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Cytokines as Suicide Risk Biomarkers

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Suicide is a major public health problem as about 40,000 people die by suicide in the U.S. annually. Prevention and treatment of suicidal behavior is therefore very important. The major problem in the prevention of suicide is early identification and treatment of suicide-prone patients. Suicide is a multifactorial problem involving clinical, genetic and neurobiological risk factors. The identification of risk factors that could accurately predict completed suicide has been therefore investigated by many researchers.

An important risk factor for completed suicide is a history of previous suicide attempts and presence of suicidal ideation, and these have been suggested as major predictors of subsequent suicide attempt or suicide. Since clinical risk factors by themselves are not strong predictors of suicide, a combination of clinical and neurobiological risk factors may improve the ability to predict suicide. In that context, several biological markers have been studied in suicidal behavior. These include 5-hydroxytryptamine (5HT)_{2A} receptors, 5-hydroxyindoleacetic acid (5HIAA), serotonin transporter (5HTT) and the dexamethasone suppression test (DST; an index of hypothalamic pituitary adrenal [HPA] axis function), for prediction of suicidal behavior or completed suicide (1).

Several studies suggest dysregulation of the immune system and cytokines in suicidal behavior. Steiner et al. (2) found increased microgliosis in the postmortem brain of suicide victims with affective disorders and schizophrenia compared with normal control subjects. Some investigators observed that the administration of proinflammatory cytokines like interferon (IFN)- α to cancer patients causes symptoms known as sickness behavior. These symptoms appear to be similar to depression, psychosis, mania and sometimes suicidal behavior. A review of IFN- α treatment of chronic hepatitis-C patients (3) showed the emergence of suicidal ideation and attempts during IFN- α treatment also suggesting that cytokines may be involved in suicide.

In order to examine if cytokine dysregulation is associated with suicide, several investigators determined cytokines and chemokines levels in plasma, cerebrospinal fluid (CSF), and postmortem brain of suicidal patients. In general, these studies indicate abnormalities of several cytokines in suicide. However, single studies do not provide adequate evidence either about their role in suicide or as potential risk factors for suicide, as they are generally of low power. Meta-analysis is an important tool to clarify these findings and improve the strength

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of evidence, taking into account the sources of heterogeneity among various studies. The accompanying paper by Black and Miller (4), who performed a meta-analysis of these studies to examine if any of the cytokines or chemokines were abnormally expressed in suicidal patients compared to non-suicidal patients or normal controls, is therefore important in identifying the role of cytokines in suicide and their potential as biomarkers.

The cytokines have been widely studied in mood disorders, schizophrenia and alcohol abuse, but there are not many studies of cytokines in suicidal patients. The cytokines in suicide have been studied in plasma, CSF and postmortem brain. In addition, *in vivo* studies of cytokines have also been conducted. In order to examine if alterations in cytokine levels are specific and/or are risk factors for suicide the comparisons of cytokine levels between suicidal patients, non-suicidal patients and normal controls were performed. Using these criteria in the meta-analysis performed by Black and Miller (4) some important findings emerged. The most significant observation of cytokine abnormalities was that interleukin (IL)-1 β was higher in suicidal patients compared with non-suicidal patients. IL-6, but not tumor necrosis factor (TNF)- α , was higher only after the removal of one study. A different pattern emerged when they (4) compared the suicidal patients against normal controls. In this case, they found that the blood levels of IL-6, IL-10, and C-reactive protein (CRP) were significantly increased in suicidal patients compared with normal controls. No differences were observed in the levels of IL-1 β and TNF- α between suicidal patients and normal controls. The results of the comparison between suicidal patients and normal controls are thus intriguing as they are not consistent with the results obtained by comparing suicidal and non-suicidal patients and raise the possibility that observed differences between suicidal patients and normal controls may be related to diagnosis, rather than to suicide. Since different diagnoses may have different risks of suicidal ideation and attempt (5), it will be important to examine the effect of diagnosis in these cases, as they rightly pointed that out (4).

IL-2 may be another cytokine with a potential of distinguishing suicidal patients vs. non-suicidal patients as in this meta-analysis a decrease in IL-2 (*in vitro*) was observed in suicidal patients compared to both non-suicidal patients and controls. Also, an interesting observation by Black and Miller (4) was that the *in vivo* blood levels of these cytokines distinguished psychiatric suicidal patients from both psychiatric patients without suicidality and also from normal controls. Another reason for this robust finding was that relatively more studies were available for the meta-analysis as opposed to single or fewer studies for other cytokines. The role of chemokines in suicide is less clear as there were only a few studies of chemokines in suicidal patients.

An issue is the suitability of peripheral cytokine measures as a function of CNS cytokines. To address this issue levels of cytokines have been studied in the CSF and postmortem brain of suicides. Although these are only single studies available for this meta-analysis, they suggest similar changes in postmortem brain of suicide subjects at least for IL-6. Most of the studies in CSF, postmortem brain or *in vitro* were either single studies or few studies for a meaningful analysis. Nonetheless, several of these studies in CSF and postmortem brain show differences between suicidal subjects compared to non-suicidal patients or normal controls for IL-1 β , IL-6, TNF- α and IL-8. The studies in postmortem brain and CSF suggest

that peripheral cytokines may be a good measure of cytokine levels in the brain. Although cytokines are also synthesized in the brain, bidirectional movements of cytokines between periphery and the CNS through several mechanisms have been suggested. Thus, peripheral cytokines could not only be suitable biomarkers for suicide, but may also mirror similar changes in the brain.

Future Studies

Cytokine receptors exist in two forms, soluble cytokine receptors and membrane-bound cytokine receptors. The soluble cytokine receptors are formed from the proteolytic cleavage of the extracellular domains of the membrane-bound receptors or by synthesis from alternatively spliced variants. These soluble receptors circulate at high concentrations in plasma and they can initiate cell activation and can also act as chaperones to extend cytokine bioavailability or may also inhibit cytokine signaling. Although there are several studies of cytokines in suicidal patients, there appears to be only one study of soluble cytokine receptors in suicide (4). Therefore, more studies of soluble cytokine receptors in suicide are needed.

As stated, cytokine receptors also exist as membrane-bound receptors. The biological or functional effects of cytokines are produced by their interaction with membrane-bound receptors initiating signaling through several signal transduction systems. Whereas soluble receptors have been studied in mood disorders and schizophrenia, the membrane-bound receptors were only recently studied by Pandey et al. in schizophrenia (6), and in bipolar disorders (7).

Most of the studies of cytokines and their soluble receptors have been performed by determining their protein levels in plasma/serum. It has been shown that blood cells share 81.9% of the transcriptome with the brain, hence, gene expression studies in general and those of cytokines in particular offer a potential window for CNS function and similar changes in the brain (8). The studies of gene expression levels of these cytokines and their receptors may be another useful strategy for examining their role as biomarkers in psychiatric illnesses and suicide. This may be particularly useful as mRNA levels in blood cells may be more stable than protein levels in plasma, since latter may show high fluctuations due to degradation. Using this strategy Padmos et al. (9) recently reported high gene expression of the proinflammatory cytokines in bipolar illness. We also reported that both protein and mRNA expression of the proinflammatory cytokines are increased in schizophrenia (6) and bipolar illness (7).

In addition to studies of cytokines and their receptors in peripheral cells, studies of cytokines in postmortem suicide brain are important in understanding their role in suicide. Until now, there appear to be only two such studies (4). These two studies focus only on the suicide brain, but it should also be examined if abnormalities in suicide brain are specific to suicide and are independent of psychiatric diagnosis. For that purpose, one needs to examine cytokines and their receptors in different suicide phenotypes, such as depression and schizophrenic suicide and in the postmortem brain of non-suicidal patients.

Cytokines as risk factors (biomarkers) have been studied in suicidal patients; however, only 20–30 percent of suicidal patients who commit suicide have a previous history of suicide attempts. It is therefore important to study cytokines as a risk factor of completed suicide as has been done for DST, since DST non-suppression was found to be a good predictor of completed suicide (10). In conclusion, the meta-analysis of cytokines by Black and Miller (4) suggests that certain specific cytokines may be important risk factors and potential biomarkers for suicidal behavior.

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References

1. Mann JJ. Neurobiology of suicidal behaviour. *Nat Rev Neurosci.* 2003; 4:819–828. [PubMed: 14523381]
2. Steiner J, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. *J Psychiatr Res.* 2008; 42:151–157. [PubMed: 17174336]
3. Sockalingam S, Links PS, Abbey SE. Suicide risk in hepatitis C and during interferon-alpha therapy: a review and clinical update. *J Viral Hepat.* 2011; 18:153–160. [PubMed: 21070503]
4. Black C, Miller BJ. Meta-analysis of cytokines and chemokines in suicidality: Distinguishing suicidal versus nonsuicidal patients. *Biol Psychiatry.* 2015; 78:XXX–XXX.
5. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry.* 2011; 68:1058–1064. [PubMed: 21969462]
6. Pandey GN, Ren X, Rizavi HS, Zhang H. Proinflammatory cytokines and their membrane-bound receptors are altered in the lymphocytes of schizophrenia patients. *Schizophr Res.* 2015; XX:XXX–XXX.
7. Pandey GN, Ren X, Rizavi HS, Zhang H. Abnormal gene expression of proinflammatory cytokines and their receptors in the lymphocytes of bipolar patients. *Bipolar Disord.* 2015; XX:XXX–XXX.
8. Liew CC, Ma J, Tang HC, Zheng R, Dempsey AA. The peripheral blood transcriptome dynamically reflects system wide biology: a potential diagnostic tool. *J Lab Clin Med.* 2006; 147:126–132. [PubMed: 16503242]
9. Padmos RC, Hillegers MH, Knijff EM, Vonk R, Bouvy A, Staal FJ, et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. *Arch Gen Psychiatry.* 2008; 65:395–407. [PubMed: 18391128]
10. Coryell W, Schlessler M. The dexamethasone suppression test and suicide prediction. *Am J Psychiatry.* 2001; 158:748–753. [PubMed: 11329397]