

Table S2 Effectors defined during the molecular characterization of the “Motives”: (1) calcification; (2) lipoprotein accumulation; (3) inflammation; (4) oxidative stress; (5) endothelial dysfunction; (6) RAA system; (7) hypertrophy; (8) myocardial fibrosis.

Gene name	Uniprot ID	Reference	Related motives	Gene name	Uniprot ID	Reference	Related motives
ACE2	Q9BYF1	Lindman BR et al, 2016 [18]; Sverdlov AL et al, 2011 [34]	6	MAP3K7	O43318	Nakamura M and Sadoshima J, 2018 [28]	7, 8
ACTA2	P62736	Perrucci GL et al, 2017 [33]	5	MAPK1	P28482	Pasipoularides A, 2016 [31]	7
ADIPOQ	Q15848	Kleinauskienė R and Jonkaitienė R, 2018 [14]	3	MAPK10	P53779	Nakamura M and Sadoshima J, 2018 [28]	7
ADRB1	P08588	Katholi RE and Couri DM, 2011 [13]	7	MAPK11	Q15759	Nakamura M and Sadoshima J, 2018 [28]	7
ADRB2	P07550	Adil SO et al, 2016 [1]; Nakamura M and Sadoshima J, 2018 [28]	7	MAPK12	P53778	Nakamura M and Sadoshima J, 2018 [28]	7
AGT	P01019	Lindman BR et al, 2016 [18]; Elmariah S and Mohler ER 3rd, 2010 [6]; Mathieu P et al, 2014 [24]; Nakamura M and Sadoshima J, 2018 [28]; Ma ZG et al, 2018 [20]	6, 7, 8	MAPK13	O15264	Nakamura M and Sadoshima J, 2018 [28]	7
AGTR1	P30556	Pasipoularides A, 2016 [31]; Ma ZG et al, 2018 [20]	6, 8	MAPK14	Q16539	Nakamura M and Sadoshima J, 2018 [28]	7
AGTR2	P50052	Lindman BR et al, 2016 [18]; Elmariah S and Mohler ER 3rd, 2010 [6]; Mathieu P et al, 2014 [24]; Katholi RE and Couri DM, 2011 [13]; Ma ZG et al, 2018 [20]	6, 7, 8	MAPK3	P27361	Pasipoularides A, 2016 [31]	7
AHSG	P02765	Kapelouzou A et al, 2015 [12]; Mathieu P and Boulanger MC, 2014 [23]	1	MAPK8	P45983	Nakamura M and Sadoshima J, 2018 [28]	7
AKAP6	Q13023	Nakamura M and Sadoshima J, 2018 [28]	7	MAPK9	P45984	Nakamura M and Sadoshima J, 2018 [28]	7
AKT1S1	Q96B36	Nakamura M and Sadoshima J, 2018 [28]	7	MATN2	O00339	García-Rodríguez C et al, 2018 [8]	1
ALPG	P10696	Lee SH and Choi JH, 2018 [16]	1	MEF2A	Q02078	Nakamura M and Sadoshima J, 2018 [28]	7
APOA1	P02647	O'Brien KD et al, 1996 [29]; Mathieu P et al, 2014 [24]	2	MGP	P08493	Doris MK et al, 2019 [5]; Mathieu P et al, 2014 [24]	1
APOB	P04114	O'Brien KD et al, 1996 [29]; Mathieu P et al, 2014 [24]	2	MLST8	Q9BVC4	Nakamura M and Sadoshima J, 2018 [28]	7
APOE	P02649	O'Brien KD et al, 1996 [29]	2	MME	P08473	Gallo G et al, 2019 [7]	3
BAK1	Q16611	Pasipoularides A, 2016 [31]	7	MMP14	P50281	Liu T et al, 2017 [19][19]	8
BAX	Q07812	Pasipoularides A, 2016 [31]	7	MMP2	P08253	Lee SH and Choi JH, 2018 [16]; Helske S et al, 2007 [9]; Liu T et al, 2017 [19]	1, 5
BCL2	P10415	Pasipoularides A, 2016 [31]	7	MMP9	P14780	Lee SH and Choi JH, 2018 [16]; Helske S et al, 2007 [9]	1, 5
BCL2L1	Q07817	Pasipoularides A, 2016 [31]	7	MSX2	P35548	Perrucci GL et al, 2017 [33]	1, 5
BGLAP	P02818	Cho KI et al, 2018 [3]	1	MTOR	P42345	Nakamura M and Sadoshima J, 2018 [28]	7
BGN	P21810	García-Rodríguez C et al, 2018 [8]	3	MYD88	Q99836	García-Rodríguez C et al, 2018 [8]; Zhan Q et al, 2017 [41]	1
BMP2	P12643	Kapelouzou A et al, 2015 [12]; Lindman BR et al, 2016 [18]; García-Rodríguez C et al, 2018 [8]; Sverdlov AL et al, 2011 [34]	1	NFATC1	O95644	Lee SH and Choi JH, 2018 [16]; Nakamura M and Sadoshima J, 2018 [28]	1, 7

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BMP4	P12644	Kapelouzou A et al, 2015 [12]; Lindman BR et al, 2016 [18]; García-Rodríguez C et al, 2018 [8]; Sverdlov AL et al, 2011 [34]	1	NFKB1	P19838	Sverdlov AL et al, 2011 [34] ; Lee SH and Choi JH, 2018 [16]	1, 3
BMP7	P18075	Osman L et al, 2006 [30]	1	NFKB2	Q00653	Sverdlov AL et al, 2011 [34] ; Lee SH and Choi JH, 2018 [16]	1, 3
CA12	O43570	Lindman BR et al, 2016 [18]; Myasoedova VA et al, 2018 [27]	1	NOS3	P29474	Towler DA, 2008 [36]; Mathieu P et al, 2014 [24]	4, 8
CAMK2D	Q13557	Nakamura M and Sadoshima J, 2018 [28]	7	NOTCH1	P46531	Lindman BR et al, 2016 [18]; Elmariah S and Mohler ER 3rd, 2010 [6]	1
CASP3	P42574	Mathieu P and Boulanger MC, 2014 [23]	1	NOX1	Q9Y558	Towler DA, 2008 [36]	4
CASP8	Q14790	Mathieu P and Boulanger MC, 2014 [23]	1	NOX4	Q9NPH5	Miller JD et al, 2008 [25]	4
CAT	P04040	Towler DA, 2008 [36]	4	NPPA	P01160	Gallo G et al, 2019 [7]	7, 8
CCL2	P13500	Lee SH and Choi JH, 2018 [16]	3	NPPB	P16860	Gallo G et al, 2019 [7]	7, 8
CD36	P16671	Syväranta S et al, 2014 [35]	3	NPPC	P23582	Gallo G et al, 2019 [7]	1, 8
CDH5	P33151	Perrucci GL et al, 2017 [33]	5	NR3C2	P08235	Katholi RE and Couri DM, 2011 [13]	7
CHP1	Q99653	Pasipoularides A, 2016 [31]	7	OLR1	P78380	Syväranta S et al, 2014 [35]	3
CMA1	P23946	Sverdlov AL et al, 2011 [34] ; Lindman BR et al, 2016 [18]; Helske S et al, 2007 [9]; Legere SA et al 2019 [17]	6, 8	P2RY2	P41231	Lindman BR et al, 2016 [18]	1
COL1A1	P02452	Perrucci GL et al, 2017 [33]; Musa TA et al, 2018 [26]; Liu T et al, 2017 [19]	5, 8	PDE5A	O76074	Nakamura M and Sadoshima J, 2018 [28]	7
COL1A2	P08123	Perrucci GL et al, 2017 [33]; Musa TA et al, 2018 [26]; Liu T et al, 2017 [19]	5, 8	PDE9A	O76083	Nakamura M and Sadoshima J, 2018 [28]	7
COL3A1	P02461	Perrucci GL et al, 2017 [33]; Musa TA et al, 2018 [26]; Liu T et al, 2017 [19]	5, 8	PECAM1	P16284	Perrucci GL et al, 2017 [33]	5
CSF1	P09603	Lee SH and Choi JH, 2018 [16]	3	PLA2G7	Q13093	Capoulade R et al, 2014 [2]; Mathieu P and Boulanger MC, 2014 [23]	1, 2
CTGF	P29279	Ma ZG et al, 2018 [20]	8	PLCE1	Q9P212	Nakamura M and Sadoshima J, 2018 [28]	7
CTNNB1	P35222	Perrucci GL et al, 2017 [33]	5	POSTN	Q15063	Martin-Rojas T et al, 2015 [21]	1
CTSD	P07339	Helske S et al, 2007 [9]	5	POU1F1	P28069	Mathieu P et al, 2014 [24]; Mathieu P and Boulanger MC, 2014 [23]	1
CTSG	P08311	Sverdlov AL et al, 2011 [34]	6	PPARGC1A	Q9UBK2	Pasipoularides A, 2016 [31]	4
CTSK	P43235	Lee SH and Choi JH, 2018 [16]; Helske S et al, 2007 [9]	1, 5	PPP3CA	Q08209	Nakamura M and Sadoshima J, 2018 [28]	7
CTSL	P07711	Lee SH and Choi JH, 2018 [16]	1	PPP3R1	P63098	Nakamura M and Sadoshima J, 2018 [28]	7
CTSS	P25774	Lee SH and Choi JH, 2018 [16]; Helske S et al, 2007 [9]	1, 5	PRKACA	P17612	Mathieu P et al, 2014 [24]	1
CXCL8	P10145	Lee SH and Choi JH, 2018 [16]	3	PRKD1	Q15139	Nakamura M and Sadoshima J, 2018 [28]	7
CYBB	P04839	Towler DA, 2008 [36]; Miller JD et al, 2008 [25]	4	RELA	Q04206	Mathieu P et al, 2014 [24]; Lee SH and Choi JH, 2018 [16]	1, 3

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CYC1	P08574	Pasipoularides A, 2016 [31]	7	RELB	Q01201	Sverdlov AL et al, 2011 [34] ; Lee SH and Choi JH, 2018 [16]	1, 3
DEPTOR	Q8TB45	Nakamura M and Sadoshima J, 2018 [28]	7	RETN	Q9HD89	Mathieu P and Boulanger MC, 2014 [23][23]	1, 4
DPP4	P27487	Cho KI et al, 2018 [3][3]	1	RPS6KB1	P23443	Nakamura M and Sadoshima J, 2018 [28]	7
EDN1	P05305	Peltonen T et al, 2008 [32]; Nakamura M and Sadoshima J, 2018 [28]; Liu T et al, 2017 [19]; Ma ZG et al, 2018 [20]	5, 7, 8	RPTOR	Q8N122	Nakamura M and Sadoshima J, 2018 [28]	7
EIF4E	P06730	Nakamura M and Sadoshima J, 2018 [28]	7	RUNX2	Q13950	Perrucci GL et al, 2017 [33]	1
EIF4EBP1	Q13541	Nakamura M and Sadoshima J, 2018 [28]	7	SELE	P16581	Cowell SJ et al, 2014 [4]; Lee SH and Choi JH, 2018 [16]	3, 5
ELN	P15502	Helske S et al, 2007 [9]	5	SIRT1	Q96EB6	Mathieu P and Boulanger MC, 2014 [23]	4
ENPP1	P22413	Mathieu P et al, 2014 [24]	1	SMAD2	Q15796	Nakamura M and Sadoshima J, 2018 [28]; Ma ZG et al, 2018 [20]	8
ENPP2	Q13822	Lindman BR et al, 2016 [18]	1	SMAD3	P84022	Nakamura M and Sadoshima J, 2018 [28]; Ma ZG et al, 2018 [20]	8
EPAC1	O95398	Nakamura M and Sadoshima J, 2018 [28]	7	SOD1	P00441	Towler DA, 2008 [36]	4
FGF1	P05230	Katholi RE and Couri DM, 2011 [13]; Liu T et al, 2017 [19]	7, 8	SOD2	P04179	Towler DA, 2008 [36]	4
GATA4	P43694	Nakamura M and Sadoshima J, 2018 [28]	7	SOD3	P08294	Towler DA, 2008 [36]	4
GRK2	P25098	Nakamura M and Sadoshima J, 2018 [28]	7	SP7	Q8TDD2	Lee SH and Choi JH, 2018 [16]	1
GRK5	P34947	Nakamura M and Sadoshima J, 2018 [28]	7	SPP1	P10451	Lee SH and Choi JH, 2018 [16]; Cho KI et al, 2018 [3]	1
HDAC1	Q13547	Nakamura M and Sadoshima J, 2018 [28]	7	TGFB1	P01137	Osman L et al, 2006 [30]; Perrucci GL et al, 2017 [33]; Katholi RE and Couri DM, 2011 [13]; Nakamura M and Sadoshima J, 2018 [28]; Ma ZG et al, 2018 [20]	1, 5, 7, 8
HDAC2	Q92769	Nakamura M and Sadoshima J, 2018 [28]	7	TGFB3	P10600	Osman L et al, 2006 [30]	1
HDAC3	O15379	Nakamura M and Sadoshima J, 2018 [28]	7	TGFBR1	P36897	Nakamura M and Sadoshima J, 2018 [28]; Ma ZG et al, 2018 [20]	8
HDAC4	P56524	Nakamura M and Sadoshima J, 2018 [28]	7	TGFBR2	P37173	Nakamura M and Sadoshima J, 2018 [28]; Ma ZG et al, 2018 [20]	8
HDAC5	Q9UQL6	Nakamura M and Sadoshima J, 2018 [28]	7	TIMP1	P01033	Helske S et al, 2007 [9]	5
HDAC9	Q9UKV0	Nakamura M and Sadoshima J, 2018 [28]	7	TIMP2	P16035	Helske S et al, 2007 [9]	5
HMGB1	P09429	Weber C and Noels H, 2011 [38]	3	TIMP3	P35625	Helske S et al, 2007 [9]	5
IBSP	P21815	Kaden JJ et al, 2004 [11]	1	TIMP4	Q99727	Helske S et al, 2007 [9]	5
ICAM1	P05362	Venardos N et al, 2014 [37]; Lee SH and Choi JH, 2018 [16]	3, 5	TLR2	O60603	Lindman BR et al, 2016 [18]; Elmariah S and Mohler ER 3rd, 2010 [6]; García-Rodríguez C et al, 2018 [8]	1, 3

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IGF1	P05019	Katholi RE and Couri DM, 2011 [13]	7	TLR3	O15455	Lee SH and Choi JH, 2018 [16]	1, 3
IL10	P22301	Kolasa-Trela R et al, 2017 [15]	3	TLR4	O00206	Lindman BR et al, 2016 [18]; Elmariah S and Mohler ER 3rd, 2010 [6]; García-Rodríguez C et al, 2018 [8]	1, 3
IL1A	P01583	Liu T et al, 2017 [19]	8	TNC	P24821	Kapelouzou A et al, 2015 [12]; Yetkin E, Waltenberger J, 2009 [39]	1
IL1B	P01584	Lee SH and Choi JH, 2018 [16]; Liu T et al, 2017 [19]	3, 8	TNF	P01375	Mathieu P et al, 2014 [24]; Lee SH and Choi JH, 2018 [16]; Mathieu P et al, 2014 [24]; Lin CP et al, 2015; Liu T et al, 2017 [19]	1, 2, 3, 4, 8
IL6	P05231	Mathieu P et al, 2015 [22]; Lee SH and Choi JH, 2018 [16]; Liu T et al, 2017 [19]	1, 3, 8	TNFRSF11A	Q9Y6Q6	Yip CY and Simmons CA, 2011 [40]; Izquierdo-Gómez MM et al, 2017 [10]	1
INS	P01308	Katholi RE and Couri DM, 2011 [13]	7	TNFRSF11B	O00300	Yip CY and Simmons CA, 2011 [40]; Izquierdo-Gómez MM et al, 2017 [10]	1
KNG1	P01042	Gallo G et al, 2019 [7]	3	TNFSF11	O14788	Yip CY and Simmons CA, 2011 [40]; Izquierdo-Gómez MM et al, 2017 [10]	1
LEP	P41159	Kolasa-Trela R et al, 2011	4, 5, 7	VCAM1	P19320	Cowell SJ et al, 2014; Lee SH and Choi JH, 2018 [16]	3, 5
LOX	P28300	Liu T et al, 2017 [19]	8	VIM	P08670	Perrucci GL et al, 2017 [33]	5
LPA	P08519	Lindman BR et al, 2016 [18]; Mathieu P et al, 2014 [24]	2	VWF	P04275	Perrucci GL et al, 2017 [33]	5
MAP2K3	P46734	Nakamura M and Sadoshima J, 2018 [28]	7	WNT11	O96014	Lee SH and Choi JH, 2018 [16]; Cho KI et al, 2018 [3]	1
MAP2K4	P45985	Nakamura M and Sadoshima J, 2018 [28]	7	WNT3A	P56704	Lee SH and Choi JH, 2018 [16]	1
MAP2K6	P52564	Nakamura M and Sadoshima J, 2018 [28]	7	WNT5A	P41221	Lee SH and Choi JH, 2018 [16]; Cho KI et al, 2018 [3]	1
MAP2K7	O14733	Nakamura M and Sadoshima J, 2018 [28]	7	WNT5B	Q9H1J7	Lee SH and Choi JH, 2018 [16]; Cho KI et al, 2018 [3]	1

a)

	D.7		D.14	
	C	Ost	C	Ost
250 kDa				
150 kDa				
100 kDa				
75 kDa				
50 kDa				
37 kDa				

b)

	Control		Severe		Control		Severe		Control		Severe	
250 kDa												
150 kDa												
100 kDa												
75 kDa												
50 kDa												
37 kDa												

c)

	Control		Severe		Control		Severe		Control		Severe	
250 kDa												
150 kDa												
100 kDa												
75 kDa												
50 kDa												
37 kDa												