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The Function of Aβ in the Healthy Brain: Beta Amyloid as an Antimicrobial Protein

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Abstract: ***There is no question as to whether or not the beta amyloid (Aβ) peptide plays a role in the exacerbation and onset of AD. There are very evident correlations between the volume of Aβ deposition in the AD brain and the severity of the symptoms of AD-typical neurodegeneration. There are certainly many factors involved in the progression of AD, of which the aggregation of Aβ peptides is only one. While many have ruminated on the mechanism by which Aβ serves to impair synaptic function and contribute to neurodegeneration, the role of this protein has yet to be fully uncovered, not just in the AD brain, but in the normally functioning brain as well. Recent research has shed light on the role of Aβ in the normal brain, offering evidence for the fact that beta amyloid functions as an antimicrobial protein, with its primary objective being to serve an immunoresponsive purpose. This text will highlight some of the critical studies on the topic, and illuminate the role that Aβ most likely plays in the functioning of the normal brain, and how this influences its pathological deposition in the AD brain.***

I. INTRODUCTION

Alzheimer's Disease (AD), The neurodegenerative ailment that affects one in every nine Americans and is the sixth leading cause of death, has thus far proven to be an irreversible degradation of neuronal function which is characterized principally by the aggregation of beta amyloid (Aβ) peptides (Frost & Li, 2017). While it is known that there is a correlation between Aβ accumulation and the onset of AD (Frost & Li, 2017; Iacobelli, 2021) , the specific mechanism by which the peptide turns pathological and impairs neuronal function, thus contributing to synaptic toxicity remains a topic on which the medical community is starkly divided. Aside from a general lack of understanding of the specific mechanisms that serve to exacerbate AD, our misunderstanding of the role that Aβ plays in the onset and progression of AD derives from the fact that there is little understanding as to the role that the protein plays in the normally functioning brain. This leaves researchers with no starting point from which a mechanism for its pathological mutation in the AD brain can be intuited. Some have proposed that the aggregation of Aβ into plaques simply blocks synaptic pathways and limits neuronal plasticity, while others argue that the protein is directly toxic to the neurons or the myelin sheaths that surround them (Frost & Li, 2017). Regardless of the means to the neurodegenerative ends that is AD and eventually death, a better understanding of the role that Aβ plays in the AD brain certainly must come via a better understanding of the role it plays in the healthy brain, if any at all. This text will review the relevant research on the topic, with the aim to illuminate the most probable function for Aβ presence in the healthy brain, and seek to explain how this normative function can mutate to such a dangerously pathological extent, as is the case with AD.

II. BETA AMYLOID AS AN ANTIMICROBIAL PROTEIN

Antimicrobial proteins and peptides, described by Battersby et al., as an adaptive immune response which are variable and each specialized to serve as anti-infectives (Battersby et al., 2016), are critical to immune function in the mind and body, and the leading theory on the role that Aβ plays in the healthy brain is that the substance is indeed an antimicrobial protein thus serving an immunological function, before it aggregates to a detrimental degree in the AD brain.

This theory is primarily substantiated by the deposition patterns and tendencies of Aβ in the diseased brain, as it has been revealed that astrocytes, which are the primary agents in the astrogliosis immune response that is triggered by cerebral pathogens, secrete Aβ as they become active (Frost & Li, 2017). That said, while correlated, a specific mechanism of causality has yet to be determined. In fact, one of the only reasons, aside from the correlation, that Aβ has historically been thought of as a causal factor of AD is the fact that there has been no established role for Aβ in a normally functioning brain. Physiologically speaking, much of the scientific community has operated under the assumption that it played no role other than exacerbating AD, and it is only in recent years that it has been thought to be an antimicrobial protein.

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Battersby et al., went on to show that antimicrobial proteins play a significant, immunoprotective role in newborn infants, as broad spectrum antibiotics which serve as a defense against common infections such as sepsis or meningitis (Battersby et al., 2016), a finding that is directly in line with studies that have shown that reduced expression of genetic components necessary for the production of Aβ will lead to higher mortality rates in transgenic mice.

β-secretase (BACE), is a key genetic component in the production of Aβ, as it cleaves APP prior to a second cleavage by γ-secretase after which the intracellular domain for APP and Aβ peptides are released into the brain, all of which constitutes the amyloidogenic pathway, which Hussain et al., uncovered as the only mechanism by which Aβ could be produced. Hence ,BACE is wholly necessary for the production and secretion of Aβ (Hussain et al., 1999). This allowed Dominguez et al., to transgenically modify mice such that BACE1 and BACE 2 were knocked out, to study how a lack of Aβ production would affect their mortality rates (Dominguez et al., 2005).

Because it is well established that antimicrobial proteins, as a class of immune cells, are antibiotics which serve a broad range of functions and protect against bacteria, fungi, viruses, and a diverse panoply of pathogens (Zaiou et al., 2007), it is safe to assume that a reduction in a specific kind of antimicrobial protein would leave one vulnerable to infection, which as we know from Battersby et al., the young are particularly vulnerable to (Battersby et al., 2016).

In keeping with this assumption, it was discovered that these BACE1 and BACE2 double knockout mice had a significantly higher mortality rate than the control mice, but this wasn't the most interesting of the findings. When the studied mice were moved to a different, pathogen-free facility, their mortality rate returned to normal (Dominguez et al., 2005). This implies that the lack of BACE1 and BACE2 expression, and hence the reduced production of Aβ itself was not the causal factor behind the increased mortality levels, but instead, the lack of β-secretase expression in mice facilitated an increased vulnerability to pathogens that allowed infections which would otherwise be handled by the immune systems of the mice, to run rampant and kill them at increased rates. This is presumably due to a lack of Aβ which would in other cases serve as an antimicrobial protective agent to stave off the pathogens. While it is possible that other factors were at play, this study established an important link between a lack of Aβ presence, and an increased susceptibility to deadly pathogens.

In an effort to further establish the antimicrobial classification of the Aβ peptide, Soscia et al. compared the protein to a known antimicrobial protein, LL-37, which is one of many antimicrobial proteins in the Cathelicidin family (Soscia et al., 2010). The study showed an increased level of activity of Aβ proteins in response to eight of the twelve pathogens to which it was introduced, a rate similar to that of LL-37 (Soscia et al., 2010; Frost & Li, 2017).

Perhaps most indicative of Aβ's antimicrobial function however is the historically observed responsiveness to the Herpes Simplex 1 (HSV-1) virus, that is a well established characteristic of Aβ in a normally functioning brain (Frost & Li, 2017). HSV-1 is a known risk factor for AD and in many cases has been shown to predetermine the onset of sporadic AD, with its viral cells later bunching around Aβ plaques (Wozniak, Mee, & Itzhaki, 2009). In an effort to examine this relationship, Bourgade et al. exposed fibroblasts, epithelial cells, and neuronal cell lines to Aβ isoforms before later exposing those same cells to HSV-1. They found that, whether or not the Aβ was added at the same time as the HSV-1, or two hours before the HSV-1, Aβ effectively inhibited the replication of HSV-1 cells by preventing the entry of the virus into healthy cells, which is thought to be done by Aβ insertion to the envelope of HSV-1 cells (Bourgade et al., 2014). It should be noted that Aβ was not able to inhibit the replication of HSV-1 when it was added two or more hours after the cell lines were exposed to the virus, although the aforementioned antimicrobial protein, LL-37 was able to inhibit HSV-1 replication independent of its time of addition relative to the HSV-1 exposure. Nonetheless, the study concluded that Aβ could be reclassified as a novel antimicrobial protein, evolved specifically to enveloped, neurotropic viruses such as HSV-1 (Bourgade et al., 2014).

Based on these findings, it is entirely likely that the reason HSV-1 is a relatively reliable predictor for the later onset of AD is that the latent, viral infection is in a constant state of combattance by the antimicrobial protein that is Aβ, and the constant production and secretion of this protein, which is also such a fundamental component of AD, leads to aggregation which triggers the onset of the neurodegenerative ailment in question, although more study on this subject must be done.

But, this finding was backed through the more recent study, Powell-Doherty et al., which once again examined the predictive nature of HSV-1 for the future onset of AD, this time examining the responsiveness of Aβ, as well as the tau protein, which is another protein correlated with the onset and progression of AD, equivalent to Aβ in terms of both progressive deposition as well as implied causality, yet much like its fellow protein, there is little to no evidence that tau plays a causal role in the exacerbation of AD. As for now, all that can definitively be said of the protein is that its presence and aggregation into neurofibrillary tangles (NFTs), is correlated with the progression of AD. But although little can be said with certainty of its role in AD it is, much like Aβ, overwhelmingly likely that tau plays some causal, or at least exacerbational, role in the onset and progression of the disease.

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This study explores the function of Aβ and tau as antimicrobial proteins utilizing HSV-1 and murine hippocampal neurons in adult mice. Cultures of these hippocampal neurons were exposed to HSV-1 and after seven days, were studied in search of Aβ and tau expression, both of which were observed at elevated levels, with Aβ characteristically colocalizing with HSV-1 (Powell-Doherty et al., 2020). This study, at the very least, shows that Aβ peptides, as well as tau, are involved in immunal responses to both acute and chronic threats by pathogens, implying that they are immune cells, an idea once again reinforced by the study of astrogliosis and Aβ secretion by Frost & Li, 2017 (Frost & Li, 2017; Iacobelli, 2021).

This study, briefly touched on earlier, is important not for describing the function of Aβ as an antimicrobial protein, but for linking Aβ to an immunoreactive response that is present, but not exclusive to AD. In short, astrogliosis is an immune response of the CNS that involves the presence of astrocytes, a type of glial cell, which serve to combat pathogens and neural insults, especially those that are characteristic of neurotropic diseases, i.e. HSV-1. In the study, Frost & Li showed that active astrocytes express β-secreatse (BACE1) with a higher prevalence than astrocytes at rest, and because this is the genetic complex necessary for the amyloid precursor protein (APP), which is the protein from which Aβ is derived, to be cleaved along with γ-secretase via the amyloidogenic pathway, these astrocytes will secrete Aβ (Frost & Li, 2017, Iacobelli, 2021). Because astrocytic glial cells outnumber neurons by a ratio of nearly ten to one, even minor secretion of Aβ by astrocytes will facilitate rapid accumulation of the protein (Iacobelli, 2021). So, it is easy to see how this process plays an important role in the onset and progression of AD, but more important to this study is the fact that astrogliosis, a CNS immune response, yields Aβ in such massive quantities. From an evolutionary perspective, an immune response so critical to our survival as astrogliosis would have evolved this mechanism of Aβ secretion purposefully, and evidence explored thus far in this paper indicates that that purpose is to serve as an antimicrobial protein.

In further support of the antimicrobial nature of Aβ, a 2012 study sought to establish links between astrocytic activity and viral infections which have been shown to facilitate the onset of viral encephalitis, a disease closely related in its physiology to AD(Bender, Frik, & Gomez, 2012). As we have examined, astrogliosis is a fundamental immune reaction for AD, but the same is true of most infections which attack the central nervous system. Various subtypes of viral infection including neuteropic herpesviruses (of which HSV-1 is a part), enteroviruses, retroviruses, and paramyxoviruses among others have been shown to trigger an astrogliotic response, and the astrocytes and microglia that serve as the constituent pieces in this defense against pathogens trigger inflammation and immune combatance against whatever viral infection is in question (Bender, Frik, & Gomez, 2012). Toll-like receptors, which are a type of protein that are amongst a class of pattern recognition receptors, play an important role in the proper function of the innate immune responses to CNS infections of any kind, and astrocytes which are active express these receptors at higher rates than astrocytes at rest (Bender, Frik, and Gomez, 2012). Recall that when active, astrocytes tend to express β-secretase (BACE), which is necessary for APP to be cleaved and propagate through the amyloidogenic pathway. Hence, active astrocytes tend to produce Aβ in greater quantities.

Because the toll-like receptors on active astrocytes are implicated in the immune response, astrocytes will be activated in every astrogliosis immune response to CNS infections, and because these astrocytes are active, they will secrete Aβ. There is no way to avoid the secretion of Aβ peptides and intracellular APP domain (which will facilitate further secretion of Aβ) in conjunction with an immune response to pathogens that threaten the CNS. While we know that a pathological abuse of this immune response will undoubtedly catalyze the pathological abnormalities observed in AD patients, the 2012 study by Bender, Frik, and Gomez shows that, although more study of the relationship between astrocytes and viral infections is necessary, it can at least be inferred that astrocytic activation in response to CNS infections is regular, and by extension, Aβ secretion is a normal, immunoreactive activity (Soscia et al., 2004).

It can now be observed that Aβ secretion by astrocytes, which themselves are activated by the presence of a pathogen in the CNS, is a fundamental component of the neural system's immune response. Linking this revelation with the findings mentioned earlier by Dominguez et al., it can be assumed that when Aβ is not available to a CNS which has been exposed to a viral pathogen, the host will be at greater risk for the exacerbation of infection, and from this it can be reasoned that Aβ plays a role in the defense against that pathogen (White et al., 2014). Because no other factors in the Dominguez et al. study, nor the Bender, Frik, and Gomez study were altered, aside from the allowed expression of BACE in the former, it is safe to assume that the immune response observed in the Bender, Frik, and Gomez study is wholly necessary for the survival of the host as opposed to the success of the pathogen, and it is purely because this response was not available to the transgenically modified mice in the Dominguez et al. study that their mortality rate shot up. Thus, while not directly necessary for survival, it is safe to assume that Aβ is necessary for defense against viral pathogens, thus substantiating an earlier cited claim by Bourgade et al. that Aβ represents a novel class of antimicrobial proteins (Bourgade et al., 2014).

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Kumar et al. showed, once again using transgenic mice, that an intracerebral injection of *Salmonella typhimurium*, in mice which had been transgenically modified to overexpress amyloid precursor protein (APP) and presenilin 1 (PSN1), both of which are genetic complexes whose expression is directly correlated to Aβ, had a higher survival rate at four weeks of age than wild type mice, implying that increased production of Aβ in youth actually serves to increase the survivability of mice, rather than present any type of danger as would be expected if Aβ only played a pathological role as it does in the AD brain (Dominguez et al., 2005). Instead, increased Aβ levels in the transgenically modified mice likely imply that the protein offers increased immunoprotective function to the transgenically modified mice that is not available to the wild type mice, and so the transgenically modified mice who have higher Aβ levels as a result of their increased APP and PSN1 expression will be better able to combat infections and pathogenic agents who may otherwise fatally compromise the CNS of wild type mice (Kumar et al., 2016).

While further study must be done to solidify the notion that Aβ serves as an antimicrobial protein, the link between its secretion and activity of astrocytes pretty clearly implicates the protein in the immunoreactive processes of the CNS. In addition, studies on transgenically modified mice have shown that Aβ levels, dependent on the age of the subject, have a direct influence on the mortality rate of the mice, and are likely involved in immunoprotective functions of the CNS.

III. PATHOLOGICAL TRANSFORMATION OF BETA AMYLOID IN AD PATIENTS

Once again, further study of Aβ in the human immune system is required to say with any certainty whether or not Aβ is an immunologically involved protein, but the mounting body of evidence on the subject certainly seems to indicate that Aβ does in fact represent a novel class of antimicrobial proteins. Study in mice has shown that when Aβ levels in youth are increased, they increase the survivability of young mice who overexpress APP and PSN1 (Dominguez et al., 2005), but as we know from historical analysis of the role that Aβ plays in the onset and progression of AD, there is a universally observed correlation between the aggregation of Aβ into plaques, and the worsening of AD's behavioral ramifications such as reduced cognition and loss of motor function (Zanetti, 2004; Soscia et al., 2010). This means that AD is an age dependent disease, but also that increased levels of Aβ are not the only factor involved in the neurodegenerative process of AD. Neither of these facts are novel revelations, but are nonetheless important to reinforce.

The question is then not one of whether or not Aβ is helpful or harmful, as we have come to understand that it can be both. Instead, the mechanism by which Aβ turns from helpful to harmful should be called into question, and once again, astrogliosis is heavily involved in this process.

While there are many theories on the methods which render Aβ neurotoxic in AD patients, the process can be thought of simply as a process in which the immunoreactive nature of glial cells in response to perceived pathogens is utilized to a pathological extent. There are several steps to this process, the first of which involves a trigger, that is variable, and may involve the expression of the apolipoprotein E4 isoform, which impairs the rate at which Aβ is cleared from the brain (Iacobelli, 2021; Lin et al., 2018; Abramov, Cannevari & Duchen 2003). The clearance is rerouted from the LRP-1 receptor to the VLDLR, which clears the pathological Aβ at a significantly slower rate. Whereas the E2 and E3 isoforms of this apolipoprotein are known to clear Aβ through LRP-1 and VLDLR at a much quicker rate than the E4 isoform (Deane et al., 2008). Up to 65% of AD cases are predicted by the presence of the ApoE4 isoform, and thus this trigger, which simply causes aggregation by rerouting the channel through which Aβ is cleared from the brain, may serve as the initial step in the onset of up to two thirds of AD cases.

The other possible trigger involves the preclinical myelin damage which triggers an initial immune response, which, as we have reiterated time and again throughout the text, is mediated by astrocytes that, when active, secrete Aβ at substantial volumes (Frost & Li, 2017).

Either of these triggers will elicit an astrogliosis immune response, in which astrocytes rush to the scene of either the preclinical myelin damage or the Aβ plaques which have accumulated due to impaired clearance as a result of ApoE4 expression. As they act on the sites, this astrogliotic response will lead to a deposition of Aβ that is greater in volume than what preceded it, triggering more astrocytes to the scene which will in turn leave behind even more Aβ, thus trapping the brain in a cycle through which an astrogliotic response is continually elicited, and the astrocytes involved continue to secrete significantly more Aβ than they clear, thereby propagating the progression of AD (Iacobelli, 2021; Frost & Li, 2017).

While there are other theories proposed which have led to ideas such as the Tau Propagation Hypothesis or the Amyloid Cascade Hypothesis, this is thus far the best model to explain the pathology of Aβ in an AD brain, and recent study has suggested that it all starts with the normal functioning of Aβ as an antimicrobial protein in a healthy brain.

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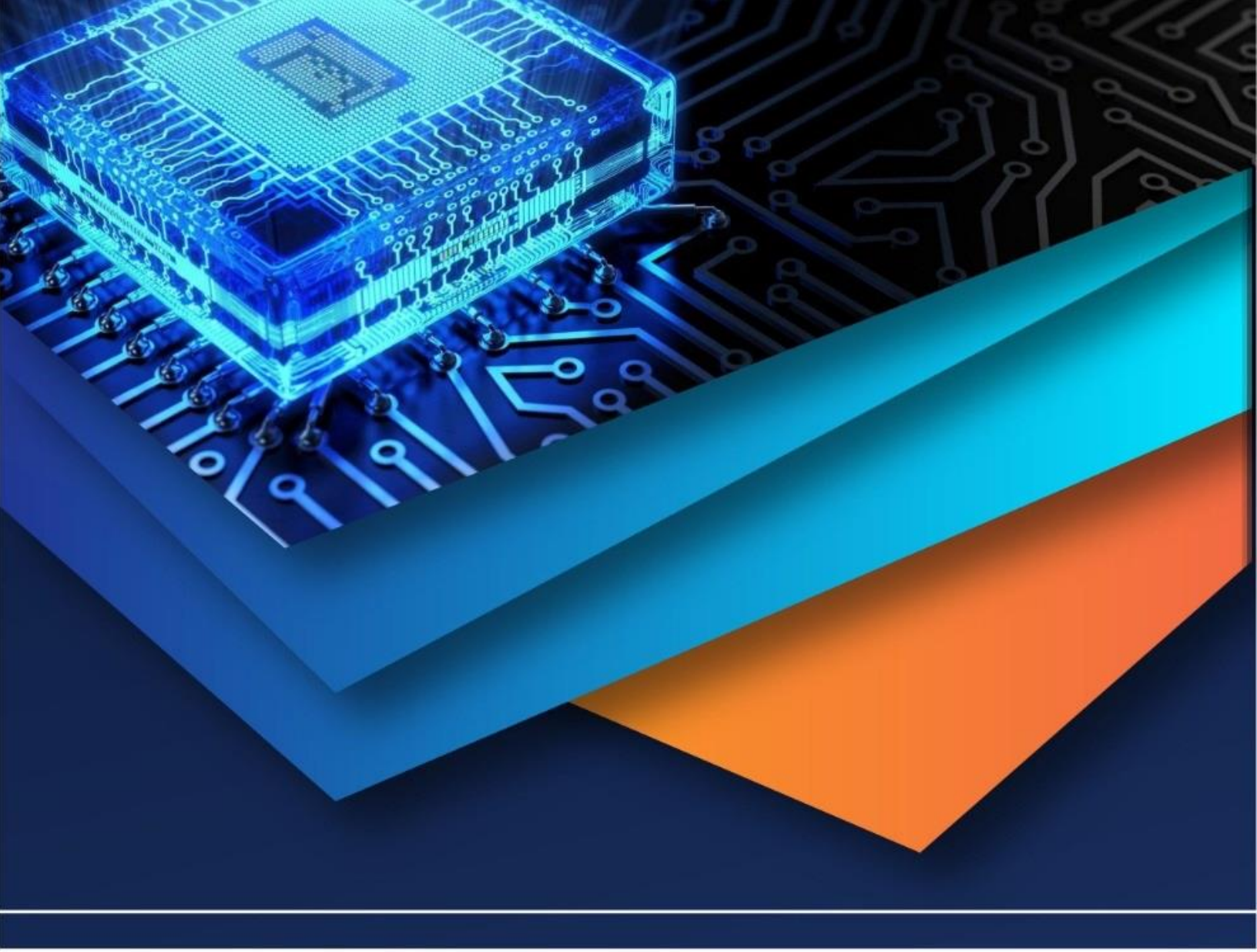

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