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Challenges to Treat Interferon Resistance in Hepatitis C Virus Infected Patients

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The host response to virus is initiated by interferon α/β (IFN) production which is the baseline of immune resistance against viral pathogens. Hepatitis C virus (HCV) infects about 170 million persons globally [1]. The major obstacle in the treatment of HCV is interferon resistance associated with each genotype of HCV, particularly the HCV GT1 and GT4. HCV eludes the host reaction over a multifaceted permutation of virus-host relations that interrupt intracellular signaling pathways and diminish the antiviral actions of IFN. Innate and adaptive immunity related to host responses and its regulation results the spread and replication of HCV. Consequently, a major challenge to the treatment responses is genetic diversity of virus and its linkage with initiation of chronic liver disease. Studies have revealed several host traits (gender, age, ethnicity, insulin resistance, obesity, alcohol intake, HIV-1 infection, degree of liver fibrosis and cirrhosis) with IFN responsiveness [2,3]. Intensive research efforts are desired to elaborate the molecular mechanisms involved in the IFN non-responsiveness and of ascertaining its predictors that could be used to plan a suitable cure regimen. Factors that may contribute to the interferon resistance are multi-factorial but clearly 1) virus-host interaction, 2) IFN signaling cascade, 3) virus mutations, 4) immune responses, 5) host`s genetic makeup may contribute for the resistance phenotype.

Viral and Host Interaction

HCV infected chimpanzees have revealed a sturdy orientation of Interferon stimulating genes (ISGs) during the early days of the infection [4]. The exact mechanisms of IFN sensitivity are not entirely understood but possibly comprise the IFN inhibition via theretinoic acid inducible gene I(RIG-I) pathway via the cleavage of MAVS (mitochondrial antiviral signalling protein) by the NS3 protease) [5]. IL28 [6] and KIR2DS [7] polymorphisms play a vital role in in the retort of chronic HCV to therapy.

Role of pegIFNα, ribavirin and IFNλ signaling

IFNα-based therapies showed resistance in the patients with stimulated endogenous IFN system [8]. The most precise extrapolation of the pegIFNα and ribavirin reaction is accomplished by the expression of ISGs of the liver biopsies [9]. IFNλ could surge high virological response in individuals with a pre-activated endogenous IFN response as USP18 (Ubl carboxyl-terminal hydrolase) does not inhibit the IFNλ signaling [10].

Viral genetic heterogeneity

The viral regions of HCV can contribute to IFN resistance via the articulation of various HCV regions like core, E1, E2, NS5A, and NS5B [11]. The SOCS-3 expression might be induced by core that quashes JAK-STAT signalling pathways [12]. Manifestation of the PIAS (protein inhibitor of activated STAT) is tempted by HCV proteins which is probably arbitrated by PP2A (protein phosphatase 2A) signaling and STAT demethylation [13] resulting the STAT1 blockage. High level of IL-8 exhibited in HCV infected individuals [14]. Mutations at amino acids 70 and 91 of core deliberateresistance to IFN-α, related with a decline in IFN-tempted phosphorylation of STAT1 and STAT2 and expression of ISGs [15]. Some regions linked with IFN-α and ribavirin sensitivity have been documented within core region known as ISDR (a.a. 2209- 2248) and IRRDR (a.a. 2334-2379) [16].

IFN-α resistance was observed in recombinant HCV genotypes of 1a and 3a identified substitutions of amino acids at position 414 of E2 and positions 345 & 348 of E1 [17]. The interface between E2 and PKR could be one contrivance by which HCV avoids the interferon [18]. Serine phosphorylation in E2 gene of HCV GT1 had expressed a role in interferon resistance [19]. Mutations related to treatment response have been reported in NS5A region which include ISDR, residues 2209 to 2248, and IRRDR, residues 2334 to 2379, in HCV genotype 1 [20,21]. These mutations were mainly observed in IFN resistant patients. Both core and NS5A express changes during the treatment so impact the therapy consequences [22]. *In vitro* study of HCV replicon cell lines, substitutions in NS3, NS4B, NS5A, and NS5B were linked with IFN non responsiveness [23]. In another study, overexpression of NS5A GT1 showed least IFN response as compared to GT-3 over sturdier binding to STAT1 [24].

Host Immune Responses associated with Interferon Resistance

The development of persistent HCV infection is the result of virus wining the fight from host immune response. During the persistent infection, interferon being a component of innate immune response might have activated at their level best to activate the effective adaptive immune response to infection clearance. However, due to a plethora of reasons (viral mutations and host genetic variation) leads to activation of non-HCV clearance immune response even with the presence of high interferon concentration [8].

Future Directions

The critical issues related to the IFN resistance need to be elucidated in more detail. The role of endogenous IFNλs, and molecular association between ISGs and *IFNL3* needs to be defined for further understandingthe

mechanism of HCV interference with IFN signalling and different type of ISG [2]. The hepatologists and virologists need to be vigilant to define the emerging extend of directly-acting antiviral (DAAs) resistance during treatment. This combination of effective next generation of DAAs with new class of IFNλs should produce good results. The IFN resistance via weak immune responses will help in the design of therapy with chemokines and cytokines co-stimulation of ISG pathways in selected patients.

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