Hepatocellular Carcinoma Prevention by Aspirin: Are Platelets the Link?

TO THE EDITOR:

Memel and colleagues[1] present a comprehensive meta-analysis including more than 2 million patients from all available clinical studies which shows that intake of aspirin was associated with a risk reduction for hepatocellular carcinoma (HCC) by 39%. This effect was robust to a variety of potentially confounding factors. The topic is important because incidence and mortality of HCC are high and still rising. The mechanism of this intriguing preventive effect remains unclear, with inhibition of cyclooxygenase-2 or prevention of platelet activation being likely possibilities. Platelets have gained attention as modulators of recruitment and activation of immune cells in the liver. If platelets are drivers of hepatocarcinogenesis, presence of genetic variants modifying their function should be associated with HCC development.

In an exploratory approach, we analyzed the following three common functionally relevant genetic variants implicated in platelet function in large cohorts that were established for investigation of HCC risk factors[2]: (i) the number of T alleles at rs1126643 in the integrin α2 gene (*ITGA2*) influences expression of the glycoprotein (GP) I/IIa receptor[3] and may mediate resistance to aspirin[4]; (ii) the AA genotype of rs168753 in the thrombin receptor protease-activated receptor 1 (*PAR1*) leads to increased receptor expression[3]; and (iii) variants at the *PAR1* rs11267092 locus have been associated with malignant disease. Our well-characterized cohorts included 298 healthy controls, patients with alcohol-associated cirrhosis without (n = 375) and with (n = 277) HCC, and patients with HCC due to hepatitis C virus-induced cirrhosis (n = 147). Less than 10% of our patients were on aspirin.

In contrast to the well-known patatin-like phospholipase domain containing 3 (*PNPLA3*) 148M risk variant, we did not find any association between the investigated polymorphisms and presence of HCC (Table 1). We cannot exclude that an effect might be seen in a considerably larger cohort or by investigating other polymorphisms regarding platelet function. However, our data indicate that other mechanisms may mediate the protective effect of aspirin on HCC development, possibly also genetic variation in cyclooxygenase-2. In line, cyclooxygenase-2 inhibition is being investigated to prevent HCC recurrence with promising results.[5]

TABLE 1. GENOTYPE DISTRIBUTION OF PLATELET RECEPTOR POLYMORPHISMS

Gene/ Polymorphism	Genotype	Healthy Controls (n = 298)	Alcohol-Associated Cirrhosis (n = 375)	Alcohol-Associated HCC (n = 277)	*P* Value vs. Healthy Controls	*P* Value vs. Alcoholic Cirrhosis	HCV-Associated HCC (n = 147)	*P* Value vs. Healthy Controls
ITGA2 /	CC	99 (33.2%)	139 (37.1%)	99 (35.7%)			49 (33.3%)	
rs1126643	CT	157 (52.7%)	189 (50.4%)	138 (49.8%)	*P* = 0.48	*P* = 0.89	74 (50.3%)	*P* = 0.83
	TT	42 (14.1%)	47 (12.5%)	40 (14.4%)	*P* = 0.91	*P* = 0.48	24 (16.3%)	*P* = 0.53
PAR1 /	AA	205 (68.8%)	261 (69.6%)	198 (71.5%)			101 (68.7%)	
rs168753	AT	87 (29.2%)	108 (28.8%)	69 (24.9%)	*P* = 0.30	*P* = 0.34	40 (27.2%)	*P* = 0.76
	TT	6 (2.0%)	6 (1.6%)	10 (3.6%)	*P* = 0.25	*P* = 0.10	6 (4.1%)	*P* = 0.21
PAR1 /	del/del	177 (59.4%)	224 (59.7%)	152 (54.9%)			84 (57.1%)	
rs11267092	del/ins	105 (35.2%)	138 (36.8%)	113 (40.8%)	*P* = 0.20	*P* = 0.25	53 (36.1%)	*P* = 0.77
	ins/ins	16 (5.4%)	13 (3.5%)	12 (4.3%)	*P* = 0.56	*P* = 0.57	10 (6.8%)	*P* = 0.54
PNPLA3 /	CC	165 (55.4%)	158 (42.1%)	66 (23.9%)			73 (49.7%)	
rs738409	CG	110 (36.9%)	169 (45.1%)	143 (51.6%)	*P* < 0.001	*P* = 0.02	58 (39.4%)	*P* = 0.41
	GG	23 (7.7%)	48 (12.8%)	68 (24.5%)	*P* < 0.001	*P* < 0.001	16 (10.9%)	*P* = 0.27

Data are given as absolutes numbers (%). All genotype distributions corresponded to the Hardy-Weinberg equilibrium.
Abbreviations: del, deletion; HCV, hepatitis C virus; ins, insertion; *ITGA2*, integrin α2; *PAR1*, protease-activated receptor 1; *PNPLA3*, patatin-like phospholipase domain-containing protein 3.

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