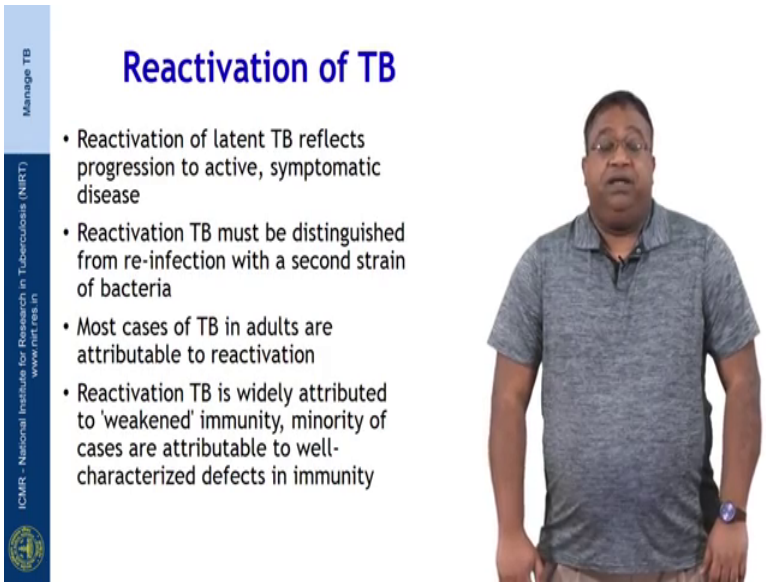

In this session we are going to mainly look at factors that impinge on the reactivation of TB. So, reactivation of latent TB pretty much reflects progression to active symptomatic disease from latent TB. And it must be distinguished from reinfection, which is usually with the second strain of bacteria.

Most cases of TB in adults are attributable to reactivation while reactivation is widely attributed to the so called weakened immunity, only a minority of cases are directly attributable to well characterized defects in immune responses.

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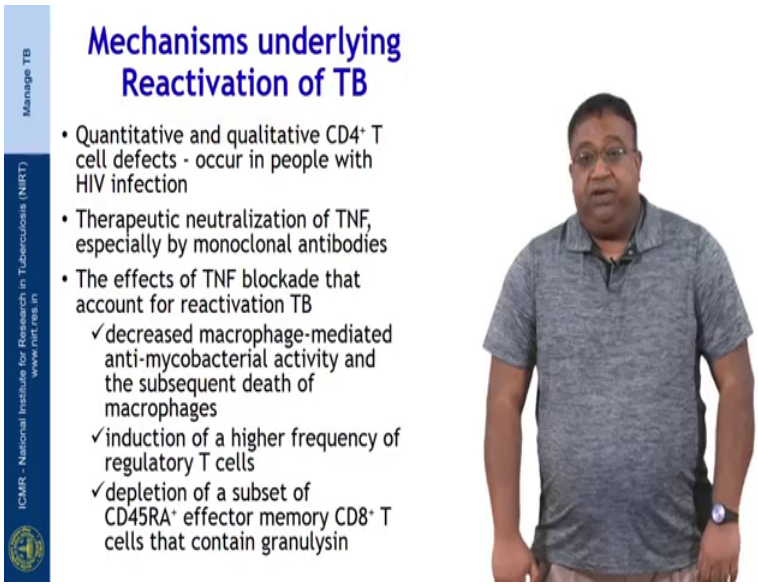

So, when we look at the mechanisms that underlie reactivation of tuberculosis, the commonest a mechanism that underlies reactivation of TB is the quantitative and qualitative T cell defects that occur in people with HIV infection, and we also know that therapeutic neutralization of TNF alpha especially by monoclonal antibodies, can also cause reactivation.

And the effects of TNF alpha blockade that account for reactivation TB include decreased macrophage mediated antimicrobial micro bacterial activity and subsequent death of macrophages, induction of a higher frequency of regulatory T cells, depletion of a subset of effector memory T cells that contain granulysin etcetera.

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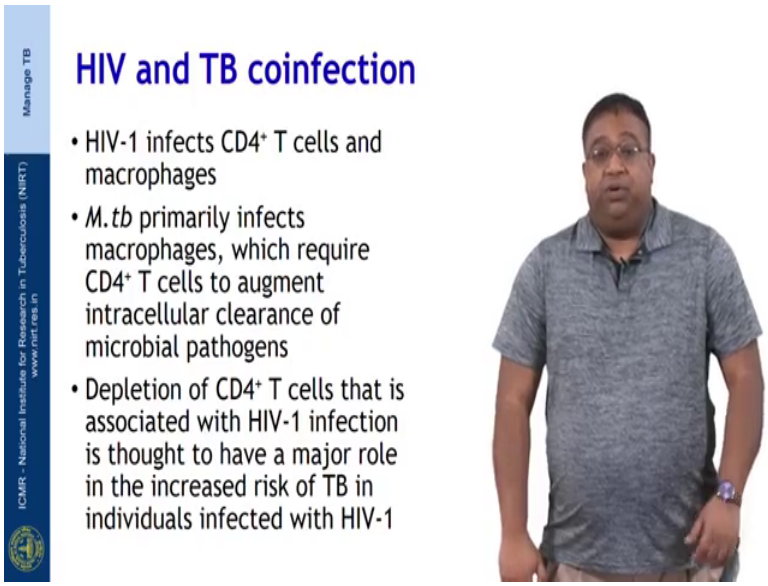

Coming to HIV and TB coinfection, HIV one in fact, CD 4 T cells as well as macrophages while M. tb primarily infects macrophages which require CD 4 positive T cells, to augment the clearance of microbial pathogens.

Therefore, the definition of CD 4 positive T cells that is associated with HIV infection is thought to have a major role in the increased risk of TB in individuals with HIV.

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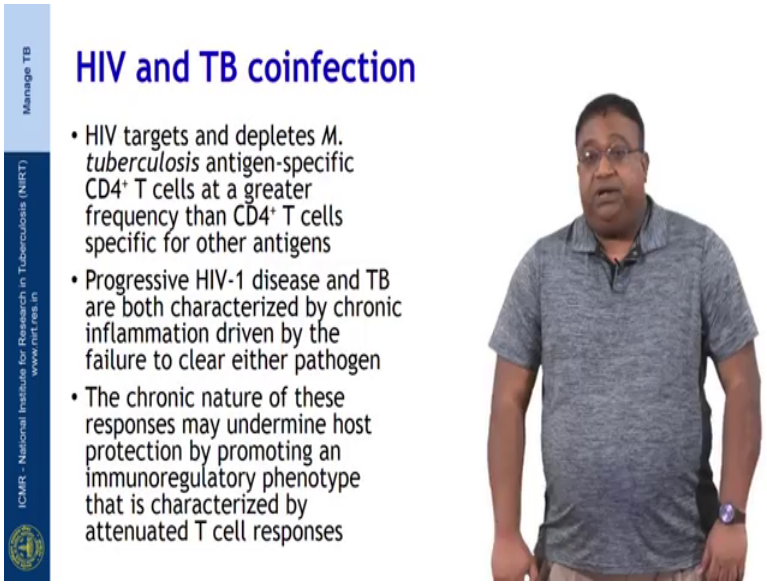

Moreover HIV targets and depletes M. tb antigen specific T-cells at a much greater frequency, than CD 4 T cells specific for other antigens. And finally, both progressive

HIV disease and TB are characterized by chronic inflammation driven by the failure to clear either pathogen and therefore, the chronic nature of these responses may undermine host protection by promoting an immunoregulatory phenotype that is characterized by attenuated T cell responses.

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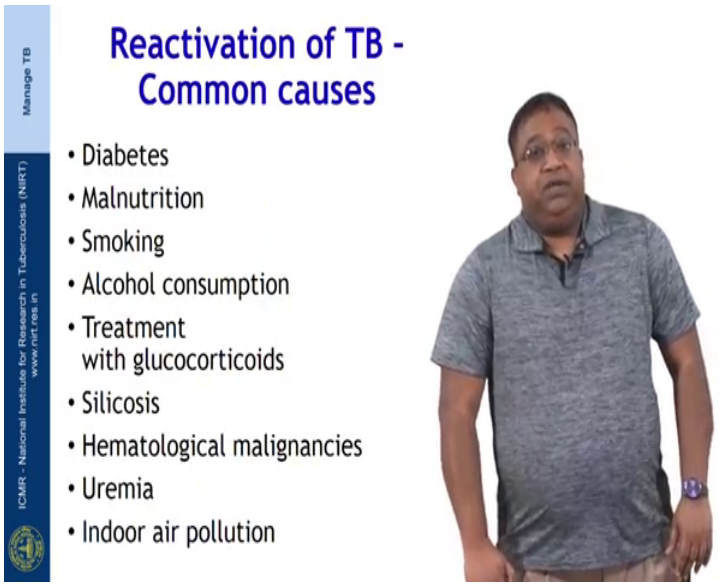

So, in terms of the other common causes of reactivation TB; diabetes, malnutrition, smoking, alcohol consumption, treatment with glucocorticoids silicosis hematological malignancies uremia and indoor air pollution are some.

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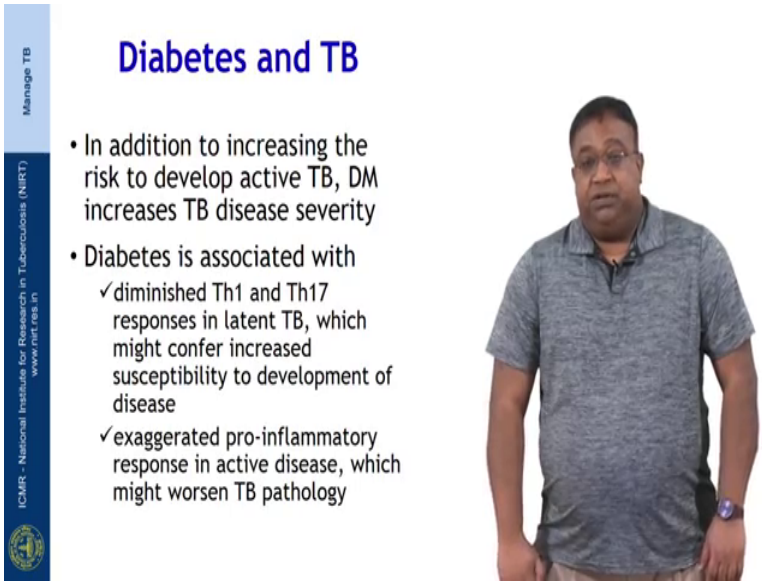

So, let us look at a few of those in a little more detail in terms of the immune response and pathogenesis. So, we know that diabetes is commonly associated with an increased risk for TB. In addition to increasing the risk to develop active TB, diabetes mellitus also increases TB disease severity.

And diabetes is typically thought to be associated or shown to be associated with diminished Th 1 and Th 17 responses in latent TB infection, which might confer increased susceptibility to development of disease. And diabetes is also associated with exaggerated pro inflammatory responses in active disease, which might actually worsen TB pathology in those with pulmonary tuberculosis.

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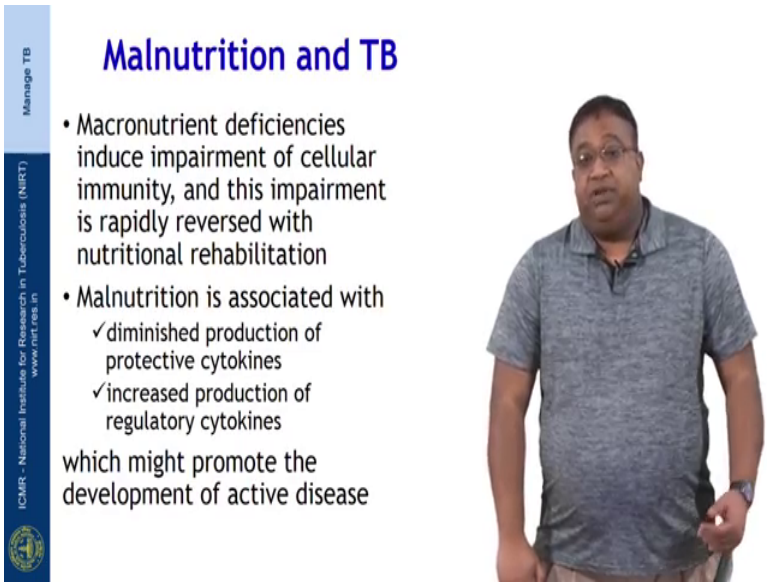

And we look at malnutrition, micronutrient deficiencies are known to it cause impairment of cellular immunity and this impairment can be rapidly reversed with nutritional rehabilitation.

Moreover malnutrition is also associated with diminished production of protective cytokines, an increased production of regulatory cytokines, both of which might contribute to the promotion of the development of active disease.

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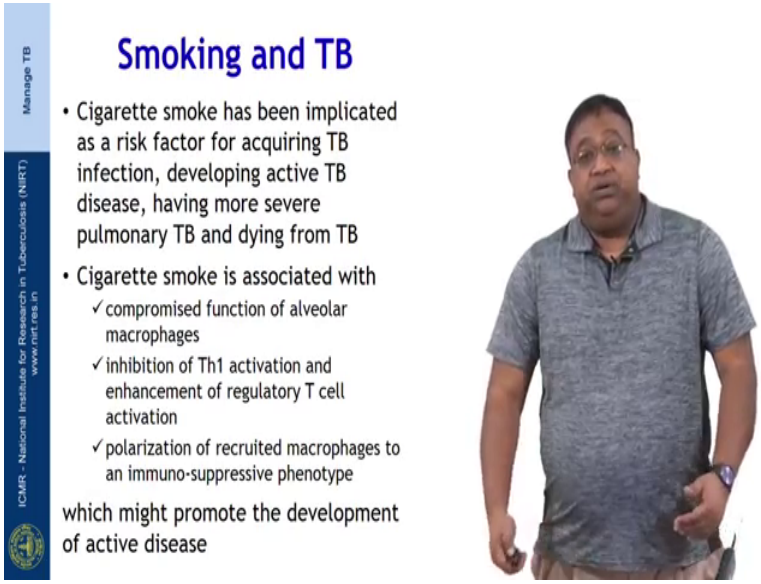

The other factor which is of importance in TB reactivation is smoking; cigarette smoke has been implicated as a risk factor for acquiring TB infection, for developing active TB disease, for having more severe pulmonary TB and also for dying from TB

We know that cigarette smoke is associated with a compromised function of alveolar macrophages, it is associated with inhibition of Th 1 activation and enhancement of regulatory T cell activation. And also is associated with the polarization of recruited macrophages to an immunosuppressive phenotype. So, all of the above basically contribute to the promotion of development of active disease in the case of smoking and tuberculosis.

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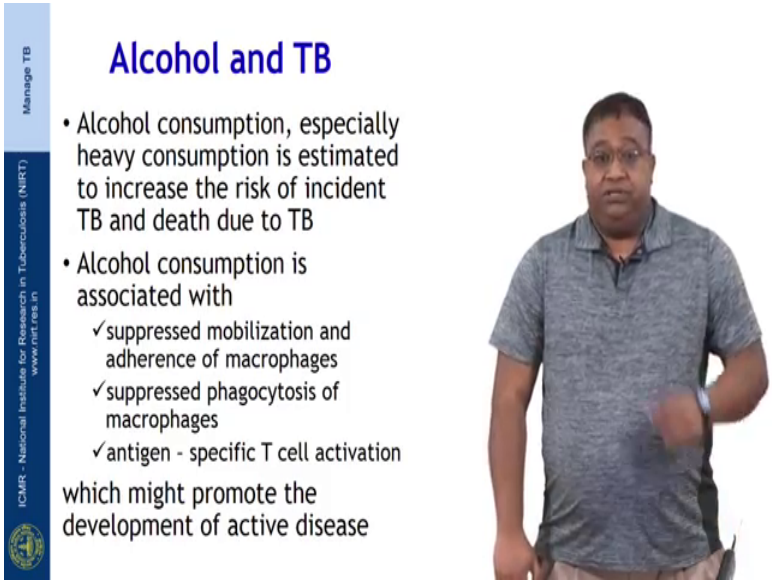

Finally, if we look at alcohol, we also know that alcohol consumption especially heavy consumption is estimated to increase the risk of incident TB as well as the risk of death due to tuberculosis.

And this is typically thought to be associated again with the impairment of certain immune responses and these include suppressed mobilization and adherence of macrophages, suppress phagocytosis of macrophages and diminished antigen specific T cell activation, all of which might contribute to the development of active disease as well.

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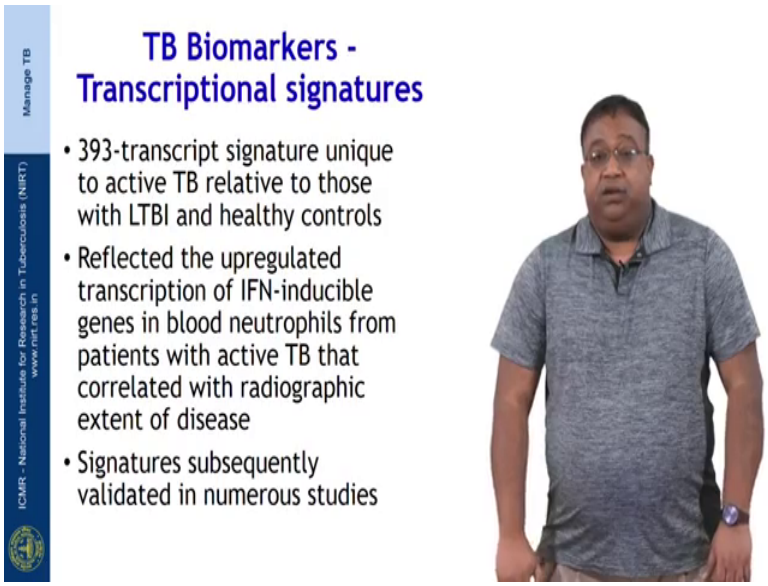

So, switching gears we are now going to look at TB biomarkers, which are basically going to be discussed under three modules, transcriptional signatures, correlates of risk and immune biomarkers. And we are interested in biomarkers in TB mainly because of the fact that the diagnosis and prognosis of TB is a very difficult phenomenon and TB biomarkers could aid in both diagnostic purposes as well as for therapeutic monitoring.

So, in terms of therapeutic the transcriptional signatures, it was initially discovered that there was a 393 transcript signature, which was unique to active TB and help distinguish those with active TB from those with LTBI and healthy controls.

The signature basically reflected an up regulated transcription of interferon inducible genes mainly, in the blood neutrophils from patients with active TB, and it turned out that the signature actually correlated with the extent of radiographic disease as well.

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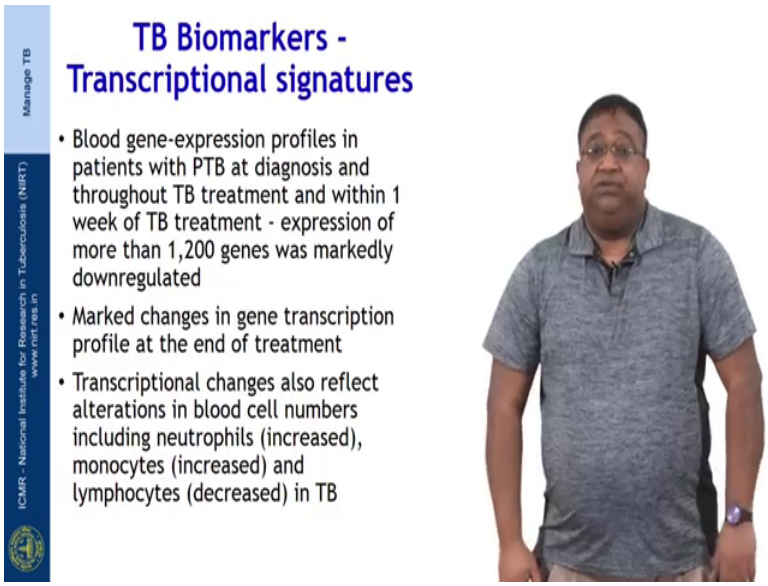

The signature is now subsequently been validated in numerous studies and we also know that the blood gene expression profile that is present at M tb at PTB in diagnosis is actually changed over the course of treatment such that, within a week of TB treatment there is a massive down regulation of more than 1200 genes when we look at transcriptional signatures. And in fact, these changes in gene transcription profile continue till the end of treatment.

So, transcriptional changes are also thought to basically reflect, changes in blood cell numbers that occur during TB infection and disease, including neutrophils which are increased, monocytes which are increased and lymphocytes which are decreased in TB disease.

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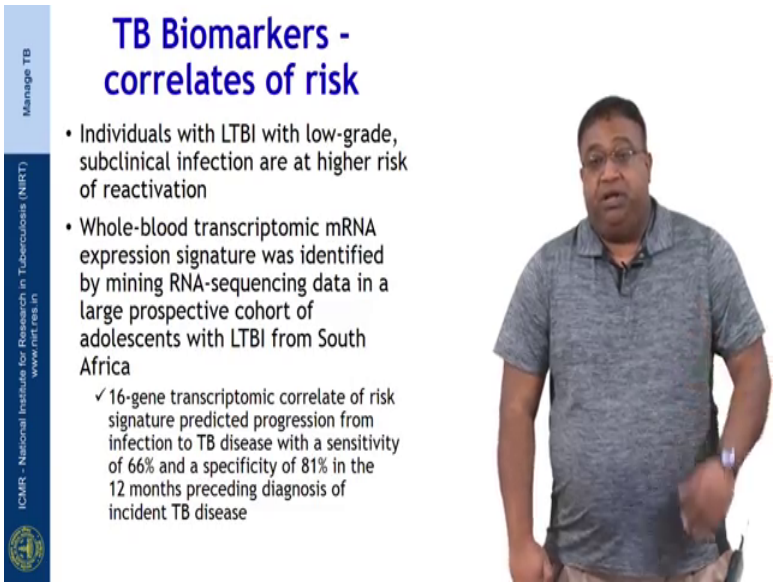

So, when we look at correlates of risk. The idea behind correlates of risk is trying to understand or identify which individuals with LTBI who have low grade subclinical infection are in the highest risk of reactivation. So, if we can identify people with the highest risk of reactivation, they can be selectively targeted for therap or for prophylactic treatment.

So, one of the few studies that have actually been able to establish a correlate of risk was a study looking at whole blood transcriptomic mRNA profile, wherein a signature was identified by mining RNA sequencing data, from a large prospective cohort of adolescents with latent tuberculosis from South Africa.

It was found that these individuals actually exhibited a 16 gene transcriptomic signature, which turned out to be a good quadrant of risk and predicted progression of infection from TB disease to from infection to TB disease with a sensitivity of about 66 percent and a specificity of about 81 percent. At least 12 months preceding the diagnosis of incident TB.

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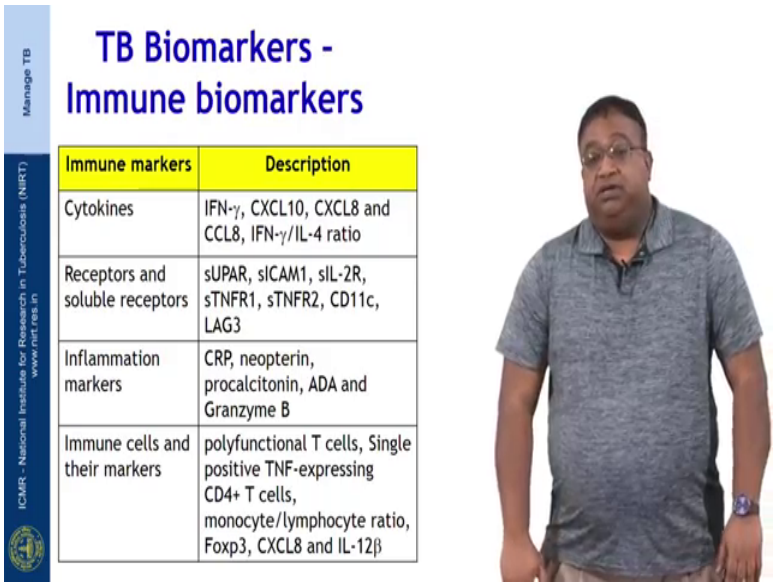

Finally we look at TB biomarkers the other area of major interest is of course, looking at immune biomarkers and these include, certain cytokines which have been associated with TB disease and this typically involves interferon gamma, CXCL 10, CXCL 8, CCL 8 and interferon gamma and IL 4 alpha ratio, the presence of receptors and soluble receptors including soluble upar, soluble icam one soluble IL 2 IL 2receptor soluble TNF alpha receptor 1 and 2, CO 11 c and lag 3.

Inflammation markers which are typically nonspecific, but also associated are associated typically with TB disease and these include C reactive protein, neopterin, procalcitonin ada and granzyme B. And finally, immune cells themselves and their markers can also be associated with active TB and help distinguish active TB from latent infection and other diseases; these include poly function of T cells, single positive TNF expressing T cells, monocyte lymphocyte ratio, Foxp 3 CXCL 8 and IL 12 beta.

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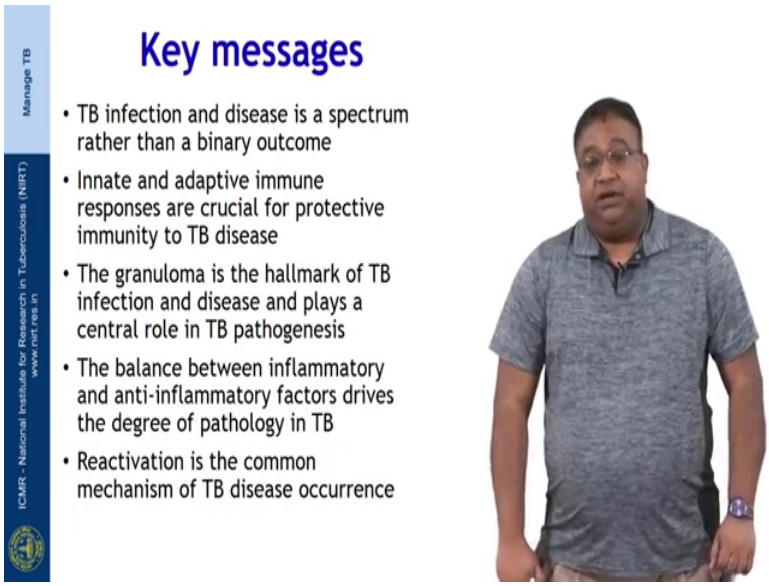

So, to conclude the key messages that I want everybody to take home from the session on the pathogenesis of TB are as follows, TB infection and disease is actually a spectrum rather than a binary outcome, innate and adaptive immune responses are crucial for a protective immunity to TB disease.

The granuloma is the hallmark of TB infection and disease and plays a central role in TB pathogenesis, the balance between intimately and anti inflammatory factors drives the degree of pathology in TB and finally, reactivation is the common mechanism of TB disease occurrence in atos with. This we come to the end of the session.

Thank you very much.